Toxoplasma gondii and Cognitive Deficits in Schizophrenia: An Animal Model Perspective

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Cognitive deficits are a core feature of schizophrenia. Epidemiological evidence indicates that microbial pathogens may contribute to cognitive impairment in patients with schizophrenia. Exposure to *Toxoplasma gondii* (*T. gondii*) has been associated with cognitive deficits in humans. However, the mechanisms whereby the parasite impacts cognition remain poorly understood. Animal models of *T. gondii* infection may aid in elucidating the underpinnings of cognitive dysfunction. Here, we (1) overview the literature on the association of *T. gondii* infection and cognitive impairment, (2) critically analyze current rodent models of cognitive deficits resulting from *T. gondii* infection, and (3) explore possible mechanisms whereby the parasite may affect cognitive function.

Key words: infection/immune system/kynurenine/learning and memory/gene–environment interactions/*Toxoplasma*

Introduction

Cognitive impairment is an important feature and serious problem in patients with schizophrenia. As many as 85% of patients exhibit some degree of cognitive dysfunction.[1] While cognition encompasses many mental processes, 7 domains are consistently impaired in schizophrenia: speed of processing, attention, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition. Three types of learning and memory that are severely affected are spatial, olfactory, and associative.[2] Dysfunction can be present prior to the onset of psychosis but more typically is observed concomitantly with positive symptoms. Unfortunately, treatment with anti-psychotics that can ameliorate positive symptoms do not significantly improve cognitive functioning.[3] As the underlying mechanisms of cognitive impairment in patients with schizophrenia are not completely understood, the development of better therapies is impeded.

Recently, there has been a growing interest in the role of infectious agents in the development of psychiatric disorders. Epidemiological and immunological clinical studies have identified microbial factors that may contribute to cognitive impairment in patients with schizophrenia. Herpes Simplex 1, Cytomegalovirus, influenza, and the protozoan *Toxoplasma gondii* (*T. gondii*) have all been implicated in the development of memory deficits in both nonschizophrenic and schizophrenic individuals.[4,5] The role of *T. gondii* exposure in schizophrenia related cognitive dysfunction is interesting in that while all other candidate pathogens are viruses, *T. gondii* is thus far the only implicated protozoan. The parasitic infection may contribute to cognitive impairment by affecting various brain systems, including glutamate (GLU) synaptic neurotransmission. Indeed, the role of GLU in schizophrenia and cognition has been extensively studied and is an important line of research. However, we still know very little about the exact mechanisms whereby *T. gondii* infection leads to cognitive impairment. Animal models of *T. gondii* infection can help advance our understanding of these mechanisms and facilitate identification of novel therapeutic targets.

In this review we will (1) overview the literature on the association of *T. gondii* and cognitive impairment, (2) critically analyze current rodent models of cognitive deficits resulting from *T. gondii* infection, and (3) explore the possible mechanisms whereby the parasite may affect cognitive function. We will propose future directions in translational research with animal models of *T. gondii* infection.

T. gondii Infectious Cycle

T. gondii is an intracellular protozoan parasite that infects approximately a third of the human population.[6] The 3 known clonal lineages of the parasite (Types I, II, and III) differ in their virulence, dissemination pattern,

growth rate, immune response activation, and prevalence.[7] Despite such differences, the 3 stages of *T. gondii's* infectious cycle are common for all strains.

In all species, the parasite starts its cycle of replication and dissemination with the tachyzoite stage. This parasite stage is present during acute infection, whereby tachyzoites actively invade any nucleated cell in the body, replicate asexually, and egress to infect other cells, destroying the host cell in the process. The second stage is noted by the localization of bradyzoite tissue cysts in skeletal muscle and most notably, the brain. The dormant tissue cysts are present in all hosts and are characteristic of chronic infection. The third stage occurs only in the feline intestinal tract and is characterized by the production of oocysts through sexual reproduction of the parasite. The infectious oocysts are excreted into the environment, where they can be transmitted to other organisms.[8] Converging evidence indicates that *T. gondii* manipulates rodent behavior to facilitate the parasite's transmission to the feline host. The behavioral effects of the parasite do not seem to be related to nonspecific changes observed in sick animals, but in fact suggest that the entire behavioral repertoire is affected to make an infected host a more likely prey for felines.[6]

