Toxoplasma Gondii Stimulates The Behavioural Changes of Rodents: Updated Evidence

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Abstract
In recent years, there have been an increased number of reports in the literatures on animal behavioural changes linked with intracellular protozoan Toxoplasma gondii. Evidence for animal behavioural changes with Toxoplasma gondii infection comes from experimental tests on animal models such as mice and rats. These studies describe the important mechanisms of behavioural changes which involving neuromodulator and neurotransmitter level. Furthermore, behavioural changes also have been identified in human as well as animal models that may also play a role in development of schizophrenia in humans.

Keywords
Toxoplasma gondii, behavioural changes, mechanism, schizophrenia.

Introduction
Toxoplasma gondii is one of the most common intracellular protozoan which infects most worldwide population leading to toxoplasmosis. Generally, toxoplasmosis was infected among species of warm-blooded animals including human as an intermediate hosts and the member of Felidae family mostly a cat1. Cat mostly acts as a definitive host which T. gondii undergoes a phase of sexual reproduction in the small intestine of the cats to culminate the formation of oocysts. The cat shed the oocysts of parasite in the environment2. The asexual reproduction occurs within warm blooded animals such as rodents and other intermediate hosts when they ingested the oocysts3. The complete life cycle of T. gondii occurs when the Felidae family consumes an infected intermediate host which enhances the transmission of parasites. Thus, the presence of parasite stimulates in the brain of infected rodents causing behavioural changes which increases the rate of predation4. In addition, previous study by Vyas and Berdoy showed that infected rodents affects its physiological function leading to behavioural changes are mostly specific due to Toxoplasma invasion blocks rodent aversion toward cat predator odor5,6. The infection of this parasite is significantly related to toxoplasmosis which is associated with economic, medical and veterinary importance3. Thus, the term T. gondii has referred as protozoan parasite belonging to phylum Apicomplexa and classified into coccidian subclass7. Infection with T. gondii is one of the most common parasitic infections in man. It is considered as the most successful protozoan parasite of warm-blooded animals. It has been found worldwide from Alaska to Australia. Approximately one-third of humanity has been exposed to this parasite. Serologic surveys indicate that T. gondii infections are common in wild carnivores including pigs, bears, felids, fox, raccoons, and skunks8. Previous study reported by Lafferty showed prevalence levels vary widely, depending on exposure, but may surpass 50% in dogs, rabbits, and sea otters; 60% in mice, rats, and wild birds; and 70% in cats, bears, deer, and humans9,10. Another study has reported that T. gondii are highly prevalent to manipulate rodent behaviour, thus enhance the likelihood of transmission to its definitive cat host11.

Prevalence of T. gondii infections in humans may be acquired by ingesting the raw or uncooked meat that contained the tissue cysts or contaminated water with oocyst. On the other hand, they became directly infected when they accidentally ingest oocysts from the environment. However, the probability of exposed adult humans and other animals getting the disease with clinical symptoms is less percentage12. Moreover, animals were easy to get infected with T. gondii as they served for food such as pigs, rabbits, and sheep. Meanwhile, horses, buffaloes, and cattle were less infected than sheep and pigs. Thus, the transmission may be occurring as humans consumed the food. In addition, food animals containing T. gondii may survive for years in tissue cysts13.

Susceptible hosts
Infection of Toxoplasma, mostly acute phase occur after the oocyst ingestion which containing sporozoites or bradyzoite. By entering the host, infective stage occur where the tachyzoite stage was form which differentiate within nucleated cells. This result ruptures of the host cell and dissemination of haematogenous through the body.

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Moreover, a protective response of immune system will develops by converting the tachyzoite to bradyzoite after acute stage. Congenital infection can be defined as a primary infection during pregnancy which leads to abortion or stillbirth. In cases of congenital infection refer to a newborn which might be develop the major ocular and consequence of neurological when exposed to T. gondii. In immunocompromised patient who suspected with acquired immunodeficiency syndrome (AIDS) and patient who undergoes organs transplantation have higher chances to get toxoplasmosis. In 1992, Luft, Remington & Sande published a paper in which they described immunocompromised-toxoplasmosis had a higher risk of disease which result in death among AIDS patient.

