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Remaining questions in the relationship between *T. gondii* infection and major mental illness

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Brune and Theiss provided an evolutionary insight into our recent findings about the potential link between anti-*T. gondii* immunity and non-neuronal function of Disrupted In Schizophrenia 1 (DISC1) [1, 2]. Specifically, they propose that *T. gondii* may manipulate human behaviors by targeting the cells enriched in DISC1 expression, particularly von Economo neurons (VENs) in the anterior cingulate (ACC) and the anterior insula. VENs are atypical projection neurons known for their unique spindle shapes and have been identified more in humans than in non-human primates [3]. Altered number of VENs have been described in the behavioral variant of frontotemporal dementia (bvFTD), autism, and suicidal psychosis [4–6]. An earlier study also reported that DISC1 protein was preferentially expressed in these neurons in histology experiments [7]. Thus, Brune and Theiss hypothesized that the impact of *T. gondii* infection might be more profound in DISC1-enriched VENs than other cells [1]. Although this intriguing hypothesis needs further investigation, we generally agree with the authors on their concept that genetic variations in the cells more numerous and/or developed in humans, such as DISC1 variation in VENs, may play a critical role in the human-*T. gondii* interaction. Here we discuss additional remaining questions to be addressed in order to understand the biological mechanisms underlying the effects of *T. gondii* infection on the brain.

First, why does *T. gondii* infection lead to mental illness in some cases but not others? *T. gondii* seropositivity is highly associated with schizophrenia, but the seropositivity rate ranges between 10 and 60% across the human population and is usually higher than the frequency of schizophrenia [8]. Thus, not all patients with schizophrenia are seropositive for *T. gondii*. Accordingly, even if *T. gondii* infection participates in a causal process for schizophrenia, it only happens in a subpopulation of those infected and explains the causality only in a subpopulation of patients with schizophrenia. Thus, only individuals with

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genetic variations in the proteins critical for anti-*T. gondii* immune responses may lead to *T. gondii*-related brain dysfunction. In this regard, variations in non-neuronal proteins such as immune molecules could play key roles. With the recent discoveries of how genetic variations in immune pathways impact mental illness [9], there is now ample opportunity to explore the relationship between these genetic variations and *T. gondii* seropositivity. A larger cohort with blood samples will be central to the success of such a study. Indeed, a very recent study using a Danish cohort showed a promising result in exploring the relationship between pathogenic infections and major mental illness [10]. Further studies using these larger cohorts would identify various genetic variations associated with infections of pathogenic agents such as *T. gondii*. In addition, heterogeneity in *T. gondii* themselves should also be considered because different strains of *T. gondii* exhibit different virulence in infected animals [11].

Second, does *T. gondii* affect brain function by directly manipulating neuronal cells, or indirectly by inducing immune responses? As Brune and Theiss pointed out [1], mouse studies showed significant changes in emotional and cognitive behaviors with the presence of persistent *T. gondii* cysts in the brain [8]. Given our findings on the modulated levels of neurotransmitters such as glutamate, GABA, and dopamine by active *T. gondii* tachyzoites and/or cysts [8], we may be able to state that *T. gondii* could ultimately contribute to psychotic and cognitive changes by directly affecting neuronal functions. At the same time, systemic and brain immune responses play a critical role to establish the formation of *T. gondii* cysts in the brain. *T. gondii* initially infects the gastrointestinal tract and then circulates through the body to reach the brain [12]. Any immune dysregulation during this phase of infection could influence the brain, as has been shown in numerous studies on the modulation of brain function and behavior by pro-inflammatory cytokines. Thus, we postulate that multiple cell types in the brain and the periphery and, accordingly, multiple genetic variations are involved in the influence of *T. gondii* infection on brain function.

Third, when does the impact of *T. gondii* infection occur in the course of mental illness? It is well established that maternal infections during early pregnancy causes congenital toxoplasmosis, which includes neurological and cognitive impairments [12]. Does *T. gondii* influence brain development during pregnancy in the case of major mental illness? Indeed, some epidemiological studies showed that high maternal *T. gondii* IgG was associated with the risk of schizophrenia in adult offspring [13]. However, other epidemiological studies observed high *T. gondii* IgG in patients with schizophrenia [8], which suggests that postnatal *T. gondii* infection may confer the risk of major mental illness. Although animal models could be useful for exploring the causal role of prenatal and/or postnatal *T. gondii* infection in brain dysfunction, the response of humans and laboratory mice to *T. gondii* infection are quite different [11]. Thus, more mechanistic studies are necessary using human cells. In this regard, a rodent model with humanized immune system or a primate model may be helpful for future studies. In particular, recent studies on laboratory mice with “wild-type” microbiota [14], or human brain cell/tissue models [15, 16], might bring about a breakthrough in studying the interaction of *T. gon*dii and brain cells in a human-relevant condition.

In conclusion, we expect that an interdisciplinary effort among epidemiologists, neurobiologists, parasitologists, and immunologists would eventually determine the actual

role of *T. gondii* infection in mental illness. A large consortium-based research effort focusing on the role of pathogenic infections in major mental illness may be required.

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