Parasitology Research (2025) 124:53
https://doi.org/10.1007/s00436-025-08498-w

RESEARCH

Association of neurobiological and immune serum biomarkers with *Toxoplasma gondii* infection in patients with schizophrenia

Olga Abramova[1,2] · Yana Zorkina[1,2] · Dmitry Goncharov[3] · Evgenia Abbazova[3] · Marina Baranets[3] · Alexander Berdalin[1] · Valeriya Ushakova[1,2,4] · Valeria Zakurazhnaya[1] · Irina Morozova[1] · Alexandra Ochneva[1,2] · Konstantin Pavlov[1,2] · Denis Andreyuk[1] · Georgy Kostyuk[1,4,5,6] · Anna Morozova[1,2]

Received: 27 December 2024 / Accepted: 28 April 2025

Abstract

Some studies suggest that *Toxoplasma gondii* infection may increase the risk of developing schizophrenia. Determining changes in blood biomarker concentrations may provide new insights into the underlying mechanisms associated with *Toxoplasma gondii* infection in schizophrenia. The aim of the study was to evaluate the concentrations of several serum neurobiological and immune parameters and to identify changes in their concentrations that could potentially be indicators of psychopathologic changes in infection. The concentration of biomarkers was determined in serum from patients with schizophrenia (uninfected $n=50$, infected $n=30$) and from mentally healthy volunteers (uninfected $n=51$, infected $n=29$) using multiplex analysis. A number of psychometric scales have been applied to assess the cognitive functioning. No significant associations were between schizophrenia and *Toxoplasma gondii* infection ($p=0.54$; OR = 1.18; 95% CI = 0.69–2.01). However, infected patients with schizophrenia had more severe cognitive impairment compared to uninfected schizophrenia patients (PDQ-20). The group of biomarkers has been identified whose concentration changes were observed only between *Toxoplasma gondii*–infected healthy individuals and individuals with schizophrenia (neurobiological indicators KLK6, UCHL1, Amyloid beta 1–42 and neurogranin; anti-inflammatory cytokine IL-10; chemokines IL-8 and MIP-1 beta), but not between uninfected groups. The hypothesis was proposed that it is possible to use these indices as indicators of the development of schizophrenic psychopathology in *Toxoplasma gondii* infection. The associations of blood biomarker concentrations with IgA and IgM antibody levels (chemokine RANTES) and with schizophrenia symptoms (hormone-like messenger KLK6; chemokines IP-10 and GRO alpha) were found. *Toxoplasma gondii* reactivation leads to a decrease in negative symptomatology and reduced FGF-21 levels in patients with schizophrenia, and increased CNTF and NGF beta levels compared to the latent form.

Keywords Schizophrenia · *Toxoplasma gondii* · Serum biomarkers · Diagnosis · Neurobiological biomarkers · Immune biomarkers

Section Editor: Aysegul Taylan Ozkan

✉ Olga Abramova
abramova1128@gmail.com

[1] Mental-Health Clinic No. 1 Named After N.A. Alexeev of Moscow Healthcare Department, Zagorodnoe Highway 2, 115191 Moscow, Russia

[2] Department of Basic and Applied Neurobiology, V. Serbsky Federal Medical Research Centre of Psychiatry and Narcology, Kropotkinsky Per. 23, 119034 Moscow, Russia

[3] "National Research Center for Epidemiology and Microbiology Named After Honorary Academician N. F. Gamaleya" of the Ministry of Health of the Russian Federation, Gamaleyi Street, 18, 123098 Moscow, Russia

[4] Lomonosov Moscow State University, Moscow, Russia

[5] Russian Biotechnological University (ROSBIOTECH), Moscow, Russia

[6] Department of Psychiatry and Psychosomatics, I. M. Sechenov First Moscow State Medical University (Sechenov University), 119435 Moscow, Russia

Published online: 21 May 2025

Introduction

Schizophrenia is a severe mental disorder affecting approximately 0.75% of the global population (Moreno-Küstner et al. 2018). This disorder is characterized by psychosis and a pathological cognitive state, and results in difficulty in distinguishing between reality and delusion. Individuals with schizophrenia typically have a reduced life expectancy, and the initial signs of the disorder often emerge during early adulthood (Rantala et al. 2022). The etiology of schizophrenia is complex and multifactorial. Genetic predisposition, environmental influences, and certain infectious agents, particularly *Toxoplasma gondii*, contribute to the risk of developing the disorder (Chaudhury and Ramana 2019).

Toxoplasma gondii is an obligate intracellular parasite of the Coccidia class (Torrey et al. 2007; Chaudhury and Ramana 2019). The definitive hosts of the parasite belong to the feline family, where the sexual cycle of *Toxoplasma gondii* development occurs. In all other vertebrate species (intermediate hosts), the parasite reproduces asexually (Torrey et al. 2007; Chaudhury and Ramana 2019). Intermediate hosts of *Toxoplasma gondii*, including humans, become infected through ingestion of oocysts from the environment or tissue cysts of other animals (Chaudhury and Ramana 2019; Rantala et al. 2022). *Toxoplasma gondii* can exist in several forms in intermediate hosts. Intermediate hosts ingest sporulated oocysts, and in their organism, the oocysts rapidly transform into tachyzoites. Tachyzoites are rapidly multiplying and invasive forms that disseminate in the host and cause symptoms of acute toxoplasmosis (Sanchez and Besteiro 2021). Tachyzoites differentiate into slowly growing cysted bradyzoites that remain largely hidden from the immune system, and in this state can remain in the organism for a long time (Cerutti et al. 2020). Bradyzoites can reactivate into actively proliferating tachyzoites and cause acute infection. Weakened immunity is most often the cause of this, for example in HIV infection and cancer (Halonen and Weiss 2013).

Toxoplasma gondii is neurotropic; the parasite migrates within brain tissue, localizing in astrocytes, microglia, and neurons. The distribution of cysts within the brain significantly influences behavioral alterations in infected hosts (Pearce et al. 2012; Chaudhury and Ramana 2019). There is published evidence that *Toxoplasma gondii* infection in humans contributes to increased aggression and impulsivity, but this has not yet been definitively proven (Beaumont et al. 2024). There is a long-standing interest in investigating the possible link between exposure to this parasite and the development of severe psychiatric disorders (Pearce et al. 2012). *Toxoplasma gondii* has been most extensively studied in schizophrenia, and the meta-analysis showed that overall, the likelihood of *Toxoplasma gondii* seropositivity was 2.73 times higher in patients with schizophrenia than in the general population (Torrey et al. 2007). Other meta-analyses have also reported an association of *Toxoplasma gondii* infection with schizophrenia and other psychiatric disorders (Sutterland et al. 2015; Contopoulos-Ioannidis et al. 2022). The impact of *Toxoplasma gondii* on the risks of developing psychiatric disorders may be a significant issue, as this parasite is highly prevalent, infecting approximately 30% of people worldwide (Torrey et al. 2007; Chaudhury and Ramana 2019). The relationship between *Toxoplasma gondii* reactivation and the development of psychiatric disorders is particularly interesting. This issue is poorly understood, but according to a meta-analysis, for example, it is possible that reactivation of latent infection may occur in schizophrenia (Sutterland et al. 2015). In addition, there are data from a study on mice, which demonstrated that reactivation of chronic *Toxoplasma gondii* infection with immunosuppressive therapy causes depressive behavior without overt symptoms of the disease (Mahmoud et al. 2016). Therefore, the question of the possible connection between reactivation of infection and the development of psychiatric disorders remains open and needs to be carefully studied.

Not every patient with schizophrenia has *Toxoplasma gondii* infection, and it may be only one possible cause of schizophrenia (Rantala et al. 2022). Genetic and environmental factors, both immune system-dependent and immune system-independent, may be involved (Bhadra et al. 2013). The heterogeneity of schizophrenia symptoms associated with toxoplasma infestation is probably due to the spontaneous distribution of parasite cysts in the host brain. This may explain the presence of individuals with *Toxoplasma gondii* infection without significant symptoms of schizophrenia (McConkey et al. 2013). Overall, the mechanisms and effects by which *Toxoplasma gondii* infection may serve as a cause or catalyst for illness are only beginning to be understood (Osman et al. 2022). It is important to find factors that mediate the development of schizophrenia in infected individuals and to develop accessible methods by which to assess the risks of developing a schizophrenia when infected, for example by analyzing blood biomarkers (Bhadra et al. 2013). Infectious diseases and psychiatric disorders can potentially lead to changes in the concentration of various blood biomarkers. Among other things, blood values that reflect the state of the immune and nervous systems, which are impaired in schizophrenia, are important (Rantala et al. 2022).

Neuroinflammation and neurodegeneration are among the hypotheses of schizophrenia. Increased concentrations of neuroinflammatory markers, activation of microglia, which are components of neuroinflammation, have been shown in both plasma (Bedrossian et al. 2016; Lee et al. 2017; Campeau et al.

2022; Pinjari et al. 2022) and brain (Trépanier et al. 2016) in schizophrenia. Uncontrolled activity of pro-inflammatory cytokines and microglia can cause schizophrenia together with genetic vulnerability and glutamatergic neurotransmitters (Na et al. 2014). It involves the participation of immune dysfunction in the pathogenesis of schizophrenia. However, whether neuroinflammation leads to the development of schizophrenia or whether the inflammatory component is a secondary step in the pathogenesis is still controversial. In turn, *Toxoplasma gondii* also modulates the immune system by infecting microglia and astrocytes and cause chronic inflammation of the CNS. The parasite suppresses astrocyte function in the brain, leading to glutamate accumulation, and nerve cell death (Chaudhury and Ramana 2019; Rantala et al. 2022). So, *Toxoplasma gondii* infection, by causing neuroinflammation and immune dysfunction, may contribute to the development of schizophrenia (Ermakov et al. 2023). Therefore, both schizophrenia and *Toxoplasma gondii* infection can potentially lead to altered immune system function, which can be detected by some immune blood parameters.

It is also necessary to mention that neuroinflammation is closely linked to neurodegeneration (Na et al. 2014). Pro-inflammatory cytokines play pleiotropic roles in the CNS that include roles in synaptic plasticity and neurogenesis (Na et al. 2014). Altered concentrations of markers of neurodegeneration have also been observed in schizophrenia (Runge et al. 2023). Accumulating biological findings support the role of neurodegenerative processes in the pathogenesis of schizophrenia (Stone et al. 2022).

Based on the above, it is important to assess the risks of schizophrenia symptoms in *Toxoplasma gondii* infection, which requires the development of a specific diagnostic approach. Therefore, the aim of our study was to evaluate the concentration of several serum biochemical parameters in patients with schizophrenia and mentally healthy controls infected with *Toxoplasma gondii* and to identify changes in their concentrations that could potentially be indicators of psychopathologic changes in this infection.

The decision was made to evaluate a large panel of diverse biomarkers, which includes both neuroinflammatory indicators and biomarkers of neurodegeneration, in order to study the problem from different aspects. In addition, in our study, the decision was made to investigate the effect of reactivation of infection on clinical and biochemical characteristics of patients.

Materials and methods

Patients

Participants with mental disorders were recruited from Mental Health Clinic No. 1 named after N.A. Alexeev within the Department of Health of Moscow. The control group consisted of healthy volunteers who attended periodic medical examinations. This research was conducted in accordance with the guidelines of the Helsinki Declaration. Experiments involving human participants were conducted in accordance with ethical guidelines (Protocol No. 2/28.10.2020 approved by the Local Ethics Committee of Mental Health Clinic No. 1 named after N.A. Alexeev within the Department of Health of Moscow). Written informed consent was obtained from all participants. A total of 353 subjects participated in the study, including 193 patients with schizophrenia and 160 healthy volunteers.