Oocysts and cysts can be transmitted to humans in a number of ways, including consuming undercooked meat infected with cysts, drinking water contaminated with oocysts, or handling soil contaminated with oocysts. When oocysts or tissue cysts are consumed, the parasite converts into actively invading and quickly replicating tachyzoites. Under surveillance and inhibitory control by the host immune system, tachyzoites enter into the dormant tissue cyst stage. However, tissue cysts are capable of rupturing, with bradyzoites transforming back into tachyzoites.[8]

In humans, the transition of bradyzoites back to tachyzoites in the brain can have serious health consequences for immune-compromized individuals (eg, HIV-infected patients). The weakened host immune system cannot control the parasite from continually invading and destroying brain cells, which results in toxoplasmic encephalitis.[8] As encephalitis is not observed in healthy people, it has long been thought that *T. gondii* infection only harms immune-compromised patients. However, it is becoming evident that *T. gondii* infection can also cause problems in immune-competent individuals. Indeed, infection has been associated with a number of behavioral changes, including cognitive deficits.

T. gondii *and Cognitive Deficits in Humans*

T. gondii exposure has been associated with cognitive impairment in nonschizophrenic and schizophrenic subjects. One of the first studies to evaluate the role of *T. gondii* infection in cognitive impairment was published in 1953 by Burkinshaw et al. They found that 89% of *T.*

gondii seropositive patients at a mental institution had severe cognitive impairments, with an intelligence quotient (IQ) below the normal range (<70). However, they could not definitively attribute the mental defects to toxoplasmosis.[6] Similarly, following a group of 24 children congenitally infected with *T. gondii,* Wilson et al. determined 4 (17%) of them had severe cognitive impairments (IQ ranging 36–62), while 6 (25%) showed a drop in intelligence over time (IQ score of 97 down to 74).[9]

A few studies have associated *T. gondii* infection with less severe cognitive changes. In 1973, Saxon et al revealed that children who were congenitally infected with *T. gondii* had significantly lower IQ scores (93.2) as compared with their age matched–uninfected controls (109.8).[10] Similarly, results from the Otis questionnaire conducted by Flegr et al revealed that young adult men (age 19–21) infected with *T. gondii* have lower verbal intelligence as compared with their uninfected counterpart.[9] Likewise, infected young adult men and the elderly (age 19–60) showed greater impairment in delayed and immediate memory as compared with uninfected controls.[9]

One caveat of these studies is that the exact time of infection is unknown. As has been reviewed in detail by Jones et al., during pregnancy the risk of vertical transmission and severity of cognitive symptoms in offspring vary across the trimesters. For instance, while there is only a 10–25% risk of vertical transmission during the first trimester, exposure at this stage leads to mental retardation in offspring. In contrast, despite the fact that women who acquire *T. gondii* during the third trimester have a 60–90% risk of passing the parasite to the fetus, infection during this developmental stage produces minimal cognitive impairment in offpsring.[11] While the study of Saxon et al. provides evidence for subtle cognitive changes due to congenital *T. gondii* infection, it is possible that infection during other life stages (eg, puberty) may cause similar outcomes. Such information can be useful in the development of preventive medication. For instance, the prospective study performed by Saxon et al. included a group of congenitally infected children who were treated with sulfadiazine and pyrimethamine for the first month after birth. The IQ of this group at 2–4 years of age was comparable with age-matched controls, while that of the untreated group was significantly lower.[10]

Studies on the effects of *T. gondii* infection on cognitive dysfunction in people with schizophrenia are inconclusive. One study found no significant association between *T. gondii* infection and cognitive deficits in patients (aged 13–75 years) although seropositive subjects performed poorer on the Trail Making Test (TMT) than seronegative patients. The age at which the individuals were first exposed to *T. gondii* was not mentioned.[4] In contrast, Brown et al. reported that patients prenatally exposed to *T. gondii* exhibited worse executive functioning and memory than unexposed schizophrenics.[12] This was evidenced by the increased number of errors made on the Wisconsin Card