Toxoplasmosis in the immunocompetent host mostly does not showed the symptoms or remain as asymptomatic. In addition, rarely occurred, immunocompetent patients who infected with toxoplasmosis may present encephalitis, sepsis syndrome, myocarditis or hepatitis. Meanwhile, the ocular lesions are frequent in T. gondii-immunocompetent patients. Mood disorders are a set of psychiatric diseases and there are main types of mood disorders such as depression, bipolar diseases, anxiety disorders and schizophrenia. Recent evidence suggests that mood disorders are the disease based on the psychological test of depression or mania which showed the higher score in that test by using the large study of clinical specimens in China from the psychiatric patient. In addition, mood disorders noted as a challenging and serious disease which affect mostly the central nervous system (CNS) mainly brain region.

**Animal behavioural changes**

T. gondii, the cause of toxoplasmosis and it was categorized as a parasite could exploit the proximate mechanism that modulates social behaviours in vertebrates. The absolute behavioural effect of T. gondii infection from infected rodents is they are more attracted to the odour of cat urine, and thus enhanced the transmission of parasite. In immunocompetent patients who suspected with acquired immunodeficiency syndrome (AIDS) and patient who undergoes organs transplantation have higher chances to get toxoplasmosis. In 1992, Luft, Remington & Sande published a paper in which they described immunocompromised-toxoplasmosis had a higher risk of disease which result in death among AIDS patient.

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**Animal behavioural changes**

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Investigation of novelty has been widely abused in behaviour's neuroscience studies and brain function in rodents. Novel object discrimination (NOD) was first introduced by Ennaceur and Delacour (1988) based on reported in 1950 by Berlyne which stated that normal rats choosing a new object compared to familiar object by spending more time in new object. This method was developed as a method for studying the memory function. The previous study performed by Hodkova showed that the toxoplasmosis-infected mice were reduced in learning ability as a result of increasing activity in the wheel running test however showed the worst results in learning tests. Certain parasites, including a notable minority of vertebrates, appear to possess the mechanisms needed to manipulate the central nervous system (CNS) of their hosts. Whereas some of the behavioral alteration linked with infection are quite universal, for example, depressed feeding or general malaise/sickness, others appear remarkable in their specificity, subtle changes only a limited repertoire of host behavioural traits for apparent selective benefit to the parasite. Previous studies reported infection of T. gondii on adult male mice showed abnormalities in spatial recognition memory measured as lack of preference for either arm of the Y maze.

Open field test is a conventional method to understand the behavioural changes of the rodent to the novel environment. It has been reported that T. gondii infections affected the locomotor activity of the mice with significantly decreasing present in the number of entries to the central part of the open field arena, whereas in the peripheral part of the open field arena showed that infected mice was significantly different during the acute Toxoplasma invasion. Notably, rodent explored the peripheral area of unfamilier environment and later they will exploring into open area which is mostly in the centre of arena.

It was experimentally proven that behavioural changes stimulate the emotional status of the animals. During the acute and chronic phase of toxoplasmosis, the self-grooming was significantly presented the emotional status. The infected mice express less self-grooming compared to uninfected controls. This happened due to brain structures of the host is connected to emotional and natural defence behaviours which located in the amygdala and hippocampus region. The previous studies by Gatkowska showed that infected brain of rodents which has been altered by parasite infection was influenced by monoamine, serotonin and dopamine level during acute and chronic phase of Toxoplasmosis.

Elevated plus maze (EPM) and open field (OF) are routinely used to investigate basic and pharmacologically modified features of anxiety–related behaviour in murine models that measure the emotional behaviour and locomotor activity. Elevated plus maze was made of polyvinyl plastic with a specific measure of 50cm in the height with two open arms (30 x 8.5 cm) and two enclosed arms (30 x 8.5 x 17.5 cm). The model is a gold standard for anxiety testing. Besides that, T. gondii induced by anxiolysis was merely detected by elevated plus maze as it sensitivity to the effect of Toxoplasma infection due to “thigmotaxis” reflection model.

The open field test (OFT), a large area has mostly used determined the animal’s emotionality and represent an animal analogue of human depression. The test is simply methods for measuring the animal response to a novel environment. OFT is defined as a procedure where an animal is placed in an enclosed area and their behaviour activity is measured.