The following inclusion criteria were applied: individuals with a history of schizophrenia (F20) diagnosis at least 1 year prior, as established during an inpatient evaluation; age range between 18 and 55 years; the participant must provide written consent for the clinical interview and the collection of blood samples for genetic testing. Two psychiatrists independently verified the diagnosis through structured clinical interviews, adhering to the International Classification of Diseases (ICD-10) diagnostic criteria. All participants were excluded if they met any of the following criteria: the presence of concomitant psychiatric disorders, including drug and substance abuse (including alcohol); organic mental disorders of any etiology; mental retardation; and severe systemic and chronic neurological conditions.

Healthy control subjects were recruited from volunteers who participated in preventive medical examinations at Outpatient Clinic No. 121 (Moscow). Participants were excluded if they met any of the following criteria: a history of psychiatric illness, a positive family history (first-degree relatives) of psychiatric illness, substance abuse, or severe somatic diseases.

Patients with schizophrenia and healthy volunteers participating in the study had not previously been treated for toxoplasmosis. Patients with schizophrenia and healthy volunteers were assessed for socio-demographics, age, sex, height, and weight. Patients with schizophrenia were tested using a series of psychometric scales. Blood was collected from patients and healthy volunteers, and serum was used to determine specific antibodies IgG, IgM, IgA to *Toxoplasma gondii*, and the avidity of IgG antibodies.

One hundred sixty people were randomly selected for multiplex analysis of blood parameters determination, and therefore, four experimental groups were formed depending on mental and infection status: Control ($n = 51$), mentally healthy volunteers without *Toxoplasma gondii* infection; Control + T ($n = 29$), mentally healthy volunteers with *Toxoplasma gondii* infection; Sch ($n = 50$), patients with schizophrenia without *Toxoplasma gondii* infection; Sch + T ($n = 30$), patients with schizophrenia and with *Toxoplasma gondii* infection.

Psychometric scales

The primary methodology for data collection was the clinician-administered, descriptive approach, which involved reviewing medical records, clarifying patient complaints, monitoring alterations in their mental and physical health, and assessing their social functioning. To measure changes in psychotic, depressive, negative symptoms, and the quality of social functioning, the scales were employed at all visits:

1. Positive and Negative Syndrome Scale (PANSS) is a widely used instrument for quantifying symptom severity in schizophrenia. It consists of 30 distinct items, organized into subscales measuring positive, negative, and general psychopathology symptoms. A higher score indicates a more severe manifestation of symptoms. The PANSS is widely recognized as the global "gold standard" for evaluating the symptomatology of schizophrenia. (Lindenmayer 2017).
2. Calgary Depression Scale for Schizophrenia (CDSS) has demonstrated high reliability in evaluating depression in schizophrenia. CDSS is a 9-item scale, with each item rated on a 0–3 scale (Reznik et al. 2023).
3. The NSA-5 scale was developed to quantify the severity of negative symptoms in individuals diagnosed with schizophrenia, comprising five items, each scored on a 0-to-4 rating scale (Reznik et al. 2023);
4. Perceived Deficits Questionnaire, 20-item (PDQ-20) has been demonstrated to be an effective tool for assessing patients' subjective perception of cognitive deficits during remission phases of schizophrenia. The PDQ-20 consists of 20 items, each evaluated on a scale ranging from 0 to 4, with the total score derived from the sum of responses across all 20 items (Strober et al. 2016; Reznik et al. 2023);
5. Progressive Supranuclear Palsy Clinical Deficits Scale (PSP)—a scale developed from the integration of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) and the Global Assessment of Functioning (GAF). The assessment takes into account four categories of functioning: potentially rewarding activities, relationships with significant others and other social connections, self-care, and disturbing and aggressive behaviors. The scale has demonstrated its reliability and efficiency as a tool for assessing individual and social performance. The PSP is a rating scale with a maximum score of one hundred, which is divided into ten equal intervals, each of which is assigned an ordinal value (Jelastopulu et al. 2014; Reznik et al. 2023).
6. Montgomery-Åsberg Depression Rating Scale (MADRS)—the scale is specifically designed to assess the severity of depressive symptoms and identify changes resulting from antidepressant therapy. The scale comprises 10 items, each rated on a scale from 0 (absence of symptoms or normal) to 6 (severe or persistent presence of a symptom), allowing a maximum total of 60 points (Hudgens et al. 2021).
7. Patient Health Questionnaire (PHQ-9) is a 9-item questionnaire that serves as a basis for the DSM-IV diagnosis of depressive disorders (Kroenke et al. 2001).
8. Self-evaluation of Negative Symptoms (SNS) evaluates all five categories of negative symptoms, including social withdrawal, blunted affect, estrangement, anhedonia, and alogia. The scale consists of 20 items, with four items per negative symptom, and the score reflects the previous week's manifestations (Wójciak et al. 2021).
9. Cognitive Complaints in Bipolar Disorder Rating Scale (COBRA) is a self-assessment instrument comprising 16 items designed to evaluate cognitive dysfunction across multiple domains. These domains include executive function, attention and concentration, processing speed, verbal learning, and memory (Bonnín et al. 2024).

Serum sample collection

Blood parameters were measured in serum. Blood samples for analysis were collected from the cubital vein in the fasting state, typically before 9 a.m. Serum was isolated immediately following blood collection via centrifugation at 3000 rpm for 10 min at 4 °C, and then stored at –80 °C until analysis.

Toxoplasma gondii serological analysis

Specific markers of *Toxoplasma gondii* infection were determined in blood serum samples: IgG antibodies to *Toxoplasma gondii* and their avidity index (AI), IgM, and IgA to *Toxoplasma gondii*. The level of antibodies and AI were determined by enzyme-linked immunosorbent assay (ELISA) using the kits "ToxoplaStripG" (TU 9398–005–4037–1634-2008), "VectoToxo-IgG" (FSR 2012/12998, Vector-Best JSC), "ToxoplaStripM" (TU 9398–005–4037–1634-2008), "VectoToxo-IgM" (FSR 2012/12999, Vector-Best JSC), "VectoToxo—IgA" (No. FSR 2012/14096, Vector-Best JSC) and "VectoToxo—IgG—avidity" (No. FSR 2019/8630, Vector-Best JSC). The results of the study were evaluated according to the manufacturer's instructions. The following values were considered as high level of IgG antibodies: titer 1:6400 and higher and 200 IU and higher when using the test systems "ToxoplaStripG" and "VectoToxo-IgG," respectively.

Toxoplasma gondii reactivation was determined by the presence of specific IgA with high avidity of IgG. Reactivation is also often accompanied by increased IgG levels, so an IgG level of more than 200 IU was considered a marker of reactivation.

Multiplex assay

Commercially available multiplex immunoassays were employed according to the manufacturer's guidelines to assess serum blood parameters (ProcartaPlex™ Multiplex Immunoassay and ProcartaPlex™ Human Neuroscience Panel 18-Plex, Thermo Fisher). The measurements were performed using a Luminex analyzer (Luminex™ 100/200™). Therefore, the concentration of two groups of markers in the blood serum was measured: neurobiological (kallikrein-6 (KLK6), S100 calcium-binding protein B (S100B), ubiquitin C-terminal hydrolase L1 (UCHL1), glial fibrillary acidic protein (GFAP), neurofilament-H (NF-H), chitinase 3 Like 1 (CHI3L1, YKL-40), ciliary neurotrophic factor (CNTF), Amyloid beta 1–42, GDNF, Total Tau, neural cell adhesion molecule 1 (NCAM-1), nerve growth factor beta (NGF beta), brain-derived neurotrophic factor (BDNF), Tau [pT181], macrophage migration inhibitory factor (MIF), TAR DNA-binding protein 43 (TDP-43), neurogranin) and immunological (fibroblast growth factor 21 (FGF-21), macrophage inflammatory protein 1 alpha (MIP-1 alpha), stromal cell-derived factor-1 alpha (SDF-1 alpha), interleukin-27 (IL-27), Interferon γ-induced protein (IP-10), interleukin-8 (IL-8), interleukin-10 (IL-10), eotaxin, interleukin-17 A (IL-17 A), chemokine (C–C motif) ligand 5 (CCL5, RANTES), macrophage inflammatory protein 1 beta (MIP-1 beta), monocyte chemotactic protein-1 (MCP-1), interleukin-9 (IL-9), growth-regulated oncogene alpha (GRO alpha), interleukin-23 (IL-23), interleukin-21 (IL-21), and interleukin-22 (IL-22)).

Statistical processing

Analysis was performed using jamovi and RStudio software. All figures were created using R Studio.

Upon receiving the data, its distribution was assessed for normality using the Shapiro–Wilk test. This assessment determined the appropriate criteria for statistical comparison: parametric or non-parametric. In the context of a normal distribution, the mean and standard deviation were utilized. In the case of an abnormal distribution, the median and interquartile range were calculated. Assuming a normal distribution, parametric analysis was conducted, using analysis of variance (ANOVA), followed by Tukey's multiple comparison tests for post hoc analysis, and data were presented as Mean ± SE. Non-parametric analysis was performed in the case of non-normal distribution using the Kruskal–Wallis test and subsequent multiple comparison tests (Dwass–Steel–Critchlow–Fligner); the data were presented as median (Q1, Q3). Differences were considered statistically significant at $p < 0.05$.

The categorical variables including the serum reactivity to *Toxoplasma gondii*, family history of mental disorders, and where the person lived (urban or rural) were compared by the use of the chi-squared test. Odds ratio (OR) and its 95% CI were calculated.

The data on blood biochemical parameters were standardized and subsequently employed for principal component analysis (PCA) within the RStudio environment. Samples were compared by mental and infection status.

A Pearson correlation analysis was conducted using the Jamovi and RStudio software for correlation assessment. A $r < -0.7$ or $r > 0.7$ and $p < 0.01$ were considered statistically significant for the correlation analysis to account for multiple comparisons.

Results

Evaluation of antibody levels to Toxoplasma gondii in mentally healthy volunteers and patients with schizophrenia

Diagnosis of *Toxoplasma gondii* infection is based on serologic tests that detect *Toxoplasma gondii*-specific IgG and IgM antibodies. IgM appear approximately 1 week after infection, and IgG antibodies appear 1–3 weeks after the appearance of IgM antibodies. The presence of IgM usually indicates an acute infection (Teimouri et al. 2020; Bollani et al. 2022). Therefore, IgM is formed during fresh, primary invasion and such an acute, clinically manifested form of toxoplasmosis is very rare (Kodym et al. 2015). IgG is an indicator of chronicity of the disease. It is also known that *Toxoplasma gondii* infection is a latent infection of the brain. Activation of infection around the cysts of the parasite can increase dopamine levels, which can lead to the formation of IgA antibodies, a marker of *Toxoplasma gondii* reactivation (Gubareva et al. 2013; Kodym et al. 2015). Avidity is the cumulative strength with which a polyclonal mix of IgG molecules reacts with several protein epitopes. The functional binding affinity of IgG binding against *Toxoplasma gondii* increases progressively after infection. Low IgG avidity values usually indicate the first few months of primary infection, while high avidity values indicate secondary infection (Teimouri et al. 2020).

Complete data was collected from 353 subjects who took part in the study (193 patients with schizophrenia and 160 healthy volunteers). Analysis of antibodies to *Toxoplasma gondii* showed the presence of specific IgG antibody markers to *Toxoplasma gondii* in 40 of 193 (20.7%) patients with schizophrenia and in 29 of 160 (18.1%) psychiatric healthy volunteers. Four psychiatric patients and four healthy volunteers had IgM +—signs of acute *Toxoplasma gondii* infection, and they did not have IgG + status. Nine psychiatric patients and ten healthy volunteers had IgA +—signs of acute *Toxoplasma gondii* infection.