Sorting Test and the greater amount of time taken to complete part B of the TMT. As the study conducted by Brown et al. also included individuals prenatally exposed to influenza, it is difficult to unequivocally conclude that *T. gondii* infection contributed to cognitive dysfunction in individuals with schizophrenia. It is also unclear whether the cognitive deficits in infected patients are more severe than in seropositive controls. Although humans are not intermediate hosts for the parasite, memory or attention abnormalities in infected individuals might be a "side-effect" of parasite manipulation as discussed in detail elsewhere.[6] As there is likely significant resemblance in the mechanisms whereby *T. gondii* impacts the brain and behavior of different species,[6] rodent models will help to better understand how *T. gondii* infection contributes to cognitive deficits in infected patients.

Cognitive Abnormalities in T. gondii–Infected Rodents

Cognitive effects of *T. gondii* have been evaluated in tests for spatial, olfactory, and associative learning and memory (table 1).

Spatial Learning and Memory

Spatial learning and memory requires the processing of external cues to complete a task. This is mainly studied in rodents through the use of mazes. The earliest reports on changes in spatial learning and memory due to *T. gondii* infection come from studies in the late 1970s. Using labyrinth test, Piekarski et al found that chronically infected adult female mice and rats showed impaired learning as compared to uninfected controls.[13] A year later, Witting's study further demonstrated that *T. gondii* infection impaired learning in both acute and chronically infected adult female mice and rats. Learning impairment was observed as early as 2 days post-infection (acute) and as late as 6 weeks post-infection (chronic). Notably, memory was found to be affected differently between the two species, with only infected mice exhibiting severe memory impairment.[14]

Although the spatial learning and memory studies using labyrinth tests provided consistent and intriguing results, this task is no longer popular. Now, Y maze, radial arm maze, or Morris water maze (MWM) is commonly employed. Y maze is a useful tool for studying spatial working (short-term) memory and spatial recognition (long-term) memory. Using Y maze, Kannan et al found that chronic infection of young adult Balb/C female mice (9-week-old) led to deficits in spatial working memory but not in spatial recognition memory. Curiously, while the effects of 2 Type II strains of *T. gondii* were compared, Pru and ME49, only infection with ME49 was associated with impairment of spatial working memory.[15] Neither parasite strain produced deficiency in spatial recognition memory in the infected female mice, as determined by the similar amount of time control and infected groups spent

Table 1. The Effects of *T. gondii* Infection on Learning and Memory in Rodents

Test	Species	Sex	Result	Ref
Spatial learning and memory				
Labyrinth	Mouse, rat	Female	Impaired learning	13
	Mouse, rat	Female	Impaired learning	14
	Mouse	Female	Impaired memory	14
	Rat	Female	No impaired memory	14
Y maze	Mouse	Female	Impaired working memory	15
	Mouse	Female	No impaired recognition memory	15
	Mouse	Female, male	No impairment	16
	Mouse	Male	No impairment	18
Radial arm maze	Mouse	Female	Impaired recognition memory	19
Morris water maze	Rat	Male	No impairment	20
Object recognition	Mouse	Male	No impairment	21
Olfactory-based learning and memory				
Social transmission of food preference	Mouse	Female	No impairment	20
	Mouse	Female	No impairment	22
	Mouse	Male	Impaired learning and memory	22
Associative learning and memory				
Passive avoidance	Mouse	Not provided	Impaired memory	24

exploring the novel arm.[15] In a different study, mice were exposed to *T. gondii* at 1 of 3 time points: (1) 8 weeks of age, (2) congenitally by infecting pregnant dams, or (3) congenitally through mating of chronically infected females.[16] It was found that male and female strain A albino mice, exposed at all 3 time points to the Beverley Type II strain of parasite, preferred the familiar arm over the novel one, while controls expectedly preferred the novel arm. Intriguingly, the groups exposed congenitally to the parasite spent more time in the familiar arm compared with the adult acquired infection group. The outcome was interpreted as *T. gondii*–induced neophobia.[16] The increased neophobia in infected mice appears different from the behavioral responses seen in rats, although the rat studies used a different paradigm.[17] Adult infected male mice demonstrated deficits in spatial recognition memory measured as lack of preference for either arm of Y maze.[18]

