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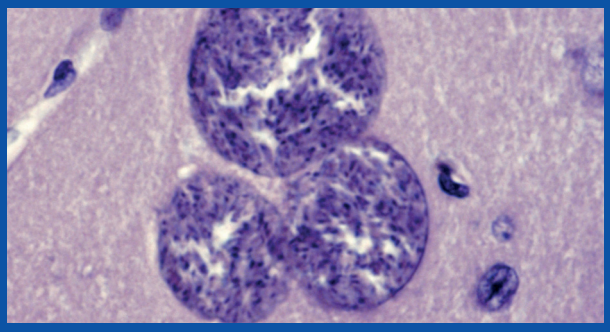


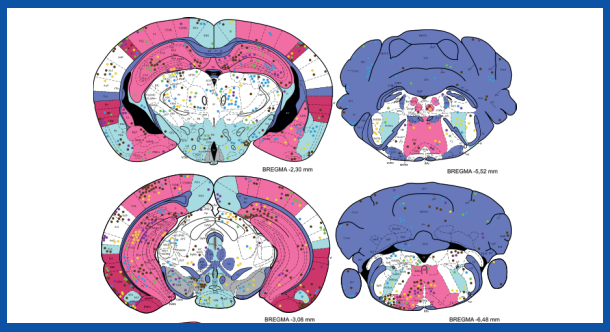

Special Issue

Effects of Latent Toxoplasmosis: Three Decades of Studies

Guest Editors:

Jaroslav Flegr
Faculty of Science, Charles University, Prague, Czech Republic

Ivan Fiala
Institute of Parasitology, Biology Centre of the Czech Academy of Sciences
České Budějovice, Czech Republic

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Special Issue on Toxoplasmosis
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The linking of toxoplasmosis and schizophrenia

Edwin Fuller Torrey[1]

[1] The Associate Director for Research at the Stanley Medical Research Institute, Rockville, Maryland, USA, and the author of Parasites, Pussycats and Psychosis: The Unknown Dangers of Human Toxoplasmosis

Abstract: Toxoplasmosis is caused by *Toxoplasma gondii* (Nicolle et Manceaux, 1908), a coccidian protist (Apicomplexa). It has a strong predilection for infecting the central nervous system. Researchers have therefore investigated its association with several neurological and psychiatric disorders, including Alzheimer's disease, attention-deficit hyperactivity disorder, autism, bipolar disorder, cerebral palsy, depression, Guillain-Barre syndrome, multiple sclerosis, obsessive compulsive disorder, Parkinson's disease, personality disorders, and schizophrenia. Among these disorders the strongest evidence for a role of *T. gondii* exists for psychosis in general and schizophrenia in particular. This paper reviews the origins of this association, briefly summarises the current evidence in support, and discusses future research strategies.

Keywords: Cats, brain cysts, epidemiology

Origins of the Association

My interest in diseases caused by infectious agents began in medical school. Viruses, such as those which cause polio, and bacteria, such as that which causes tuberculosis, appeared to be the heart of medicine. After medical school I spent two years as a Peace Corps physician in Ethiopia where I became acquainted with parasites, especially those which cause malaria and onchocerciasis (river blindness) (Torrey 1966).

My sister had developed schizophrenia when I was at university. Thinking about the possible causes of her disease as a young psychiatrist, infectious agents did not cross my mind until 1971 when I met Carlton Gajdusek, a neurologist who had just returned from Papua New Guinea. There he had discovered a chronic and ultimately fatal brain disease called kuru, caused by an infectious "slow virus", for which he was ultimately awarded a Nobel Prize.

I asked Carlton whether he thought that schizophrenia might also be caused by an infectious agent. He told me that he had already considered that possibility and had injected some chimpanzees with cerebrospinal fluid from individuals with schizophrenia, although it was not clear what he expected to happen. He also told me that he had never seen a case of schizophrenia in the most remote parts of Papua New Guinea which had had contact with Western civilization for only a few years. An anthropologist had made a similar observation in 1929 (Seligman 1929).