Chi-squared test showed no difference in the incidence of *Toxoplasma gondii* infection between healthy subjects and patients with schizophrenia ($\chi^2 = 0.38$, df = 1, $p = 0.54$); the odds ratio was OR = 1.18, 95% CI = 0.69–2.01. Therefore, a significant association was found between schizophrenia and infection status with seroprevalence. Additionally, the power of the study was assessed as sufficient. For this, data from a recent meta-analysis were used. According to data from this study, the weighted seropositivity rate for patients with schizophrenia is 45% and for controls 30% (Contopoulos-Ioannidis et al. 2022). The required sample size should be 376 individuals in both groups to capture such a difference in proportion with a power of 80%, i.e., 188 in the schizophrenia group and 188 in the control group (chi-squared power calculation: $w = 0.1445908$; $N = 375.4268$; df = 1; sig.level = 0.05; power = 0.8; N is the number of observations). The numbers of the groups are comparable in our case. Consequently, our population indeed has no association of schizophrenia and toxolasmosis, and the group sizes in our experiment are sufficient for such a conclusion.

Evaluation of antibody levels between groups of controls and patients with schizophrenia and seropositivity to *Toxoplasma gondii* showed no differences between groups (Table 1).

Effect of Toxoplasma gondii on symptomatology in patients with schizophrenia

The infectious status was determined of patients with schizophrenia and detected IgG antibodies to *Toxoplasma gondii* in 40 patients out of 193. Also, all patients with schizophrenia were tested using a series of psychometric scales, and the results are presented in Table 2. Further *Toxoplasma gondii*-positive and *Toxoplasma gondii*-negative patients were compared and found significant differences only on the PDQ-20 scale—patients with *Toxoplasma gondii* had a higher score on this scale ($p = 0.04$) compared to patients without *Toxoplasma gondii*, indicating a more pronounced impairment of cognitive function as assessed by the PDQ-20 self-assessment questionnaire in patients with *Toxoplasma gondii*. Evaluation of individual PDQ-20 scales showed significant differences only in the retrospective memory scale—this index was elevated in patients with *Toxoplasma gondii* (Table 2).

Study of the effect of Toxoplasma gondii on biological markers in blood in healthy volunteers and patients with schizophrenia

Complete data was collected from 160 people, from whom blood was drawn for determination of biomarkers in serum. General characteristics of the study population (for 160 persons: Control ($n = 51$), Control + T ($n = 29$), Sch ($n = 50$), Sch + T ($n = 30$)) are shown in Table 3. The groups did not differ from each other in terms of age, height, and weight. However, significant differences were found in the educational level and marital status of the study participants. Patients with schizophrenia had lower levels of education and were more likely to have single marital status compared to healthy controls.

KW analysis showed that some serum parameters differed between the patient and control groups, taking into account infection status (Table 4). Considering FDR correction, significant differences were shown for 15 blood parameters: KLK6, S100B, UCHL1, Amyloid beta 1–42, NCAM-1, NGF beta, neurogranin, MIP-1 alpha, IP-10, IL-8, IL-10, RANTES, MIP-1 beta, MCP-1, and GRO alpha, of which 7 neurobiological parameters and 8 immunological parameters.

The posterior analysis showed differences between groups for each of the 15 parameters. The results of the posterior analysis for neurobiological blood parameters are presented in Fig. 1. The control groups (Control and Control + T) differed significantly in all seven neurobiologic parameters. For *Toxoplasma gondii* infection, controls had the following in their blood: decreased KLK6 concentration ($p < 0.001$), increased S100B ($p < 0.001$), increased UCHL1 ($p < 0.001$), decreased Amyloid beta 1–42 ($p < 0.001$), decreased NCAM-1 ($p = 0.03$), increased NGF beta ($p < 0.001$), and decreased neurogranin ($p = 0.04$) (Fig. 1). Meanwhile, the

Table 1 Comparison of class-specific reactivity to *Toxoplasma gondii* antigens in serum samples obtained from individuals with schizophrenia and in samples obtained from control subjects

Class of antibody	Antibody levels		χ^2	df	p
	Control with *Toxoplasma gondii* ($n = 29$)	Patients with schizophrenia and *Toxoplasma gondii* ($n = 40$)			
IgG, median (Q1; Q3)	180 (94; 300)	150 (85; 262)	0.56	1	0.45
IgM, median (Q1; Q3)	0 (0;0); (IgM + $n = 4$)	0 (0;0); (IgM + $n = 4$)	0.72	1	0.40
IgA, median (Q1; Q3)	0 (0;0.6); (IgA + $n = 10$)	0 (0;0.3); (IgA + $n = 9$)	0.17	1	0.68
Avidity, median (Q1; Q3), %	74 (68; 84)	81 (73; 86)	1.12	1	0.29

*The analysis was performed using Kruskal–Wallis test. Significant p-values (< 0.05) are highlighted in bold

Table 2 Results of psychometric scales in patients with schizophrenia ($n = 193$) with regard to infection status: No—no evidence of *Toxoplasma gondii* infection ($n = 153$); Yes—evidence of *Toxoplasma gondii* infection ($n = 40$)

Scales	*Toxoplasma gondii*	Mean/median	SE/quartiles	X^2/F	df	*p*
CDSS	No	10	3; 15	0.17	1	0.68
	Yes	9	5; 14.5			
NSA5	No	11.2	0.37	0.35	1	0.55
	Yes	10.7	0.63			
PANSS Positive	No	22	18; 27	0.22	1	0.64
	Yes	22	19.7; 27.2			
PANSS Negative	No	25	21; 29.2	0.001	1	0.98
	Yes	25	21.5; 30			
PANSS General	No	46.5	41; 53	0.02	1	0.89
	Yes	46.0	38.7; 52.2			
MADRS	No	14.0	7; 24	0.06	1	0.80
	Yes	14.5	5.7; 24			
PHQ9	No	9.0	4; 13	0.07	1	0.79
	Yes	7.5	5; 13.7			
PSP	No	55	40; 62	2.51	1	0.11
	Yes	51	35.5; 55.5			
SNS	No	16.2	0.72	0.03	1	0.87
	Yes	16.5	1.12			
COBRA	No	18	11; 25	0.45	1	0.50
	Yes	19	13; 25.5			
PDQ-20 Total score	**No**	**18,5**	**11; 32**	**4.25**	**1**	**0.04**
	Yes	**24.0**	**15.7; 38.2**			
PDQ-20 Concentration	No	5.5	3; 8	2.43	1	0.12
	Yes	6	5; 10			
PDQ-20 Retrospective Memory	**No**	**4**	**2; 8**	**4.12**	**1**	**0.04**
	Yes	**6**	**3; 9**			
PDQ-20 Prospective Memory	No	4	1; 8	3.68	1	0.055
	Yes	5.5	3; 8			
PDQ-20 Planning/Organization	No	5	2; 9	1.80	1	0.18
	Yes	6	3.7; 10			

*The analysis was performed using Kruskal–Wallis test or ANOVA test. Significant *p*-values (< 0.05) are highlighted in bold

schizophrenia patient groups (Sch and Sch + T) did not differ in any of the parameters. However, some differences were found between control and schizophrenia. KLK6 concentration was higher in Sch and Sch + T groups compared to Control + T group (respectively, $p = 0.006$, $p = 0.002$, Fig. 1A). S100B concentration was higher in the Sch group compared to Control ($p = 0.002$; Fig. 1B). UCHL1 was decreased in Sch + T compared to Control + T ($p = 0.008$; Fig. 1C). Sch ($p = 0.01$) and Sch + T ($p = 0.002$) patient groups had higher Amyloid beta 1–42 concentration compared to Control + T (Fig. 1D). NCAM-1 concentration was reduced in Sch + T compared to Control ($p < 0.001$; Fig. 1E). NGF beta concentration was higher in Sch compared to Control ($p = 0.002$) and Control + T ($p = 0.004$), and in Sch + T compared to Control + T ($p = 0.006$) (Fig. 1F). Neurogranin concentration was higher in Sch ($p = 0.01$) and Sch + T ($p = 0.02$) groups compared to Control + T (Fig. 1G). Therefore, statistically significant differences in many neurobiological blood parameters were observed between Control + T and Sch + T groups, while fewer differences were observed between Control and Sch.

The results of a posteriori analysis for immunologic blood parameters are presented in Fig. 2. The control groups (Control and Control + T) differed significantly only in two immunologic indices; in case of toxoplasmal infestation in the blood of controls, there was an increase in the concentration of MIP-1 alpha ($p = 0.01$) and a decrease in IL-10 ($p < 0.001$) (Fig. 2). At the same time, groups of patients with schizophrenia (Sch and Sch + T) did not differ from each other in any of the parameters. Some differences were also found between controls and schizophrenia. The concentration of MIP-1 alpha and MIP-1 beta was significantly lower in patients with schizophrenia compared to controls. The Sch group had lower concentration of MIP-1 alpha compared to

Table 3 General characteristics of study population on biomarker research in serum blood

Variable\statistic	Categories	Group value				X^2/F	df	*p*
		Control	*Control + T*	*Sch*	*Sch + T*			
N (% of total)		51 (31.9)	29 (18.1)	50 (31.2)	30 (18.8)	-	-	-
Age, mean (SE) years		35.7 (1.1)	36.6 (1.3)	33.9 (1.3)	39.1 (1.5)	2.53	3	0.06
Height, mean (SE) cm		172.2 (1.1)	169.4 (1.7)	168.6 (1.2)	171.1 (1.8)	1.61	3	0.19
Weight, mean (SE) kg		73.1 (2.4)	73.6 (3.1)	69.6 (2.3)	75.5 (3.3)	0.87	3	0.46
Sex, *n* (% of total)	Female	32 (20.0)	19 (11.9)	40 (25.0)	22 (13.8)	4.11	3	0.25
	Male	19 (11.9)	10 (6.3)	10 (6.3)	8 (5.0)			
Education								
Primary school, *n* (% of total)		0 (0)	0 (0)	3 (1.9)	1 (0.6)	121.2	18	**< 0.001**
Incomplete secondary, *n* (% of total)		1 (0.6)	0 (0)	6 (3.8)	2 (1.3)			
Complete secondary, *n* (% of total)		11 (6.9)	3 (1.9)	12 (7.5)	7 (4.4)			
College, *n* (% of total)		0 (0)	0 (0)	25 (15.6)	17 (10.6)			
Unfinished higher education, *n* (% of total)		0 (0)	0 (0)	2 (1.3)	1 (0.6)			
Higher, *n* (% of total)		39 (24.4)	23 (14.4)	1 (0.6)	2 (1.3)			
Scientific degree, *n* (% of total)		0 (0)	3 (1.9)	1 (0.6)	0 (0)			
Family								
Married, *n* (% of total)		15 (9.4)	11 (6.9)	10 (6.3)	7 (4.4)	27.06	12	**0.008**
Informal marriage, *n* (% of total)		4 (2.5)	3 (1.9)	1 (0.6)	2 (1.3)			
Lives alone but has a partner, *n* (% of total)		9 (5.6)	3 (1.9)	0 (0)	0 (0)			
Divorced, *n* (% of total)		4 (2.5)	3 (1.9)	6 (3.8)	6 (3.8)			
Single, *n* (% of total)		19 (11.9)	9 (5.6)	33 (20.6)	15 (9.4)			

*The analysis was performed using ANOVA test or chi-squared test. Significant *p*-values (< 0.05) are highlighted in bold

Control ($p = 0.004$) and Control + T ($p < 0.001$), and the Sch + T group compared to Control ($p < 0.001$) and Control + T ($p < 0.001$) (Fig. 2A). The Sch group had lower MIP-1 beta concentration compared to Control + T ($p = 0.009$), and the Sch + T group compared to Control ($p = 0.03$) and Control + T ($p = 0.002$) (Fig. 2B). Sch ($p < 0.001$) and Sch + T ($p < 0.001$) schizophrenia patient groups had lower IL-8 concentrations compared to Control + T (Fig. 2C). Conversely, IL-10 concentration was elevated in Sch ($p = 0.002$) and Sch + T ($p < 0.001$) groups compared to Control + T (Fig. 2D). Conversely, RANTES concentration was elevated in the Sch group compared to Control ($p < 0.001$), and in the Sch + T group compared to Control ($p < 0.001$) and Control + T ($p = 0.001$) (Fig. 2E). IP-10 concentration was also elevated in patients with schizophrenia, in the Sch group compared to Control ($p = 0.007$), and in the Sch + T group compared to Control ($p < 0.001$) and Control + T ($p = 0.008$) (Fig. 2F). MCP-1 concentration was elevated in patients with schizophrenia, in the Sch group compared to Control ($p = 0.006$), and in the Sch + T group compared to Control ($p < 0.001$) and Control + T ($p = 0.006$) (Fig. 2G). For GRO alpha, the only significant difference was observed—its concentration was higher in Sch compared to Control ($p = 0.01$; Fig. 2H). Therefore, the control and schizophrenia groups differed significantly from each other in various indices (Control and Sch—MIP-1 alpha, RANTES, MCP-1, GRO alpha, IP-10; Control + T and Sch + T—MIP-1 alpha, IP-10, IL-8, IL-10, RANTES, MIP-1 beta, MCP-1). This suggests that there are general differences between controls and patients with schizophrenia regardless of infection status.