**The mechanism of behavioural changes of infected rodents**

Toxoplasmosis caused by intracellular T. gondii has the capability to change the behaviour of the intermediate host.
especially natural aversion towards cat scent hence increasing the predation rate. So far, however, there has been little discussion about the mechanism of behavioural manipulation that is still remaining unclear. In order to understanding the behavioural changes of toxoplasmosis, more researches have been done for identify the mechanism this effect which involved the parasite’s cysts in brain regions. Researchers have been suggested that neurotransmitter of dopamine level may be the one factor that involved in behavioural changes of toxoplasmosis.

Energy consumption and metabolites of active secretion are the major factors contributing in behavioural manipulation. Therefore, the parasite-induced behavioural changes in rodent may lead due to the inflammation by-product and encephalitis with infection of T. gondii. On the other hand, some hypothesis had been created and said that animal behavioural alterations may affect the neurotransmitters level due to the development of the tissue cysts in brain of Toxoplasma-infected mice. Human and animals are likely to get toxoplasmosis, which can lead to mental abnormalities and motor deficit. These effects have been shown in infected mouse on the previous studies conducted by Stibb which is reported the dopamine, homovanillic acid, norepinephrine, serotonin and 5-hydroxyindoleacetic acid were measured in infected mouse with acute and chronic toxoplasmosis.

Previous studies showed that the neurological basis of anxiety, which often use the reaction of potential prey to cat stimuli as a model, have found that blocking the normally anxiogenic N-methyl-D-aspartic acid receptors (NMDAR) in the amygdala, and provision of serotonin (5-HT) antagonists, causes rats to approach cat odors “fearlessly.” in much the same way that T. gondii–infected rats do. A significant differences in levels of homovanillic acid, norepinephrine, and in particular, dopamine have been observed between T. gondii–infected and uninfected mice; all are substances that mediate, among others, locomotor activity, mood, learning, memory, and cerebral blood flow.

Several studies have identified an association between dopamine with animal behavioral changes. Dopamine antagonist is used for treatment of psychiatric disorder which was detected in the brain of infected mice induced by the T. gondii. The parasite-induced behavioural alterations lead to an increase of dopamine level in neural cell of infected mice. Furthermore, dopamine metabolism may increase a cytokine level such as Interleukin-2 and IL-6 which precisely affect the neuromodulator level including dopamine (DA). A continuous production of pro-inflammation cytokines is necessary for resistance to acute and chronic T. gondii infection. However, the development of schizophrenia is identified when the unbalancing of dopamine level is detected in brain regions of mesolimbic and mesocortical area.

Affective disorders

The first systematic study of psychiatric disorders was reported in 1953, however from then on many research have been performed. As a consequence of T. gondii, it appears that neurotropism is causative factor of schizophrenia and the parasite of T. gondii. An intracellular Toxoplasma gondii that commonly infected human population mostly approximately 30-50% were considered as chronic infections. Meanwhile, acquired infection is considered as an asymptomatic stage in which the previous study reported that such infections may contribute to psychiatric and neurological signs. For example, the previous studies have demonstrated in the intermediate host of rodent showed that T. gondii infections kill its host and changes the behavioural repertoire of an infected rodent, thus enhances the transmission of the definitive host life cycle by increasing the predation by cats.

Recent studies indicate that infectious agents, Toxoplasma gondii, may contribute to some cases of schizophrenia. Schizophrenia is a serious form of neuropsychiatric disorder characteristic by changes of behavioural, emotion and thinking which causes mental illness in human. Approximately 1% of the population was affected by this disorder and several studies reported some cases of schizophrenia linked with the infectious agents, T. gondii. However, the genetic variants and environmental risk factors have been proposed to play a major contribution in the schizophrenia. In addition, mood disorders noted as a challenging and serious disease which affect mostly the central nervous system (CNS) mainly brain region. Brain disorder is the faster increasing rate in developing and developed country.