Radial 8-arm maze is also widely used to study spatial working memory and spatial recognition memory.

The increased number of arms compared to the Y maze adds complexity to the rodent's task, helping to uncover more subtle deficits in learning and memory. One study with *T. gondii*–infected rodents used radial arm maze to assess spatial recognition memory only. This task requires rodents to remember the maze arm with food rewards, in order to reach the food more quickly on following days. Compared to uninfected controls, chronically infected adult female mice (10 weeks of age) of a mixed Balb/C:C57BL/6 background spent more time searching for the food reward,[19] suggesting a deficit in spatial recognition memory. Notably, this deficiency was not seen in chronically infected female mice in Y maze.[15]

MWM is another task to evaluate spatial learning and memory. As with Y and radial arm mazes, the MWM protocol can be modified to assess both spatial working memory and spatial reference memory. Using MWM, Vyas et al evaluated the effects of *T. gondii* infection on spatial memory in rats.[20] They found that control and chronically infected male rats spent the same amount of time in the quadrant that previously contained the escape platform, indicating no deficit in spatial memory.[20] Spatial recognition memory in infected rodents was also examined in object recognition and spatial placement tests. It was determined that chronic infection of 8-week-old C57BL/6 male mice did not affect cognitive functions in these tests.[21]

Olfaction-Based Learning and Memory

The social transmission of food preference (STFP) test is based on olfaction and represents another type of cognitive test used on infected rodents. This task requires intact olfaction and sufficiently high levels of social nonaggressive interactions. Two groups used STFP to evaluate cognitive effects of chronic *T. gondii* infection in young adult Balb/C mice. Both studies found that *T. gondii* infection did not affect learning and memory in female mice as evidenced by their consumption of greater amounts of "familiar" food (the one that was previously presented by a social partner) compared with "novel" one.[20,22] In contrast, memory deficit was observed in infected males, as evidenced by consumption of similar amounts of both types of food. Notably, gender-dependent effects of *T. gondii* on olfaction-related behaviors have also been documented in human studies. Flegr et al. found that cat odor attractiveness increased for infected men while decreased for infected women.[23]

Associative Learning and Memory

Associative learning and memory can be studied in active and passive avoidance tests. To date, only one study has evaluated the effect of congenital exposure to *T. gondii* on passive avoidance in adult mice. In this study, mice were exposed to *T. gondii* on embryonic days 5, 10, and 15. It was found that congenital infection during early and intermediate gestation (5 and 10 days respectively) but not late gestation (15 days) leads to impaired passive avoidance in adult mice. This was demonstrated by a shorter latency time to enter the dark chamber and a greater number of entries into the dark chamber.[24]

The inconsistent results of the rodent studies can be explained by experimental differences, including rodent sex, species, and strain.[25] For example, direct effects of *T. gondii* on sex hormone production and the role of sex hormones in susceptibility to infection were shown to influence sex-related cyst burden and temporal differences in cytokine production in the brain.[26,27] Such differences can contribute to sex-dependent behaviors, emphasizing the importance of testing male and female animals. With regard to species-specific differences, milder cognitive abnormalities were reported in rats compared to mice. The variable outcomes could be explained by differential resistance between two species. Unlike mice, rats are less susceptible to *T. gondii* infection and exhibit the clinical course and in utero transmission that may better mimic the human situation.[25] Notably, greater resistance in rats appears to be related to later stages of infection as the early dissemination of parasites has been found to be very similar between species.[28] However, it remains unclear how species-specific brain physiology and behavioral biology can contribute to variable cognitive deficits produced by *T. gondii*.