Group and infection status were considered qualitative variables, whereas the tested biochemical variables were considered quantitative variables in PCA analysis. Only those parameters for which significant differences were found between groups with FDR correction were considered as biochemical variables (Table 2). The PCA analysis showed potential differences between the control groups (C and Control + T) (Fig. 3), which formed two separate groups on the PCA biplot, but not between the groups of patients with schizophrenia (Sch and Sch + T), which is consistent with the results that were obtained when the blood parameters were compared separately between groups.

After stratification according to groups, PCA revealed that the first (Comp 1) and second (Comp 2) principal components explained most of the variance. Comp 1 and Comp 2 explained 57.1% and 14.9% of the variance in the Control group, 48.4% and 17.1% of the variance in the Control + T group, 50.3% and 15.5% of the variance in the Sch group, and 54.9% and 22% of the variance in the Sch + T group (Figure A1). The main Comp 1 in Sch, Sch + T, and Control groups is well represented by the cluster of positively correlated variables Amyloid beta 1–42, IL-10, UCHL1, S100B;

Table 4 Evaluation of changes in serum parameters in patients with schizophrenia and healthy controls with regard to infection status

Serum parameters	Control ($n = 51$)		Control + T ($n = 29$)		Sch ($n = 50$)		Sch + T ($n = 30$)		X^2	df	p	FDR
	Median	Q1; Q3	Median	Q1; Q3	Median	Q1; Q3	Median	Q1; Q3				
Neurobiological parameters												
KLK6, pg/ml	1624	1013; 2048	875	644; 1158	1323	937; 1656	1378	955; 1685	22.66	3	0.000048	**< 0.001**
S100B, pg/ml	0	0; 0	0.30	0.12; 0.297	0.12	0; 0.46	0	0; 0.297	22.67	3	0.0000043	**< 0.001**
UCHL1, pg/ml	0	0; 121	236	121; 471	121	0; 272	0	0; 200	22.33	3	0.000056	**< 0.001**
GFAP, pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	1.2	3	0.75	0.85
NF-H, pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	0.34	3	0.95	1
YKL-40, pg/ml	3965	3299; 5090	4710	3876; 5252	5073	3471; 6043	4603	3246; 5850	4.4	3	0.22	0.34
CNTF, pg/ml	0	0; 0.73	0	0; 0.17	0	0; 0.60	0	0; 0.02	3.85	3	0.28	0.4
Amyloid beta 1–42, pg/ml	0.15	0; 0.76	0	0; 0	0	0; 0.51	0	0; 0.86	19.7	3	0.0002	**< 0.001**
GDNF, pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	1.78	3	0.61	0.77
Total Tau, pg/ml	0.91	0; 3.31	0	0; 1.08	0	0; 4.24	0	0; 3.82	3.92	3	0.27	0.4
NCAM-1, pg/ml	98247	68,313; 123,275	69,115	63,624; 85,218	79,657	63,957; 101,486	64,298	44,360; 78,793	18.76	3	0.0003	**< 0.001**
NGF beta, pg/ml	0	0; 1.45	2.45	2.22; 2.67	2.220	0; 2.45	1.129	0; 2.48	35.36	3	0.0000001	**< 0.001**
BDNF, pg/ml	469	237; 815	845	483; 1281	439	184; 901	457	225; 872	9.23	3	0.026	0.055
Tau [pT181], pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	0.31	3	0.96	0.99
MIF, pg/ml	44	30; 53	54	42; 71	44	27; 70	37	30; 55	7.93	3	0.047	0.09
TDP-43, pg/ml	344	92; 774	418	207; 668	255	0; 817	145	0; 630	4.92	3	0.18	0.29
Neurogranin, pg/ml	3499	1935; 5581	1733	623; 3304	3882	1549; 7831	3368	1971; 6981	13.27	3	0.0041	**0.01**
Immunological parameters												
FGF-21, pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	2.21	3	0.53	0.69
MIP-1 alpha, pg/ml	6.5	2.4; 22.4	21.7	8.4; 30.9	2.9	0.83; 5.3	1.8	0.81; 4.21	53.8	3	1,2E-11	**< 0.001**
SDF-1 alpha, pg/ml	1041	882; 1189	904	838; 1000	977	801; 1210	1051	870; 1267	5.54	3	0.14	0.25
IL-27, pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	1.63	3	0.65	0.76
IP-10, pg/ml	9.63	7; 12	11	9; 14	12	9; 19	16	11; 27	26.71	3	0.0000068	**< 0.001**
IL-8, pg/ml	4.13	2.56; 9.46	7.09	5.13; 12.44	2.86	1.88; 4.81	2.98	2.31; 3.83	29.65	3	0.0000016	**< 0.001**
IL-10, pg/ml	0.12	0; 0.49	0	0; 0	0	0; 0.26	0.12	0; 0.44	19.85	3	0.00018	**< 0.001**
Eotaxin, pg/ml	50	39; 71	51	42; 62	48	36; 64	44	38; 55	3.69	3	0.3	0.41
IL-17 A, pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	6.62	3	0.08	0.15
RANTES, pg/ml	5.37	3.49; 6.40	6.12	5.10; 7.79	7.30	5.56; 8.63	8.90	6.66; 10.11	34.98	3	0.00000012	**< 0.001**
MIP-1 beta, pg/ml	168	129; 201	172	142; 215	143	120; 168	133	116; 152	18.39	3	0.00037	**< 0.001**
MCP-1, pg/ml	19	10; 42	30	18; 49	38	20; 63	43	34; 60	23.13	3	0.000038	**< 0.001**
IL-9, pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	5.45	3	0.14	0.24
GRO alpha, pg/ml	3.16	2.16; 4.42	3.44	2.82; 4.90	5.28; 6.52	2.657	2.97	2.38; 4.79	10.08	3	0.018	**0.04**
IL-23, pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	0.88	3	0.83	0.91
IL-21, pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	1.78	3	0.62	0.75

Table 4 (continued)

Serum parameters	Control ($n = 51$)		Control + T ($n = 29$)		Sch ($n = 50$)		Sch + T ($n = 30$)		X^2	df	p	FDR
	Median	Q1; Q3	Median	Q1; Q3	Median	Q1; Q3	Median	Q1; Q3				
IL-22, pg/ml	0	0; 0	0	0; 0	0	0; 0	0	0; 0	0.04	3	0.99	0.99

*The analysis was performed using Kruskal–Wallis test. Significant p-values (< 0.05) are highlighted in bold

Comp 1 in Control + T group is represented by other variables—IL-8, MIP-1 alpha, MIP-1 beta, KLK6. Therefore, the Control + T group differs from other groups.

Correlation of antibody concentration with neurobiologic and immune blood parameters and psychometrics

Correlations of *Toxoplasma gondii* infection antibodies with significant blood parameters were compared in Control + T and Sch + T groups, and with psychometric scales in Sch + T group, the results are presented in Figure A2. No significant correlations ($p < 0.01$) were found in the Control + T group for these measures, but the Sch + T group showed a single significant but not strong positive correlation of RANTES concentration with IgA ($r = 0.58$ $p < 0.001$) and IgM ($r = 0.61$ $p < 0.001$) antibodies.

Correlation of concentrations of immune and neurobiologic blood parameters with psychometric characteristics in patients with schizophrenia

Correlation analysis was performed to determine associations between psychometric scale scores and significant blood parameters in the Sch and Sch + T groups, and the results are presented in Figure A3. The Sch group had no significant correlations. However, a sufficient number of weak but significant correlations were found in the Sch + T group: PANSS General had a positive correlation with KLK6 concentration ($r = 0.51$; $p = 0.004$); MARDS was also positively correlated with KLK6 concentration ($r = 0.48$; $p = 0.007$); PSP had a negative correlation with IP-10 ($r = -0.56$; $p = 0.002$) and GRO alpha ($r = -0.52$; $p = 0.003$). Therefore, the neurobiological index KLK6 was positively correlated with the severity of general symptoms of schizophrenia and with the severity of depressive symptoms in patients with schizophrenia and *Toxoplasma gondii*. Immunologic indices IP-10 and GRO alpha were positively correlated with the severity of impairments in social and personal functioning.

Correlation of concentrations of immune and neurobiological blood parameters with each other

Correlation analysis was performed to determine the associations between significant blood parameters in each experimental group, and the results are presented in Figure A4 and Table S1. It was shown that all groups were characterized by predominantly positive significant relationships between the concentrations of blood parameters (Supplementary material, Table S1).