I was intrigued by the possibility that schizophrenia did not exist in some parts of the world, so I travelled to Papua New Guinea in 1972 and spent two months examining the hospital records. I found that Gajdusek was correct – the prevalence of schizophrenia was ten times higher in areas of Papua New Guinea where people had had contact with traders, missionaries, and other aspects of Western civilization for up to 100 years, compared to areas which had had such contact for less than 30 years (Torrey et al. 1974). This pattern was consistent with an infectious agent, which I believed was most likely a virus. In retrospect, Papua New Guinea had no indigenous felids, so the protist *Toxoplasma gondii* (Nicolle et Manceaux, 1908) would not have existed in the remote areas. By contrast, traders and missionaries often bring their cats with them when working in developing countries.

In 1973 I was joined in my research by Michael Peterson, a young psychiatrist who was also interested in infectious agents as possible causes of schizophrenia. We published as a hypothesis an article in *Lancet* on "Slow and latent viruses in schizophrenia" (Torrey and Peterson 1973). We did not have any research funding but a virologist at the National Institutes of Health kindly allowed us to use a corner of his laboratory, so we started to collect serum and cerebrospinal fluid from patients and controls.

I also published a paper in 1973 in the *Schizophrenia Bulletin*, titled "Is schizophrenia universal? An open question" (Torrey 1973). I had become interested in the epidemiology of schizophrenia and reviewed research suggesting that its prevalence varied significantly in different parts of the world. Specifically, I reported that "the prevalence of schizophrenia in developing areas appears to be roughly correlated with the degree of Western acculturation and the exposure to Western technology."

*Address for correspondence: The Stanley Medical Research Institute, 9800 Medical Center, Suite C-050, Rockville, MD 20850. E-mail: torreyf@stanleyresearch.org; 0000-0002-1231-5291

Fig. 1. Cats may be suspected as reservoirs of the (infectious) agent. Generated with AI by www.freepik.com.

Over the next several years I continued to explore its epidemiology, culminating in my 1980 book *Schizophrenia and Civilization* (Torrey 1980). In that book, I also detailed evidence suggesting that schizophrenia is a relatively recent disease which has only existed for about 200 years and in 2002, I co-authored a book on that subject: *The Invisible Plague: The Rise of Mental Illness from 1750 to the Present* (Torrey and Miller 2002). I believe that the epidemiology of schizophrenia is consistent with an infectious etiology and thus epidemiology has strongly influenced my thinking and research.

TWO QUESTIONS

If infectious agents are truly causing some cases of schizophrenia, two questions must be answered. First, what is the infectious agent? I initially assumed that it was probably a virus and became especially interested in those in the herpes family (Herpesviridae). The second question is how the infectious agent is transmitted to humans.

As early as 1952, it had been suggested that multiple sclerosis was caused by an infectious agent and that "dogs or cats may be suspected as reservoirs of the (infectious) agent" (Steiner 1952). In 1977, researchers reported that three sisters had developed multiple sclerosis shortly after their pet dog experienced a severe neurological illness (Cook and Dowling 1977). An outpouring of dog research followed, and one neurology journal designated 1977 "The year of the dog" (Alter et al. 1979). I had not previously considered pets as possible origins of infectious agents causing schizophrenia and found this research of interest. Thus, in my 1980 book, *Schizophrenia and Civilization*, I ridiculed the psychoanalytic theory that mothers cause schizophrenia by suggesting that "the schizophrenogenic mother should be replaced by that of a schizophrenogenic cocker spaniel, cat, canary or turtle" (Torrey 1980, p. 181).

In *Schizophrenia and Civilization*, I summarised the research suggesting that not only was schizophrenia very uncommon in some areas of the world, but that it was common in other areas. Foremost among the latter was Ireland, where for 200 years people had claimed that psychosis was common. For example, in 1894 a psychiatrist in Ireland claimed that "Ireland alone of all civilized countries…possesses the unique and unenviable distinction of a continuously increasing amount of insanity with a continuously decreasing population. The proportional rate of increase in Ireland is far beyond what exists elsewhere" (Drapes 1894). The high prevalence was said to exist both among people living in Ireland, especially in low-income areas in western Ireland and also among Irish immigrants in the United States and England. Carefully done contemporary studies appeared to support such claims (Walsh and Walsh 1970, O'Hare and Walsh 1974).