T. gondii *Effects on the Brain*

Numerous studies have evaluated the molecular, cellular and immune effects of *T. gondii* on the brain. In vitro experiments have demonstrated that tachyzoites infect and form cysts within microglia, astrocytes, and neurons.[27] Activated microglia and astrocytes limit parasite replication and spread by stimulating expression of the NF-kB family of transcription factors to regulate production of pro- and antiinflammatory cytokines.[27] In turn, cytokines (eg, IL-1, IL-6, and TNF-alpha) can influence synaptic neurotransmission and potentially contribute to cognitive deficits.[29]

In addition to the effects of immune activation (eg, indirect mechanisms), it has been recently shown that the parasite itself is able to affect dopamine neurotransmission in the brain (eg, a direct mechanism). McConkey and his colleagues in a series of elegant experiments have demonstrated that the parasite expresses homologs of enzymes involved in the dopamine synthesis pathway: phenylalanine and tyrosine hydroxylase.[30] In vitro work with PC12 cells has demonstrated that *T. gondii* cysts can increase cellular release of dopamine.[31] Additionally, in vivo work has shown that parasite cysts can synthesize dopamine, and that infection increases whole-brain dopamine levels in infected mice.[32] Yet, a recent study reports no changes in monoamine content in the frontal

cortex and striatum of congenitally infected CD-1 mice.[33] Future studies are clearly needed to further evaluate alterations in dopamine neurotransmission in infected rodents in vivo and link these changes to behavioral abnormalities, including cognitive impairment. However, it seems less likely that only dopamine changes will be able to explain the entire spectrum of behavioral responses in infected animals. In the context of this review, it seems that more attention should be paid to GLU neurotransmission, alterations which are strongly associated with cognitive dysfunction in schizophrenia.

Administration of noncompetitive *N*-methyl-D-aspartic acid receptor (NMDAR) antagonists, phencyclidine and ketamine to nonpsychotic individuals can lead to behavioral changes that mimic positive, negative, and cognitive symptoms, including alterations in attention, memory, and reasoning. Subsequent studies using NMDAR antagonists, brain imaging, human postmortem samples, genetic approaches, and pre-clinical animal models have provided further evidence of the importance of GLU and its receptors in cognitive functioning.[34] These studies have suggested that dysfunction in NMDAR may be responsible for aspects of cognitive deficits in people with schizophrenia. However, it has been recently proposed that hyperfunction of NMDAR mediated through activation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors can also contribute to the pathophysiological mechanisms of cognitive impairment in schizophrenia.[34]

The link between *T. gondii* and changes in GLU neurotransmission remains poorly studied. Upregulation of a GLU receptor antagonist has been mostly evaluated. An endogenous metabolite of tryptophan metabolism and a NMDAR antagonist, kynurenic acid (KYNA), has been hypothesized to be a pathogenic link between *T. gondii* infection and cognitive impairment in schizophrenia.[35] Elevated levels of KYNA can lead to excessive stimulation of the NMDAR, affecting GLU neurotransmission and resultant cognitive function.[35] Thus, diminishing elevated KYNA levels is predicted to ameliorate cognitive deficits. Knockout mice with deletion of the enzyme that converts kynurenine into KYNA, kynurenine aminotransferase II, have lower levels of KYNA and perform better in cognitive tests compared to control mice.[36] As rodents infected with *T. gondii* and patients with schizophrenia have increased KYNA levels in brain,[35] one could predict that reduction of levels of this NMDA antagonist may have therapeutic effects.