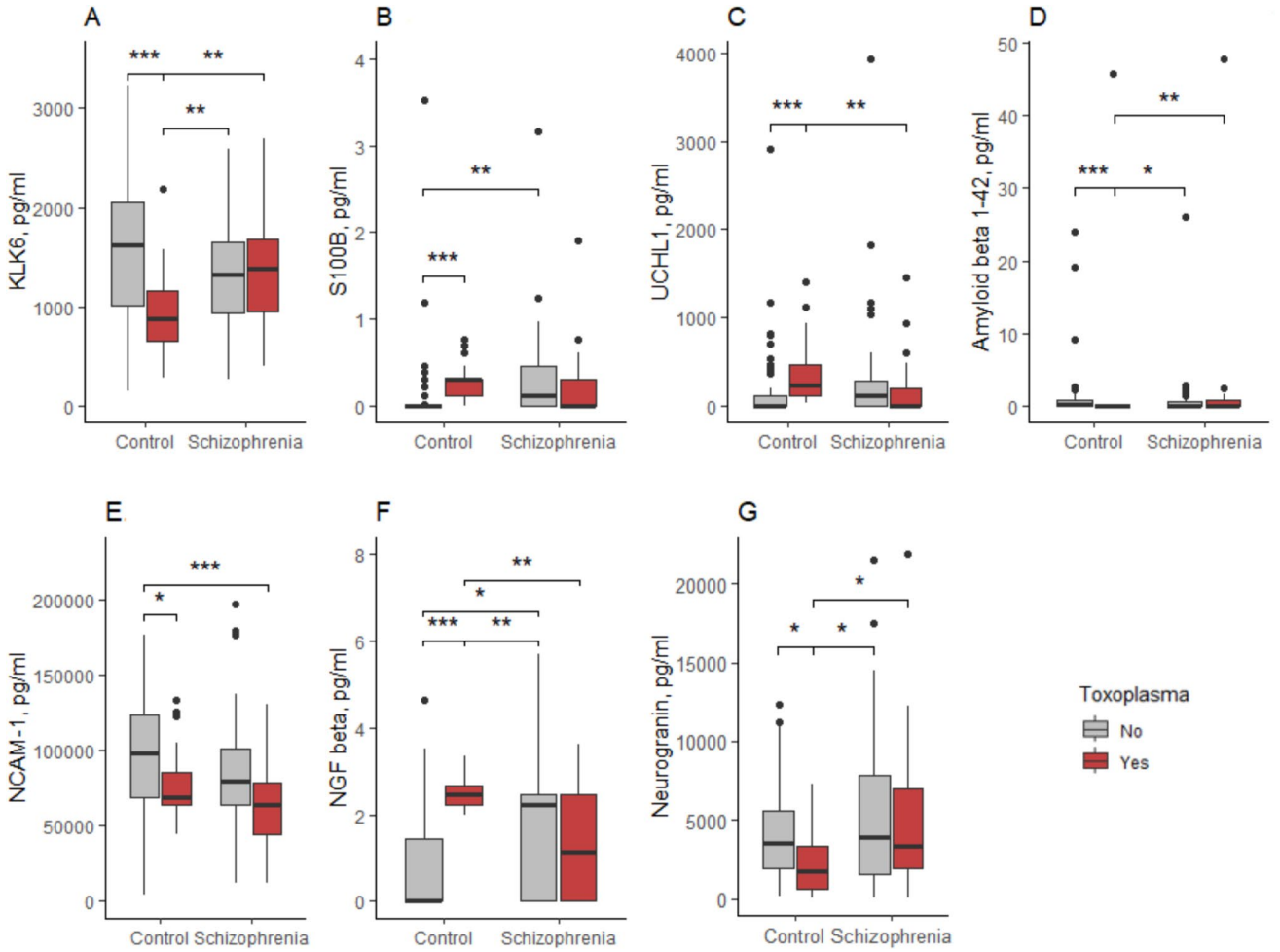

Fig. 1 Concentration of neurobiologic parameters in blood of patients with schizophrenia taking into account infection status. **A** Blood KLK6 concentration. **B** Blood S100B concentration. **C** Blood UCHL1 concentration. **D** Blood Amyloid beta 1–42 concentration. **E** Blood NCAM-1 concentration. **F** Blood NGF beta concentration. **G** Blood neurogranin concentration. Data are expressed as Med (Q1; Q3) in boxplots. Black horizontal lines—medians; Black points—outliers; Red boxes—data on a person with *Toxoplasma gondii* infection; Grey boxes—data on a person without *Toxoplasma gondii* infection; *- <0.05, **- <0.01, ***- <0.001; No—absence of *Toxoplasma gondii* infection; Yes—presence of *Toxoplasma gondii* infection; Control—mentally healthy volunteers; Schizophrenia—patients with schizophrenia

The Control and Control + T groups showed two similar clusters of associated immune blood parameters (cluster 1: MIP-1 alpha, MIP-1 beta and IL-8; cluster 2: RANTES, IP-10, MCP-1). However, another cluster of predominantly neurobiological parameters (IL-10, S100B, UCHL, Amyloid beta 1–42, NGF beta) was observed in the Control group, which was weakly expressed in Control + T. It is noteworthy that the Sch group was similar to Control, as a cluster of associated parameters (IL-10, S100B, UCHL, NGF beta, IL-8) similar to Control could be identified, and a group-specific cluster (neurogranin, KLK6, NCAM-1) could be identified. In the Sch + T group, it was possible to identify a cluster that was observed in Control and Sch (IL-10, S100B, UCHL, NGF beta, IL-8, Amyloid beta 1–42) and another cluster specific to this group (MIP-1 alpha, MIP-1 beta, NCAM-1, neurogranin). Therefore, the Control, Sch, and Sch + T groups appeared similar to each other with a large cluster of associated blood parameters (IL-10, S100B, UCHL, NGF beta, IL-8, Amyloid beta 1–42); in the Control + T group, this cluster was weakly expressed. However, the control and schizophrenia patient groups were similar to each other by small clusters. Overall, the correlation analysis confirms that the control groups differed more in blood parameters than the schizophrenia groups.

Effect of reactivation of Toxoplasma gondii infection on schizophrenia symptoms and blood biomarker concentrations

In addition, the effect of *Toxoplasma gondii* reactivation has been studied on patients with schizophrenia and

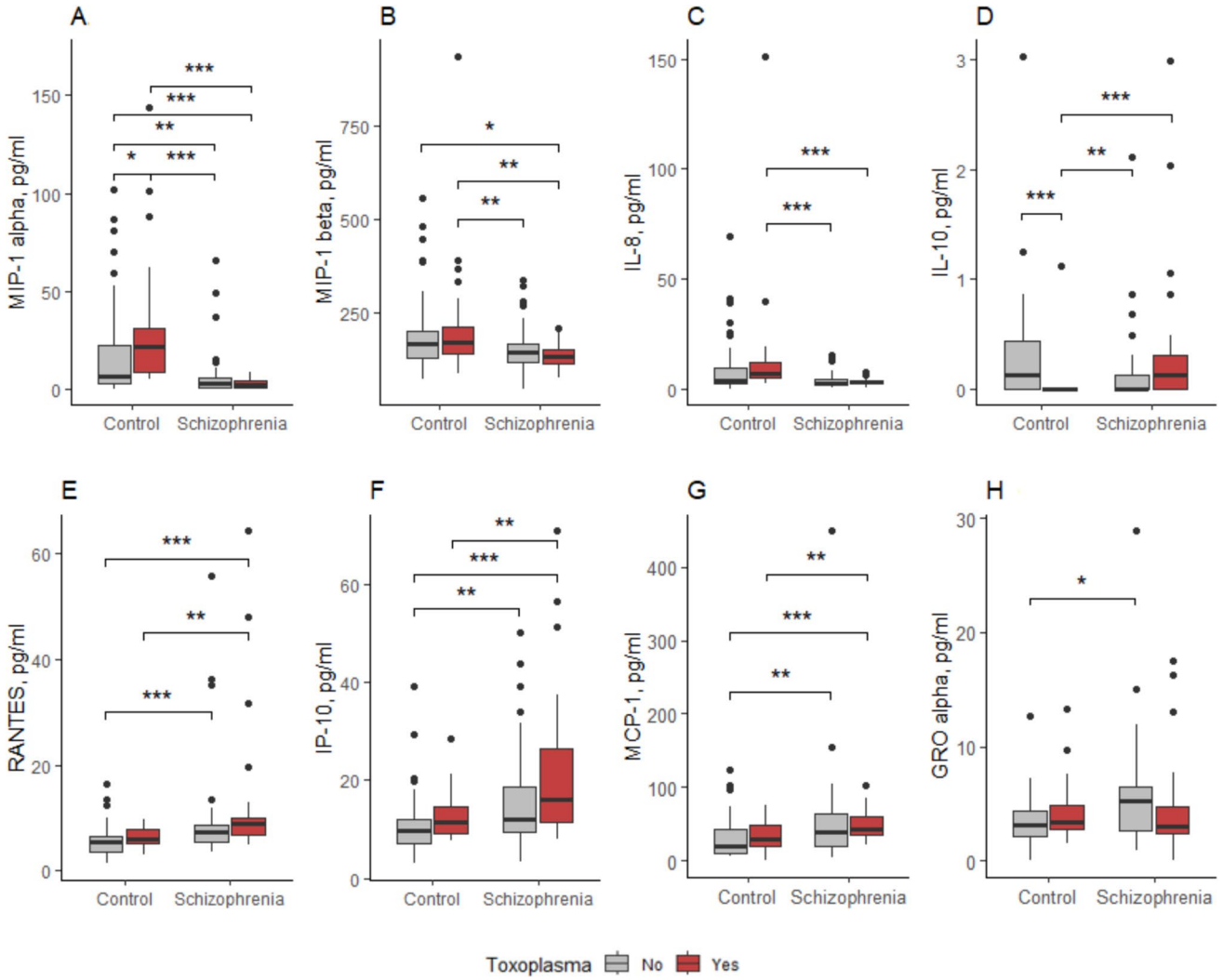

Fig. 2 Concentration of immunologic indices in blood in patients with schizophrenia taking into account infection status. **A** Blood MIP-1 alpha concentration. **B** Blood MIP-1 beta concentration. **C** Blood IL-8 concentration. **D** Blood IL-10 concentration. **E** Blood RANTES concentration. **F** Blood IP-10 beta concentration. **G** Blood MCP-1 concentration. **H** Blood GRO alpha concentration Data are expressed as Med (Q1; Q3) in boxplots. Black horizontal lines—medians; Black points—outliers; Red boxes—data on a person with *Toxoplasma gondii* infection; Grey boxes—data on a person without *Toxoplasma gondii* infection; *- <0.05, **- <0.01, ***- <0.001; No—absence of *Toxoplasma gondii* infection; Yes—presence of *Toxoplasma gondii* infection; Control—mentally healthy volunteers; Schizophrenia—patients with schizophrenia

mentally healthy individuals. For this purpose, the course of the disease was determined for each infected subject (reactivation or latent) and compared clinical and biochemical parameters between the different forms. Detailed results are presented in Supplementary material (Table S2, Table S3). The Control + T group had increased concentrations of the neurotrophins CNTF ($\chi^2 = 4.69$; $p = 0.03$) and NGF beta ($\chi^2 = 4.89$; $p = 0.03$) in blood during *Toxoplasma gondii* reactivation compared to latent controls. The Sch + T group had a statistically significant decrease in blood FGF-21 concentration ($\chi^2 = 6.17$; $p = 0.01$) in patients with reactivation compared to the latent form; it was noted that that the latent group had an increase in FGF-21 levels in 5 out of 15 individuals, but no increase in this biomarker was observed in reactivation group.

The Sch + T group had significant differences on two psychometric scales between reactivation and latent form. A decrease in the PANSS Negative and SNS scores was observed in during reactivation, indicating a decrease in negative symptoms in schizophrenic patients during *Toxoplasma gondii* reactivation. A reduction in symptoms on the PANSS scale was observed, specifically in the symptoms of emotional withdrawal, difficulty in abstract thinking and lack of spontaneity and flow of conversation.