I was intrigued by the possibility of an area with an unusually high rate of psychosis. In 1982 I therefore spent seven months working in Ireland in the Roscommon County Psychiatric Hospital. In addition to collecting sera and cerebrospinal fluid from patients and controls, I carried out prevalence studies with my Irish colleagues. We confirmed that in the area under study, 4% of the population over the age of 40 were actively psychotic, one of the highest rates reported anywhere in the world (Torrey et al. 1984). Strikingly, the high rate was only found for people who were born before World War II; the rate among younger individuals did not differ from the rate for Ireland as a whole.

While living in Ireland I considered various explanations for this puzzling pattern and noticed that cats were very common in the area under study. In retrospect, I suspect that the answer is as follows. During WWII, many men from this area went to work in the Liverpool shipyards and sent money home. Much of the money was used to improve the housing in that area, which had been very poor. For many families this meant the difference between a house with a dirt floor, on which cats may defecate, and thus spread infective oocysts of *T. gondii*, and a wooden floor on which cats were much less likely to defecate. Studies have shown that people who live in houses with dirt floors are more likely to be infected with *T. gondii* (Ademe 2022).

Throughout the 1980s I continued attempts to identify infectious agents which may cause some cases of schizophrenia. My research was helped immeasurably in 1979 when Robert Yolken, a pediatric virologist, agreed to help even though I still did not have any funding for the research. In 1982 we published a paper in *Science* on cytomegalovirus antibodies in patients with schizophrenia (Torrey et al. 1982). Our research was finally put on a solid financial footing in 1989 when Ted and Vada Stanley, whose son had developed a psychotic disorder, offered to fund the Stanley Medical Research Institute (SMRI). SMRI established the Stanley Laboratory for Developmental Neurovirology at Johns Hopkins University Medical Center with R. Yolken as the director.

At that time, I also began collecting research data from families in which one or more members had developed psychosis. Many such families were members of the National Alliance for the Mentally Ill (NAMI). In 1992, 165 NAMI parents whose child had developed psychosis, and 165 well-matched controls completed a two-page questionnaire. In addition to asking about childhood illnesses, vaccinations, developmental milestones, childhood coordi-

nation, and family history, we included a question whether the family had owned a cat between the psychotic person's birth and age 10. Fifty one percent of the families with psychosis had owned a cat, compared to 38% of the controls. This result was statistically significant ($p = 0.02$) by itself, but because of the number of questions being asked, true significance would have required a P value of 0.01 (Torrey and Yolken 1995).

Based on these preliminary findings, we undertook a follow-up study in 1997. Professional interviewers at the University of Maryland's Survey Research Center carried out a twenty-minute telephone interview with 262 randomly selected NAMI members in which a family member had psychosis. The interviewers also obtained two matched controls for each case. The interview included several questions regarding household pets, including cat ownership between birth and age 13. The results were strikingly similar to the preliminary survey: 52% of the cases compared to 42% of controls had owned a cat ($p < 0.01$) (Torrey et al. 2000). Since exposure to cats in childhood can occur in many settings in addition to having one at home, I interpreted the results of the two studies as strong evidence that cats may play a role in causing some cases of psychosis.

The possibility that cats might carry an infectious agent causing psychosis led us to re-evaluate our assumption that the infectious agent was probably a virus. *Toxoplasma gondii* clearly deserved a closer look. We identified reports claiming that some people with toxoplasmosis have delusions and hallucinations (Kramer 1966, Ladee 1966). We also found reports dating to as early as 1953 (Kozar 1953) that individuals with psychosis have a significantly higher prevalence of antibodies to *T. gondii* than controls. Most early studies were carried out in Eastern Europe or China, which we visited at that time, and were not widely known by Western researchers. In 2007 we published a metanalysis of 42 such studies, two of which we did ourselves, reporting a significant association between psychosis and antibodies to *T. gondii* ($p = 0.00001$; OR = 2.73) (Torrey et al. 2007).

There were other reasons to suspect that *T. gondii* was playing some role in causing schizophrenia. A study of 600 individuals with first episode schizophrenia reported that those infected with *T. gondii*, compared to those not infected, had more severe delusions and hallucinations (Wang et al. 2006). Other studies demonstrated how *T. gondii* can affect human behaviour. Jaroslav Flegr and his colleagues in the Czech Republic published studies in the 1990s describing how infection with *T. gondii* can affect human personality traits (Flegr and Hrdý 1994). They also showed that the parasite decreases human reaction times thereby causing *Toxoplasma*-infected humans to be more likely to be involved in motor vehicle accidents (Flegr et al. 2002).