The GLU system can also be affected by the host immune system's response to *T. gondii* infection via secreting cytokines (eg, IL-6 or TNF-alpha).[29] Another immune mechanism of GLU synaptic dysfunctions may be related to production of anti-NMDAR antibodies. Indeed, recent studies have implicated autoantibodies to the NMDAR in the causation of cognitive deficits.[37] While it remains to be seen whether such autoantibodies are produced by *T. gondii* infection, it has been reported that the infection-induced IgG antibodies are able to cross-react with neural epitopes, including the NMDAR.[38] It is also possible that the immune response to the parasite could alter numbers of NMDAR similar to the decreased expression of NMDAR due to prenatal infection with cytomegalovirus.[39] In addition, *T. gondii* could impact NMDAR functioning by affecting major histocompatibility complex (MHC) signaling.[40] Indeed, *T. gondii* infection has been shown to decrease neural MHC II expression,[41] which has been associated with cognitive deficits in CD-4 knockout mice.[42] Collectively, these studies suggest that the host immune response could affect GLU neurotransmission, resulting in cognitive impairment in infected individuals. However, more studies are clearly needed to provide a better understanding of the underlying molecular pathways.

Future Directions

Rodent models of cognitive dysfunction associated with *T. gondii* infection disease are important for advancing our knowledge of the molecular pathogenesis and the development of therapeutics. However, there are still several lines of work that need to be improved. In addition to schizophrenia, cognitive impairments are associated with other disorders, including obsessive-compulsive, bipolar disorder and Alzheimer's disease.[43,44] It is possible that there is substantial commonality in the pathophysiology of cognitive dysfunction in all these illnesses. Therefore, to create a more comprehensive rodent model of cognitive impairment associated with schizophrenia, it is necessary to model other schizophrenia-like behavioral changes as well.[45]

Given that microbes probably interact with genetic factors to contribute to psychiatric disease, there is a need in developing animal models based on interactions between *T. gondii* infection and candidate genes (eg, Disrupted in Schizophrenia 1 [*DISC1*]). *DISC1* was first identified in a balanced chromosomal translocation (1:11) (q42.1; q14.3) that segregates in a Scottish pedigree with major mental disorders.[46] *DISC1* is located within a region of the human genome identified as likely to harbor a susceptibility gene for schizophrenia, mood disorders, and autism spectrum disorders in individuals who do not carry the translocation. Numerous investigations have implicated DISC1 and interacting partners in neurodevelopment, adult neurogenesis in the hippocampus, and synaptic neurotransmission in adulthood.[47] In the context of this review, it has been shown that prenatal immune activation induced by poly I:C to mimic viral infection produces the behavioral abnormalities previously unseen in mutant DISC1 mice without prenatal challenge.[48] Therefore, combining genetic mutations and *T. gondii* infection may better model the pathogenesis of cognitive impairments in schizophrenia.

One needs to take into account timing of infection. Prenatal and early postnatal models of *T. gondii* infection

mimic different human conditions. Prenatal infection in rodents would be related to a situation where circulating antiparasitic antibodies in the blood of a pregnant woman may be potentially pathogenic due to cross-reactivity with the fetal brain.[49] In contrast, early childhood *T. gondii* infection seems to be best modeled by preadolescent infection in rodents to affect postnatal development of cortical areas involved in cognitive functions.[47] A quite different pathophysiological mechanism (eg, altered neurotransmission) could be modeled by infection of adult animals.

Last but not the least, new insights into the mechanisms of cognitive impairments in schizophrenia will be obtained with pharmacological studies similar to the one pioneered by Webster and her associates who treated the behavioral abnormalities in infected rats with antipsychotics and mood-stabilizer medications.[50] Further work is clearly needed in this direction with existing and new antiparasitic drugs, cognitive enhancers, and compounds targeting dopamine and GLU neurotransmission.

Conclusions

Available data suggest that *T. gondii* infection may contribute to cognitive deficits in people with schizophrenia. Such abnormalities may be subserved by different mechanisms, including alterations in GLU synaptic neurotransmission. However, there is a need to generate more sophisticated animal models of infection-induced cognitive dysfunction, likely through a combination of genetic and environmental factors, taking into account timing of infection and use of pharmacological approaches to further our understanding of the pathophysiology of cognitive abnormalities in schizophrenia. All such work will hopefully facilitate the development of novel therapeutics to aid those suffering from this devastating disease.

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