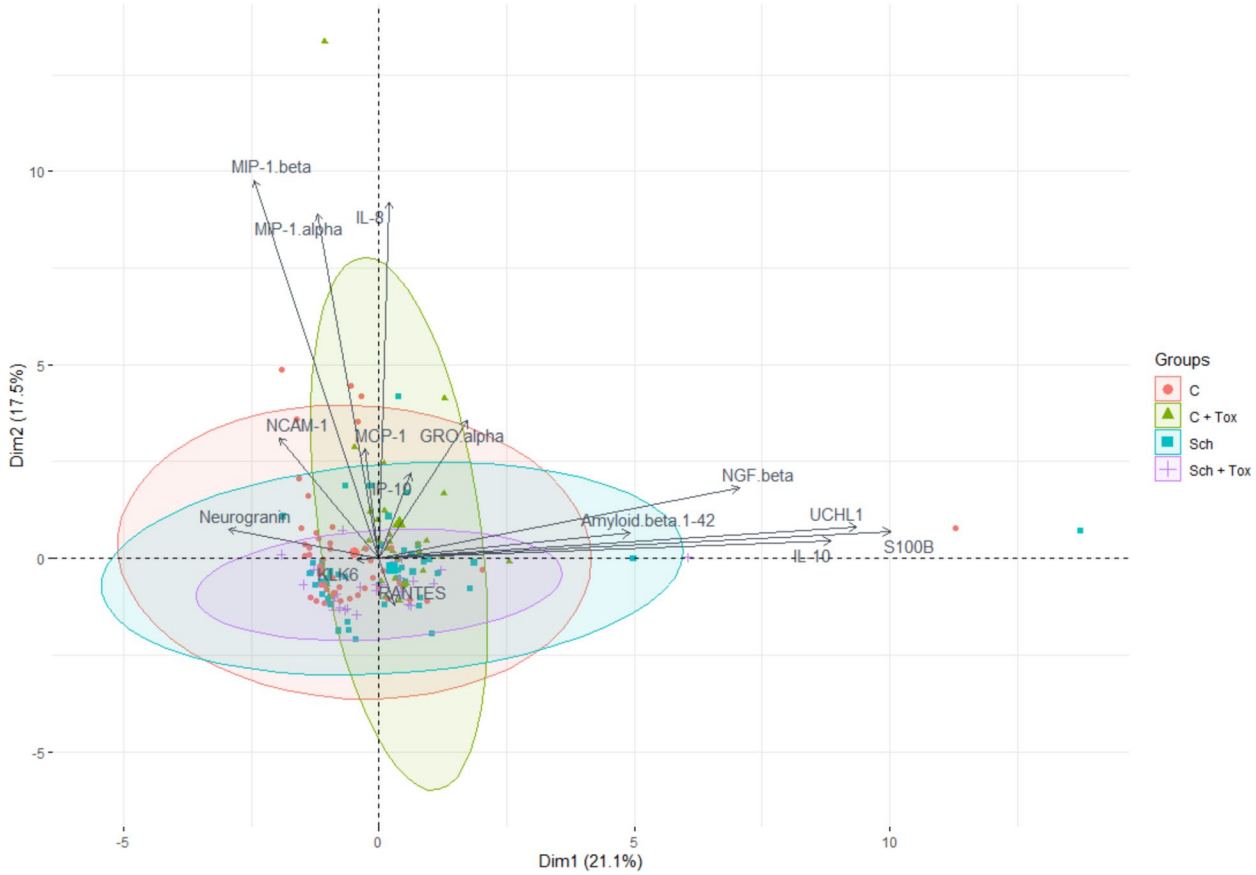

Fig. 3 PCA score plot of all signify biochemical blood parameters stratified according to groups; Dim1, component 1; Dim2, component 2; C ($n = 51$), mentally healthy volunteers without *Toxoplasma gondii* infection; C + Tox ($n = 29$), mentally healthy volunteers with *Toxoplasma gondii* infection; Sch ($n = 50$), schizophrenia patients without *Toxoplasma gondii* infection; Sch + Tox ($n = 30$), schizophrenia patients with *Toxoplasma gondii* infection

Discussion

Many studies have previously shown that seroprevalence and antibody levels to *Toxoplasma gondii* were higher in patients with schizophrenia than in healthy subjects. However, no such effect was found in our study. It is known that the prevalence of *Toxoplasma gondii* infection can be different in different regions; this applies also to different regions of Russia (Torrey et al. 2007; Stepanova et al. 2019). Therefore, our results were compared with a limited number of studies conducted in the same region of Russia (Moscow city), and there was some rather contradictory data. The prevalence of *Toxoplasma gondii* infection was at the level of 25% in the general population of Moscow city residents (Stepanova et al. 2017, 2019), which roughly coincides with our data. However, in patients with schizophrenia, specific IgG antibodies to *Toxoplasma gondii* were detected in 40% of patients in one study (Stepanova et al. 2019), or in 16% of patients in another study (Romanov et al. 2020). It should be discussed that the power of our study was evaluated and was shown to be sufficient to assess the lack of association between schizophrenia and toxoplasmosis in our population. If we consider the available meta-analyses that show such an association, such as the study by Contopoulos-Ioannidis et al. (2022), they indicate a great heterogeneity of studies. The publications may have a bias because only positive results are published and results with missing linkage are not published. That is why meta-analysis has these results. Therefore, it is very important to publish negative results, which our study also demonstrated.

It was found that PDQ-20 scores increased in patients with schizophrenia in the presence of seropositivity to *Toxoplasma gondii*. Therefore, *Toxoplasma gondii* infection may lead to greater cognitive decline in patients with schizophrenia. Similar results were presented by Dickerson et al. (2014), who found that *Toxoplasma gondii* infection can increase the risk of cognitive decline in individuals without psychiatric disorders and in individuals with bipolar disorder

(Dickerson et al. 2014), making infected psychiatric patients more vulnerable and requiring increased attention.

Our study showed certain differences in the content of some serum parameters in patients with schizophrenia and *Toxoplasma gondii* infection, as well as certain patterns in the associations of blood parameters with psychometrics. At present, there are not many studies showing changes in blood parameters in schizophrenia and *Toxoplasma gondii* infection. Such studies have mainly focused on the determination of blood cholesterol, triglycerides and lipoproteins (Flegr et al. 2014; Sagud et al. 2018; Xu et al. 2020), glucocorticoids (Beaumont et al. 2024), kynurenine (Okusaga et al. 2016), dopamine (Ibrahim Ali et al. 2020; Ammar et al. 2024), and metabolomic parameters (Osman et al. 2022). Therefore, it has been previously revealed that *Toxoplasma gondii* infection in patients with schizophrenia may lead to changes in the concentration of some blood biomarkers. Our study focused on another class of blood biomarkers that have been previously poorly studied in *Toxoplasma gondii* infection and schizophrenia—immune and neurobiological biomarkers.

Our study demonstrated that *Toxoplasma gondii* infection resulted in significant changes in the concentration of some neurobiological blood parameters (KLK6, S100B, UCHL1, Amyloid beta 1–42, NCAM-1, NGF beta, neurogranin) and immune parameters (MIP-1 alpha and IL-10) in mentally healthy individuals. The *Toxoplasma gondii*–infected control group differed in blood parameters from all other groups. In contrast, *Toxoplasma gondii* infection did not lead to changes in the concentration of blood parameters in schizophrenia patients, as shown by statistical criteria, PCA analysis and correlation analysis. Schizophrenia itself is associated with significant biochemical changes in the body and in the blood. For example, patients with schizophrenia can have altered concentrations of inflammatory markers, BDNF, monoamines, oxidative stress markers, and low molecular weight metabolites (Lai et al. 2016). And therefore we hypothesized that the effect of *Toxoplasma gondii* infection may not be apparent in the general biochemical abnormalities due to such changes in schizophrenia. However, one interesting pattern was observed. The control and schizophrenia groups without *Toxoplasma gondii* infection differed from each other only in two neurobiological parameters (NGF beta and S100B), the concentration of which increased in schizophrenia. However, more pronounced differences were found between the control group and the schizophrenia group with *Toxoplasma gondii* infection in the following parameters: KLK6, UCHL1, Amyloid beta 1–42, NGF beta, neurogranin. Most of these blood parameters do not coincide with the groups without infection (except NGF beta), so we hypothesized that it is possible to use these parameters as indicators of the development of schizophrenic psychopathology in *Toxoplasma gondii* infection. Furthermore, the control and schizophrenia groups differed significantly from each other in various immune parameters. Control and schizophrenia without *Toxoplasma gondii* differed in MIP-1 alpha, RANTES, MCP-1, GRO alpha, IP-10; and Control and schizophrenia with *Toxoplasma gondii*—MIP-1 alpha, IP-10, IL-8, IL-10, RANTES, MIP-1 beta, MCP-1. Therefore, here, we can observe rather general differences in immunologic parameters between healthy individuals and patients with schizophrenia regardless of *Toxoplasma gondii* infection. However, IL-8, IL-10, and MIP-1 beta, which were not observed in the groups without infection, can be identified during infection, which could also potentially indicate the development of psychopathology in *Toxoplasma gondii*.

The first group has demonstrated potential relevance as biomarkers for the development of schizophrenic psychopathology during *Toxoplasma gondii* infection. It includes several neurobiological indicators that may represent alterations in nervous system function. Among them is KLK6, a hormone-like messenger that signals cells to changes in the extracellular proteolytic environment (Yoon et al. 2022). Interestingly, KLK6 in patients with schizophrenia and *Toxoplasma gondii* infection was positively correlated with the severity of general symptoms of schizophrenia and with the severity of depressive symptoms, and its serum concentration was elevated in this group compared with *Toxoplasma gondii* seropositive controls. This suggests that this marker may be associated with the development of schizophrenia symptoms. UCHL1 is a multifunctional protein expressed in neurons. It plays an important role in the regulation of the level of free ubiquitin in cells and redox state (Mi and Graham 2023). A decrease in serum UCHL1 has previously been shown in patients with schizophrenia (Demirel et al. 2017). However, in our experiment, such a decrease was only shown in seropositive groups but not in *Toxoplasma gondii* infection healthy controls and patients. This indicates the importance of the *Toxoplasma gondii* infection factor in measuring UCHL1 in patients with schizophrenia. Amyloid beta 1–42 plays an important role in many cellular functions including synaptic activity, neuronal survival, ion channel formation, and neurotoxicity. Its aggregation contributes to neurodegenerative pathologies (Butterfield and Boyd-Kimball 2004). The *Toxoplasma gondii* infection has been proposed as a risk factor in the pathophysiology of Alzheimer's disease (Ortiz-Guerrero et al. 2020), so changes in blood amyloid levels during infection may be a pattern. Neurogranin is a small protein normally expressed in granule-like structures of pyramidal cells in the hippocampus and cortex. It is involved in synaptic plasticity, synaptic regeneration, and long-term potentiation (Xiang et al. 2020). As an important synaptic component, neurogranin is a potential and promising biomarker to improve the diagnosis, prognosis,

and severity assessment of neurological and psychiatric diseases, including schizophrenia (Xiang et al. 2020).

As mentioned above, three immune biomarkers have been identified among blood parameters that may indicate the development of psychopathology in *Toxoplasma gondii*. Among them, anti-inflammatory cytokine IL-10 is involved in maintaining tissue homeostasis during infection (Ouyang and O'Garra 2019), as well as chemokines IL-8 and MIP-1 (Lesińska et al. 2014; Vilotić et al. 2022). In addition, a positive correlation was found between RANTES chemokine concentration and IgA and IgM antibodies in the group of schizophrenia patients seropositive for *Toxoplasma gondii*. This phenomenon was not observed in the control group with *Toxoplasma gondii*. Furthermore, the chemokines IP-10 and GRO alpha were positively correlated with the severity of impairments in social and personal functioning in patients with schizophrenia and *Toxoplasma gondii*. Uninfected patients with schizophrenia had no correlations of blood parameters and scales. Therefore, in our study, blood concentrations of several chemokines may be associated with schizophrenia in *Toxoplasma gondii* infection. In general, cytokines and chemokines are signaling proteins that comprehensively regulate the proliferation and activation of immune cells. Dysregulation of these proteins is associated with neuroinflammation and with many diseases, including schizophrenia (Ermakov et al. 2023).

It is important to discuss here the neuroinflammatory mechanisms of action of *Toxoplasma gondii* infection. Animal studies have demonstrated that *Toxoplasma gondii* infection can be a cause of inflammation in the CNS. Chronic infection with *Toxoplasma gondii* causes mice to have decreased anxiety, increased exploratory behavior, and loss of fear of predators, also persistent inflammation (Boillat et al. 2020). Chronic infection also impairs cognitive function in mice in behavioral tests and reduces the expression of genes associated with synaptic plasticity, signal transduction, and cognitive behavior. Meanwhile, infection significantly increases the expression of genes associated with pro-inflammatory responses (He et al. 2022). Therefore, the potential impact of *Toxoplasma gondii* infection on neuronal function in humans and the increased risk of psychiatric and neurodegenerative diseases should be considered, but caution should be exercised when comparing the behavioral effects of toxo *Toxoplasma gondii* infection plasma between humans and animals (Boillat et al. 2020). Although our experiment showed no differences in blood parameters between groups of patients with schizophrenia, it is possible to evaluate inflammatory processes in control groups, the differences between which are significant. Here, infection led to an increase in the concentration of the inflammatory cytokine MIP-1 alpha and a decrease in the concentration of the anti-inflammatory cytokine IL-10. This indicates the possible presence of an inflammatory process in the *Toxoplasma gondii*–infected control group. It is conceivable that *Toxoplasma gondii* infection may also lead to inflammation in patients with schizophrenia, but inflammatory processes in schizophrenia do not occur solely due to infection, so it is difficult to assess exactly its contribution. It is important to note that reactivation of *Toxoplasma gondii* in the study participants did not lead to changes in inflammatory markers in the blood, and therefore probably did not affect inflammation.