Previous study suggested that T. gondii infection lead to the brain tissue damage which induced schizophrenia. The transmission of T. gondii to humans occur in various ways such as raw and undercooked meat containing tissue cysts, drinking water contaminated with oocysts and risky cat contact; oocysts deposited in the soil. For this reason, several attempts have been made to show a correlation of T. gondii antibodies in schizophrenia patients and other several psychiatric disorders. In addition, acute toxoplasmosis infection in individual of immunocompetent also showed an increased incidence of psychiatric disorders likes bipolar disease. Furthermore, studies conducted by researchers show that alteration in psychomotor performance and delayed in reaction time have been demonstrated in animal models as well as human who have been infected with T. gondii. Previous studies have reported humans with chronic toxoplasmosis have increased mortality or risk of traffic accidents associated with schizophrenia. This happened due to the prolongation of reaction time.

The mechanism of T. gondii infected a human being is not known, however alterations in neuromodulation involving specific system and direct impact on the brain and interaction of gene-environment are hypothesized. Several studies investigating the mechanism for behaviour analysis in human brain have been carried out on brain activity alteration during T. gondii infection. Recently, in vitro studies have shown that T. gondii can produce an enzyme for dopamine synthesis which characterized by tyrosine hydroxylase. Dopamine is an important component in the neuromodulation system.
and play a key roles in attention, learning and motivation, mood, sleep patterns and sociability, however alteration in dopamine level in brain will lead to neurological condition. Additionally, Prandovszky studied in vitro of PC12 cells also have been identified that cyst of T. gondii rise the dopamine releasing. Thus, the first neurotransmitter has been demonstrated by a higher concentration of dopamine which affects the brains of T. gondii-infected rodent and humans indicate in schizophrenia.

Recent evidence suggests that the mechanism of schizophrenia is associated with metabolism of tryptophan and dysregulation of immune system. Tryptophan metabolism involves an essential amino acid (tryptophan) used as a protein and basic precursor of the neurochemical mediators such as serotonin and melatonin. Moreover, the deficiency of tryptophan causes diminished level of serotonin in brain and depression. Studies showed that more than 95% of L-tryptophan in mammals is catalyzed via the kynurenic pathway which involving two catalyzing enzymes; tryptophan 2, 3-dioxygenase (TDO) and indoleamine 2, 3-dioxygenase (IDO). Interesting, interferon-y (IFN-y) and interleukin-2 (IL-2) of immune response was responsible to stimulated the IDO activity by degraded the intracellular tryptophan which resulting in restricting the growth of T. gondii.

In immunological activity, T. gondii infection regulates a strong TH1 immune response such as IFN-y. In central nervous system, the induction of IFN-y plays a key role in controlling infection of T. gondii by regulating replication of tachyzoite and preventing toxoplasmic encephalitis, meanwhile favouring bradyzoite and formation of cysts. Since, IFN-y regulates IDO which degrades tryptophan (essential serotonin precursor) which reduced serotonin level. At the end, the imbalance and disturbance of cytokines lead to production of kynurenic acid (KYNA) in the brain and became the factor that contributing to psychotic symptoms as well as schizophrenia.

Cognitive deficits is a major problem in patient especially schizophrenia. Approximately, 85% of patients exhibit some degree of cognitive abnormalities. T. gondii infection play important role in development of cognitive dysfunction by affecting brain system such as glutamate (GLU) synaptic neurotransmission. Previous study in animal models showed that the kynurenic acid (KYNA) level is higher in the brains of T. gondii-infected mice. The kynurenine mechanism is regulated by up-regulation of tryptophan 2, 3-dioxygenase (TDO) in liver or/and indoleamine 2, 3-dioxygenase (IDO) induced by IFN-y. Additionally, humans with schizophrenia also have been demonstrated to be in higher level of KYNA. Moreover, KYNA plays a role as an endogenous NMDA receptor antagonist and the final product in central nervous system. It is blocking the nicotinic acetylcholine receptors which result in hypofunction of glutamatergic system. This is due to accumulation of metabolite (kynurenine) which linked to cognitive deficit.

Conclusion

This paper has demonstrated and understanding that Toxoplasma gondii can change animal behavior as well as in human with affect many mechanisms of neurophysiological and neuromodulator. More information on behavioural changes in humans and animals linked with Toxoplasmosis would help us to establish a greater degree of accuracy on this matter.

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Authors’ contributions

SSCO, MAMM, NM, and MO were involved in reviewing the manuscript and delivered intellectual content to the study. All authors read and approved the final manuscript.

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