Thus, by the early years of this century, I had become personally convinced that some cases of psychosis, especially schizophrenia, were caused by *T. gondii* carried by cats. Thus, when I gave talks on our research to advocacy groups, I began closing my talks with the following:

"In conclusion, my take home message is that schizophrenia is a CATastrophe which produces a CATalogue of symptoms, including CATatonia, and CATalapsy. Part of its etiology includes CATacholamines. Do you think it is merely by chance that we are making research progress on schizophrenia using CATscans and PETscans?"

Recent studies

Over the past 20 years, a large number of studies have supported the possible role of *T. gondii* in causing some cases of psychosis, including schizophrenia. There have been at least 20 additional studies examining the possible association between cat ownership and the development of schizophrenia or psychotic-like symptoms. A 2023 meta-analysis of 17 such studies carried out in 11 countries reported "a significant positive association between broadly defined cat ownership and an increased risk of schizophrenia-related disorders…We found that individuals exposed to cats had approximately twice the odds of developing schizophrenia" (OR = 2.24; adjusted, pooled estimate) (McGrath et al. 2023).

Several additional studies have also reported that, among individuals with schizophrenia, those who are infected with *T. gondii* have more severe symptoms. For example, a study of 246 individuals with schizophrenia reported that those infected with *T. gondii* were sicker, especially with more negative symptoms, than those not infected (Esshili et al. 2016).

Similarly, there have now been over 100 studies, 16 from Iran alone (Montazeri et al. 2023), comparing the prevalence of antibodies against *T. gondii* in individuals with psychosis and controls. The single largest study, involving almost 82,000 blood donors in Denmark, reported a significant association between having antibodies to *T. gondii* and a diagnosis of schizophrenia (OR = 1.5). (Burgdorf et al. 2019). At least 25 of these antibody studies included individuals diagnosed with bipolar disorder, many of whom also had psychotic features (Cossu et al. 2022).

It is surprising that most of the antibody studies have reported a significant association with individuals with psychosis, given the number of known possible confounding factors. For example, it is known that the antipsychotic medication being taken by most subjects in these studies depresses the antibody response (Leweke et al. 2004). Antibodies to *T. gondii* are also known to wane over time so that sera stored for several years may no longer test positive as they did initially (Konishi 1989). There are also suggestions that the clinical outcome of an infection by *T. gondii* may differ depending on whether the infection was by a tissue cyst or an oocyst, although both types of infections would produce antibodies (Dubey 2004).

Similarly, there are many strains of *T. gondii* with some strains being more likely than others to infect the brain and cause psychosis (Xiao and Yolken 2015). The timing of the infection could also be critical as it is for many infectious agents. For example, it is possible that an initial infection in childhood may produce brain changes leading to psychosis whereas a primary infection in adulthood may not do so (Kannan et al. 2016).

Finally, host genetics also plays a role as it does for most infectious agents. Some people are more susceptible than others to become infected with *T. gondii*. For example, a particular HLA gene renders some people more susceptible to becoming infected with *T. gondii* that affects the brain (Suzuki 2002). Similarly, a particular COMT genotype makes people more susceptible to developing schizophrenia if they become infected with *T. gondii* (Rovira et al. 2022).

Conclusion and future studies

The data thus suggest that *T. gondii* may cause some cases of psychosis, including schizophrenia. Therefore, cat ownership in childhood should be considered a risk factor for this disease. However, this is not proven and does not apply to initial infections that occur in adulthood. It also does not apply to cats which have been kept indoors since birth and thus are very unlikely to have become infected with toxoplasmosis; such cats should be considered safe as pets. To clearly establish a cause-and-effect relationship between toxoplasmosis and schizophrenia would require either finding the parasite in *post-mortem* brain tissue in association with the disease, or finding a drug which both suppresses the parasite and improves the clinical symptoms of infected individuals.

Relatively few psychiatric studies have looked for evidence of toxoplasmosis in human brain tissue. One study used nested-polymerase chain reaction to examine *post-mortem* orbital frontal cortex from 24 psychiatric patients, including 14 with schizophrenia, and five with bipolar disorder and 24 normal controls; none were positive (Conejero-Goldberg et al. 2003). In another negative study, *post-mortem* tissue from the frontal, parietal and temporal areas was studied, using a panel of RT-PCR diagnostic probes, from a single individual diagnosed with schizophrenia and serologically positive for *T. gondii* (Melzer et al. 2010).