Related to the topic of Toxoplasma gondii reactivation, it is necessary to discuss another interesting trend that our study showed, namely the reduction of negative symptoms in patients with schizophrenia and reactivation. Regarding depression, meta-analyses have demonstrated that *Toxoplasma gondii* infection is not associated with depression (Sutterland et al. 2015; Nayeri Chegeni et al. 2019). Therefore, our results suggest a slightly different mechanism of the infection's effect on depressive symptoms, which remains to be investigated. In addition, patients with schizophrenia did not have increased levels of the hormonal metabolic regulator FGF-21 when reactivated compared to the latent form. However, such an increase should be observed in schizophrenia and depression according to other studies (Qing et al. 2015; Mason et al. 2022). The control group with reactivation had increased concentrations of the neurotrophins CNTF and NGF beta. This is generally associated with the absence of depressive symptoms in human and animal studies (Garcia et al. 2012; Martino et al. 2013; Zhou et al. 2024). The data obtained in our study thus indicate an improvement of depressive symptoms in patients with schizophrenia and biochemical changes in the blood that may be associated with this improvement. Indeed, this is a very interesting phenomenon that requires a careful study of its mechanisms. Currently, the role of *Toxoplasma gondii* reactivation in the progression of psychiatric disorders is poorly understood. Therefore, further studies are needed to clarify the role of *Toxoplasma gondii* in the clinical characteristics of depressive symptoms in schizophrenia.

It is important to note that this study has limitations. Many additional factors beyond diagnosis and infection, such as the influence of antipsychotic medications in patients with schizophrenia, the presence of other diseases, the influence of dietary patterns, alcohol and substance use, smoking, the presence of pets, and other factors that were not considered in this study, may influence blood biomarker concentrations. In addition, some differences were found in the social status of the study participants, namely in their level of education and marital status. These differences could potentially be factors that influenced the results of the study. Finally, our study did not take into account many possible comorbid infectious diseases that could affect the immune and mental status of the patient. Participants were excluded from the study if they had medical conditions such as HIV

and hepatitis, but did not take into account, for example, diseases such as Herpes virus and cytomegalovirus.

Conclusions

In conclusion, *Toxoplasma gondii* infection leads to changes in some blood parameters. Mostly significant changes are observed in mentally healthy individuals; however, when comparing healthy individuals infected with *Toxoplasma gondii* and individuals with schizophrenia, it was possible to identify a group of biomarkers whose changes are not observed between the uninfected groups (neurobiological indicators KLK6, UCHL1, Amyloid beta 1–42 and neurogranin; anti-inflammatory cytokine IL-10; chemokines IL-8 and MIP-1 beta). The hypothesis has been proposed that it is possible to use these indices as indicators of the development of schizophrenic psychopathology in *Toxoplasma gondii* infection. Also, associations of blood parameters were found with the content of IgA and IgM antibodies (chemokine RANTES), with symptoms of schizophrenia (hormone-like messenger KLK6; chemokines IP-10 and GRO alpha). It should also be noted that our study did not demonstrate a significant association between schizophrenia and infection status with seroprevalence ($p = 0.54$; OR = 1.18; 95% CI = 0.69–2.01), but infected patients with schizophrenia showed more severe cognitive impairment (PDQ-20 scale). Therefore, *Toxoplasma gondii* infection may lead to more severe cognitive decline in patients with schizophrenia. In addition, our study included an evaluation of the effect of *Toxoplasma gondii* reactivation on schizophrenia symptoms and blood biomarkers. It was found that patients with schizophrenia and *Toxoplasma gondii* reactivation had reduced negative symptoms and appropriate blood biochemical changes. Our work is the first to investigate not only the prevalence of toxoplasma among different patient groups, but also correlations with serum biomarkers and with clinical data, which represents a certain diagnostic value of the data presented in it. This opens prospects for the identification of neurobiological mechanisms of the influence of *Toxoplasma gondii* infection on the development of psychiatric diseases.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00436-025-08498-w.

Author contribution All authors contributed to the study conception and design. All authors read and approved the final manuscript. Conceptualization: Morozova Anna, Zorkina Yana, Abramova Olga; Methodology: Zorkina Yana, Goncharov Dmitry; Formal analysis and investigation: Abramova Olga, Zorkina Yana, Abbazova Evgenia, Baranets Marina, Berdalin Alexander, Zakurazhnaya Valeria, Morozova Irina, Ochneva Alexandra, Pavlov Konstantin, Ushakova Valeriya; Writing—original draft preparation: Abramova Olga, Zorkina Yana; Writing—review and editing: Abramova Olga, Zorkina Yana, Goncharov Dmitry, Ushakova Valeriya; Funding acquisition: Kostyuk Georgy; Resources: Kostyuk Georgy, Andreyuk Denis, Morozova Anna; Supervision: Kostyuk Georgy, Morozova Anna.

Funding The article processing was supported by ANO 'Moscow Center for Innovative Healthcare Technologies'.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This study was conducted according to the guidelines of the Declaration of Helsinki. The procedures involving experiments on human subjects were performed in accordance with the ethical standards (Protocol No. 2/28.10.2020 of the Local Ethic Committee of Mental Health Clinic No. 1,named after N.A. Alexeev of the Department of Health of Moscow).

Consent to participate Informed consent was obtained from all participants.

Competing interests The authors declare no competing interests.

References

Abdel-Latif M, Shaapan M, Salah H, Abu-Sarea EY (2020) Toxoplasmosis in schizophrenic patients: immune-diagnosis and serum dopamine level. Pak J Biol Sci: PJBS 23(9):1131–1137. https://doi.org/10.3923/pjbs.2020.1131.1137

Ammar AM, Nabi SA, El-Ghani HMA (2024) Correlation between toxoplasmosis and schizophrenia in Egyptian patients and its impact on dopamine serum levels. Acta Trop. 256:107263. https://doi.org/10.1016/j.actatropica.2024.107263

Beaumont E, Brodeur J, Thomas F, Dujon AM, Lupien SJ, Consortium Signature (2024) Toxoplasma gondii infection in people with schizophrenia is related to higher hair glucocorticoid levels. Front Psychiatry. 15:1286135. https://doi.org/10.3389/fpsyt.2024.1286135

Bedrossian N, Haidar M, Fares J, Kobeissy FH, Fares Y (2016) Inflammation and elevation of interleukin-12p40 in patients with schizophrenia. Front Mol Neurosci. 9:16. https://doi.org/10.3389/fnmol.2016.00016. (**Published 2016 Mar 22**)

Bhadra R, Cobb DA, Weiss LM, Khan IA (2013) Psychiatric disorders in toxoplasma seropositive patients–the CD8 connection. Schizophr Bull 39(3):485–489. https://doi.org/10.1093/schbul/sbt006

Boillat M, Hammoudi PM, Dogga SK, Pages S, Goubran M, Rodriguez I, Soldati-Favre D (2020) Neuroinflammation-associated aspecific manipulation of mouse predator fear by *Toxoplasma gondii*. Cell reports 30(2):320-334.e6. https://doi.org/10.1016/j.celrep.2019.12.019

Bollani L, Auriti C, Achille C, Garofoli F, De Rose DU, Meroni V, Salvatori G, Tzialla C (2022) Congenital toxoplasmosis: the state of the art. Front Pediatr. 10:894573. https://doi.org/10.3389/fped.2022.894573

Bonnín CM, Sánchez-Moreno J, Lima F et al (2024) Factors associated with the discrepancy between objective and subjective cognitive impairment in bipolar disorder. J Affect Disord 349:210–216. https://doi.org/10.1016/j.jad.2024.01.012

Butterfield DA, Boyd-Kimball D (2004) Amyloid beta-peptide(1–42) contributes to the oxidative stress and neurodegeneration found in Alzheimer disease brain. Brain Pathol. 14(4):426–32. https://doi.org/10.1111/j.1750-3639.2004.tb00087.x

Campeau A, Mills RH, Stevens T et al (2022) Multi-omics of human plasma reveals molecular features of dysregulated inflammation and accelerated aging in schizophrenia. Mol Psychiatry 27(2):1217–1225. https://doi.org/10.1038/s41380-021-01339-z

Cerutti A, Blanchard N, Besteiro S (2020) The bradyzoite: a key developmental stage for the persistence and pathogenesis of toxoplasmosis. Pathogens. 9(3):234. https://doi.org/10.3390/pathogens9030234

Chaudhury A, Ramana BV (2019) Schizophrenia and bipolar disorders: the toxoplasma connection. Trop Parasitol. 9(2):71–76. https://doi.org/10.4103/tp.TP_28_19

Contopoulos-Ioannidis DG, Gianniki M, Ai-Nhi Truong A, Montoya JG (2022) Toxoplasmosis and schizophrenia: a systematic review and meta-analysis of prevalence and associations and future directions. Psychiatr Res Clin Pract. 4(2):48–60. https://doi.org/10.1176/appi.prcp.20210041. (**Published 2022 Apr 22**)

Demirel ÖF, Cetin İ, Turan Ş, Sağlam T, Yıldız N, Duran A (2017) Decreased expression of α-Synuclein, Nogo-A and UCH-L1 in patients with schizophrenia: a preliminary serum study. Psychiatry Investig 14(3):344–349. https://doi.org/10.4306/pi.2017.14.3.344

Dickerson F, Stallings C, Origoni A, Katsafanas E, Schweinfurth L, Savage C, Khushalani S, Yolken R (2014) Antibodies to *Toxoplasma gondii* and cognitive functioning in schizophrenia, bipolar disorder, and nonpsychiatric controls. J Nerv Ment Dis. 202(8):589–93. https://doi.org/10.1097/NMD.0000000000000166

Ermakov EA, Mednova IA, Boiko AS, Buneva VN, Ivanova SA (2023) Chemokine dysregulation and neuroinflammation in schizophrenia: a systematic review. Int J Mol Sci. 24(3):2215. https://doi.org/10.3390/ijms24032215

Flegr J, Príplatova L, Hampl R, Bicikoviá M, Ripova D, Mohr P (2014) Difference of neuro- and immunomodulatory steroids and selected hormone and lipid concentrations between toxoplasma-free and toxoplasma-infected but not CMV-free and CMV-infected schizophrenia patients. Neuro Endocrinol Lett 35(1):20–27

Garcia N, Santafé MM, Tomàs M, Priego M, Obis T, Lanuza MA, Besalduch N, Tomàs J (2012) Exogenous ciliary neurotrophic factor (CNTF) reduces synaptic depression during repetitive stimulation. J Peripher Nerv Syst. 17(3):312–23. https://doi.org/10.1111/j.1529-8027.2012.00419.x

Gubareva EV, Goncharov DB, Domonova ÉA et al (2013) Use of immunological and molecular biological methods to diagnose cerebral toxoplasmosis in HIV infection. – Med. Parazitol. (Mosk.). No. 1. S. 7–12. – in Russian

Halonen SK, Weiss LM (2013) Toxoplasmosis. Handb Clin Neurol 114:125–145. https://doi.org/10.1016/B978-0-444-53490-3.00008-X

He Y, Xu D, Yan Z, Wu Y, Zhang Y, Tian X, Zhu J, Liu Z, Cheng W, Zheng K, Yang X, Yu Y, Pan W (2022) A metabolite attenuates neuroinflammation, synaptic loss and cognitive deficits induced by chronic infection of *Toxoplasma gondii*. Front Immunol. 13:1043572. https://doi.org/10.3389/fimmu.2022.1043572

Hudgens S, Floden L, Blackowicz M et al (2021) Meaningful change in depression symptoms assessed with the Patient Health Questionnaire (PHQ-9) and Montgomery-Åsberg Depression Rating Scale (MADRS) among patients with treatment resistant depression in two, randomized, double-blind, active-controlled trials of esketamine nasal spray combined with a new oral antidepressant. J Affect Disord 281:767–775. https://doi.org/10.1016/j.jad.2020.11.066

Jelastopulu E, Giourou E, Merekoulias G, Mestousi A, Moratis E, Alexopoulos EC (2014) Correlation between the Personal and Social Performance scale (PSP) and the Positive and Negative Syndrome Scale (PANSS) in a Greek sample of patients with schizophrenia. BMC Psychiatry. 14:197. https://doi.org/10.1186/1471-244X-14-197. (**Published 2014 Jul 8**)

Kodym P, Malý M, Beran O, Jilich D, Rozsypal H, Machala L, Holub M (2015) Incidence, immunological and clinical characteristics of reactivation of latent Toxoplasma gondii infection in HIV-infected patients. Epidemiol Infect 143(3):600–607. https://doi.org/10.1017/S0950268814001253

Kroenke K, Spitzer RL, Williams JB (2001) The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16(9):606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Lai CY, Scarr E, Udawela M, Everall I, Chen WJ, Dean B (2016) Biomarkers in schizophrenia: a focus on blood based diagnostics and theranostics. World J Psychiatry. 6(1):102–117. https://doi.org/10.5498/wjp.v6.i1.102. (**Published 2016 Mar 22**)

Lee EE, Hong S, Martin AS, Eyler LT, Jeste DV (2017) Inflammation in schizophrenia: cytokine levels and their relationships to demographic and clinical variables. Am J Geriatr Psychiatry 25(1):50–61. https://doi.org/10.1016/j.jagp.2016.09.009

Lesińska M, Hartleb M, Gutkowski K, Nowakowska-Duława E (2014) Procalcitonin and macrophage inflammatory protein-1 beta (MIP-1β) in serum and peritoneal fluid of patients with decompensated cirrhosis and spontaneous bacterial peritonitis. Adv Med Sci. 59(1):52–6. https://doi.org/10.1016/j.advms.2013.07.006

Lindenmayer JP (2017) Are shorter versions of the positive and negative syndrome scale (PANSS) doable? A critical review. Innov Clin Neurosci 14(11–12):73–76

Mahmoud ME, Ihara F, Fereig RM, Nishimura M, Nishikawa Y (2016) Induction of depression-related behaviors by reactivation of chronic *Toxoplasma gondii* infection in mice. Behav Brain Res 298(Pt B):125–33. https://doi.org/10.1016/j.bbr.2015.11.005

Martino M, Rocchi G, Escelsior A, Contini P, Colicchio S, de Berardis D, Amore M, Fornaro P, Fornaro M (2013) NGF serum levels variations in major depressed patients receiving duloxetine. Psychoneuroendocrinology. 38(9):1824–8. https://doi.org/10.1016/j.psyneuen.2013.02.009

Mason BL, Minhajuddin A, Czysz AH, Jha MK, Gadad BS, Mayes TL, Trivedi MH (2022) Fibroblast growth factor 21 (FGF21) is increased in MDD and interacts with body mass index (BMI) to affect depression trajectory. Transl Psychiatry. 12(1):16. https://doi.org/10.1038/s41398-021-01679-y

McConkey GA, Martin HL, Bristow GC, Webster JP (2013) *Toxoplasma gondii* infection and behaviour–location, location, location? J Exp Biol 216(1):113–119. https://doi.org/10.1242/jeb.074153

Mi Z, Graham SH (2023) Role of UCHL1 in the pathogenesis of neurodegenerative diseases and brain injury. Ageing Res Rev. 86:101856. https://doi.org/10.1016/j.arr.2023.101856

Moreno-Küstner B, Martín C, Pastor L (2018) Prevalence of psychotic disorders and its association with methodological issues. A

systematic review and meta-analyses. PLoS One. 13(4):e0195687. https://doi.org/10.1371/journal.pone.0195687

Na KS, Jung HY, Kim YK (2014) The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 48:277–286. https://doi.org/10.1016/j.pnpbp.2012.10.022

Nayeri Chegeni T et al (2019) Is there any association between *Toxoplasma gondii* infection and depression? A systematic review and meta-analysis. PloS one 14(6):e0218524. https://doi.org/10.1371/journal.pone.0218524

Okusaga O, Duncan E, Langenberg P, Brundin L, Fuchs D, Groer MW, Giegling I, Stearns-Yoder KA, Hartmann AM, Konte B, Friedl M, Brenner LA, Lowry CA, Rujescu D, Postolache TT (2016) Combined Toxoplasma gondii seropositivity and high blood kynurenine–linked with nonfatal suicidal self-directed violence in patients with schizophrenia. J Psychiatr Res. 72:74–81. https://doi.org/10.1016/j.jpsychires.2015.10.002

Ortiz-Guerrero G, Gonzalez-Reyes RE, de-la-Torre A, Medina-Rincón G, Nava-Mesa MO (2020) Pathophysiological mechanisms of cognitive impairment and neurodegeneration by Toxoplasma gondii infection. Brain Sci 10(6):369. https://doi.org/10.3390/brainsci10060369

Osman E, Mohammad Zahariluddin AS, Sharip S, Md Idris Z, Tan JK (2022) Metabolomic profiling reveals common metabolic alterations in plasma of patients with toxoplasma infection and schizophrenia. Genes (Basel). 13(8):1482. https://doi.org/10.3390/genes13081482

Ouyang W, O'Garra A (2019) IL-10 Family cytokines IL-10 and IL-22: from basic science to clinical translation. Immunity. 50(4):871–891. https://doi.org/10.1016/j.immuni.2019.03.020

Pearce BD, Kruszon-Moran D, Jones JL (2012) The relationship between *Toxoplasma gondii* infection and mood disorders in the third National Health and Nutrition Survey. Biol Psychiatry. 72(4):290–5. https://doi.org/10.1016/j.biopsych.2012.01.003

Pinjari OF, Dasgupta SK, Okusaga OO (2022) Plasma soluble P-selectin, Interleukin-6 and S100B protein in patients with schizophrenia: a pilot study. Psychiatr Q 93(1):335–345. https://doi.org/10.1007/s11126-021-09954-3

Qing Y, Yang J, Wan C (2015) Increased serum fibroblast growth factor 21 levels in patients with schizophrenia. Aust N Z J Psychiatry. 49(9):849–50. https://doi.org/10.1177/0004867415575380

Rantala MJ, Luoto S, Borráz-León JI (2022) Krams I (2022) Schizophrenia: the new etiological synthesis. Neurosci Biobehav Rev 142:104894. https://doi.org/10.1016/j.neubiorev.2022.104894

Reznik AM, Syunyakov TS, Mudrak AV et al (2023) Treatment of depression with vortioxetine and second generation antipsychotics during the period of remission formation in schizophrenia (interim data analysis). Consort Psychiatr. 4(1):18–36. https://doi.org/10.17816/CP3728. (**Published 2023 Mar**)

Romanov DV, Brazhnikov AI, Andreyuk DS, Zakharova NV, Bravve LV, Kovaleva VA, Abbazova EV, Goncharov DB, Titova IV, Domonova EA, Kostyuk GP (2020) Schizophrenia and toxoplasmosis: association with catatonic symptoms. Consort Psychiatr. 1(1):22–29. https://doi.org/10.17650/2712-7672-2020-1-1-22-29

Runge K, Balla A, Fiebich BL et al (2023) Neurodegeneration markers in the cerebrospinal fluid of 100 patients with schizophrenia spectrum disorder. Schizophr Bull 49(2):464–473. https://doi.org/10.1093/schbul/sbac135

Sagud M, Vlatkovic S, Svob Strac D et al (2018) Latent *Toxoplasma gondii* infection is associated with decreased serum triglyceride to high-density lipoprotein cholesterol ratio in male patients with schizophrenia. Compr Psychiatry 82:115–120. https://doi.org/10.1016/j.comppsych.2018.02.002

Sanchez SG, Besteiro S (2021) The pathogenicity and virulence of *Toxoplasma gondii*. Virulence 12(1):3095–3114. https://doi.org/10.1080/21505594.2021.2012346

Stepanova EV, Kondrashin AV, Sergiev VP, Morozova LF, Turbabina NA, Maksimova MS, Brazhnikov AI, Shevchenko SB, Morozov EN (2017) Significance of chronic toxoplasmosis in epidemiology of road traffic accidents in Russian Federation. PLoS One. 12(9):e0184930. https://doi.org/10.1371/journal.pone.0184930

Stepanova EV, Kondrashin AV, Sergiev VP, Morozova LF, Turbabina NA, Maksimova MS, Romanov DV, Kinkulkina MA, Lazareva AV, Morozov EN (2019) Toxoplasmosis and mental disorders in the Russian Federation (with special reference to schizophrenia). PLoS One. 14(7):e0219454. https://doi.org/10.1371/journal.pone.0219454

Stone WS, Phillips MR, Yang LH, Kegeles LS, Susser ES, Lieberman JA (2022) Neurodegenerative model of schizophrenia: growing evidence to support a revisit. Schizophr Res 243:154–162. https://doi.org/10.1016/j.schres.2022.03.004

Strober LB, Binder A, Nikelshpur OM, Chiaravalloti N, DeLuca J (2016) The perceived deficits questionnaire: perception, deficit, or distress? Int J MS Care 18(4):183–190. https://doi.org/10.7224/1537-2073.2015-028

Sutterland AL, Fond G, Kuin A, Koeter MW, 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 Psychiatr Scand. 132(3):161–79. https://doi.org/10.1111/acps.12423

Teimouri A et al (2020) Role of *Toxoplasma gondii* IgG avidity testing in discriminating between acute and chronic toxoplasmosis in pregnancy. J Clin Microbiol 58(9):e00505-20. https://doi.org/10.1128/JCM.00505-20

Torrey EF, Bartko JJ, Lun ZR, Yolken RH (2007) Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis. Schizophr Bull. 33(3):729–36. https://doi.org/10.1093/schbul/sbl050

Trépanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP (2016) Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. Mol Psychiatry 21(8):1009–1026. https://doi.org/10.1038/mp.2016.90

Vilotić A, Nacka-Aleksić M, Pirković A, Bojić-Trbojević Ž, Dekanski D, Jovanović Krivokuća M (2022) IL-6 and IL-8: an overview of their roles in healthy and pathological pregnancies. Int J Mol Sci. 23(23):14574. https://doi.org/10.3390/ijms232314574

Wójciak P, Domowicz K, Zabłocka M, Michalak M, Rybakowski JK (2021) Association of negative symptoms of schizophrenia assessed by the BNSS and SNS scales with neuropsychological performance: a gender effect. Front Psychiatry. 12:797386. https://doi.org/10.3389/fpsyt.2021.797386. (**Published 2021 Dec 24**)

Xiang Y, Xin J, Le W, Yang Y (2020) Neurogranin: a potential biomarker of neurological and mental diseases. Front Aging Neurosci. 12:584743. https://doi.org/10.3389/fnagi.2020.584743

Xu F, Ma X, Zhu Y, Sutterland A, Cheng R, Miao S, Chen J, Qiu L, Zhou Y (2020) Effects of *Toxoplasma gondii* infection and schizophrenia comorbidity on serum lipid profile: a population retrospective study from Eastern China. Microb Pathog. 149:104587. https://doi.org/10.1016/j.micpath.2020.104587

Yoon H, Triplet EM, Simon WL, Choi CI, Kleppe LS, De Vita E, Miller AK, Scarisbrick IA (2022) Blocking Kallikrein 6 promotes developmental myelination. Glia. 70(3):430–450. https://doi.org/10.1002/glia.24100

Zhou B, Mu K, Yu X, Shi X (2024) Serum levels and clinical significance of NSE, BDNF and CNTF in patients with cancer-associated ischemic stroke complicated with post-stroke depression. Actas Esp Psiquiatr. 52(4):474–483. https://doi.org/10.62641/aep.v52i4.1667