At the Stanley Brain Laboratory, directed by Maree Webster, we also screened 195 *post-mortem* specimens for *T. gondii* cysts. The brains included both psychiatric cases and controls; 120 of them were included because they tested serologically positive for *T. gondii* antibodies to maximise the chances of finding cysts. Two formalin-fixed sections, one from the prefrontal cortex and one from the temporal cortex, were screened from each brain using a method similar to that used by Mexican researchers who reported *T. gondii* cysts in the brains of some individuals who died by suicide (Mendoza-Larios et al. 2023). An alternate strategy, being used in the Stanley Laboratory of Developmental Neurovirology, is to develop antibodies specific to the *T. gondii* cyst protein and then use them to screen cerebrospinal fluid and/or blood from patients with psychosis (Xiao et al. 2021).

There are several reasons why *T. gondii* cysts may be present in the brain but not detected by such studies. Most important, we may be looking in the wrong areas, especially if the cysts are few in number. Alternatively, the cysts may have been present initially but are no longer present. Studies in mice have reported that such cysts decrease rapidly after about 6 months (Melzer et al. 2010). Another possibility is that we are using the wrong primers, or the primers are too weak to detect the cysts. Most of the *post-mortem* tissue that is available for such studies has been either frozen or fixed. It is possible that these procedures destroy the ability to detect the cysts (Villegas et al. 2010).

The second possible strategy for confirming a cause-and-effect relationship between *T. gondii* and schizophrenia would be to find a drug which both suppresses the parasite and simultaneously improves the clinical symptoms of infected individuals. The standard treatment for infections with *T. gondii* is pyrimethamine, trade name Daraprim, a drug also used to treat malaria. For treating toxoplasmosis pyrimethamine is usually used in combination with sulfadiazine or another sulfonamide antibiotic. For treating infections anywhere except the brain, this combination is moderately effective for most cases but there are significant side effects. However, when *T. gondii* infects the brain, it is a different story. The blood-brain barrier blocks many drugs from getting into the brain. Furthermore, in the brain, *T. gondii* forms tissue cysts which are metabolically relatively inactive and therefore do not respond well to treatment by many drugs. The bottom line is that we currently have no effective treatment for infections by *T. gondii* in the brain.

Given the need for better drugs to treat psychosis, a few attempts have been made to treat patients with schizophrenia using drugs thought to be effective against *T. gondii*. Between 2009 and 2014, four such randomly controlled trials were reported (Chorlton 2017). Two trials used antibiotics – azithromycin and trimethoprim – and the other two trials used antiparasitic drugs, artemisinin and artemether. None of the four trials reported significant improvement in the symptoms of individuals with schizophrenia. This was not surprising given the fact that none of the four drugs have good penetration into the brain. In addition, three of the four trials used patients who had been sick for many years. To be effective it is quite possible that an anti-*Toxoplasma* drug would have to be given in the earlier stages of the illness (Neville et al. 2015).

One place in which to look for better treatments for toxoplasmosis is the development of better antipsychotics. The chemical structure of many effective antiparasitic drugs is very similar to the structure of antipsychotic drugs. As early as 1891, it was reported that the phenothiazine dye, methylene blue, was effective in suppressing the parasite that causes malaria. Sixty years later the first effective antipsychotic, chlorpromazine, was developed; it is also a phenothiazine. Based on this history, we tested 12 antipsychotic and mood stabiliser drugs to ascertain their effectiveness in inhibiting *T. gondii* in cell culture. All of the 12 drugs except lithium demonstrated some ability to inhibit *T. gondii*, and two of them – the antipsychotic haloperidol and the mood stabilizer valproate – were even more effective than the antibiotic trimethoprim which is used to treat toxoplasmosis and was used in the study as the comparator drug (Jones-Brando et al. 2003).

Thus, it is possible that some of the effectiveness of antipsychotic drugs used to treat psychosis comes from their ability to suppress *T. gondii* or other infectious agents. It is also possible that the ultimate solution to the toxoplasmosis treatment problem will come from the development of better antipsychotics. Given the complexity of the *T. gondii* organism and its many strains, it will not be easy to develop better treatments for this parasite, but it can be done.

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