THE RELATIONSHIP BETWEEN FELINES, TOXOPLASMOSIS, AND HUMANS: A LITERATURE REVIEW

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ABSTRACT

Toxoplasma gondii is a protozoan that causes the disease known as Toxoplasmosis (Ajioka & Morrissette, 2009). This parasite has been studied extensively since its discovery in 1908. Though it was discovered in the early 1900s and has been studied since it was first observed, its impact on behavior, personality, and the brain had long remained a virtual enigma. It was not until the early 2000s and more recent years that research started getting produced about the parasite and how it alters behavior. Recent studies have shown that Toxoplasma gondii can cause significant damage to brain regions, specifically the amygdala and the cerebral cortex (Ihara et al., 2016). Research findings have shown a correlation between infection with the parasite and aggression, suicidal ideation, intermittent explosive disorder, road rage, neuropsychiatric disorders, altered behavior, and personality changes (Coccaro et al., 2016; Desmettre, 2020). The purpose of this literature review is to further explore and synthesize the relevant literature to understand the disease and its impact on behavior more thoroughly.

INTRODUCTION

The following literature review will examine the correlation between all mammals and toxoplasmosis but will start by examining the Felidae family (hereinafter referred to as "felines") and toxoplasmosis. Research on how the parasite impacts felines and rodents has offered promising findings and resulted in the discovery of the parasite. Additionally, felines are the only hosts that the parasite undergoes sexual reproduction in, based on available and published research (Carruthers & Suzuki, 2007). Felines can carry a parasitic disease called toxoplasmosis. Felines first receive the *Toxoplasma gondii* parasite from mice and other rodents before passing it to *Homo sapiens sapiens* (hereinafter referred to as "humans"). Felines can also be infected by *T. gondii* through contact with feces from another cat that is shedding the parasite (Centers for Disease Control and Prevention [CDC], 2018). According to the CDC (2022), the parasite will typically become infective one to five days after it has passed in a cat's feces, and it can take up to two weeks for the cat to shed the parasite. The parasite can live for many months, contaminating soil, vegetables, fruit, grass, litter boxes, and sandboxes (CDC, 2022). More than forty million individuals in the United States alone carry the *T. gondii* parasite; however, a small percentage of individuals notice the effects of the parasite since the immune system customarily precludes the zoonotic disease from manifesting (CDC, 2018). The definition of toxoplasmosis will be included to gain a better grasp of the subject. Toxoplasmosis is commonly and best defined as a parasitic disease caused by the parasite *Toxoplasma gondii* (Mayo Clinic Staff, 2022). There are a plethora of ways that a *T. gondii* infection can occur, including consuming undercooked meat or shellfish, accidentally ingesting undercooked or contaminated meat or shellfish after handling them, and not properly washing hands—this occurs because toxoplasmo-

sis can be absorbed (CDC, 2018). Others include eating food that has been contaminated through contact with undercooked, contaminated meat or shellfish via knives, utensils, and cutting boards; consuming water that is contaminated with the parasite; receiving an organ or blood transplant that has been contaminated with the parasite; and transmission from mother-to-child (CDC, 2018). Additionally, it is important to mention that one can mistakenly swallow the parasite after contact with cat feces that contain *T. gondii*. For example, handling a feline's litter box could be a carrier (CDC, 2022). Ingesting oocysts is another way of becoming infected with the parasite (Carruthers & Suzuki, 2007; Vyas et al., 2007). A congenital infection with tachyzoites can also cause infection—what is particularly interesting about this way of infection is how it occurs. During the acute stage, tachyzoites are proliferated in numerous organs, and the parasite forms cysts in the brain that allow for chronic infection (Carruthers & Suzuki, 2007). Brain cells, astrocytes, and neurons may be infected, with some studies indicating that an infected individual's immune response is compromised due to the cysts embedded in the brain by the parasite (Carruthers & Suzuki, 2007). While damage to the brain, organs, and eyes can occur, many individuals that are infected with the parasite will be asymptomatic (CDC, 2018). As the CDC (2018) has stated, toxoplasmosis is an often overlooked yet serious disease. Scholarly articles and empirical research have been published on the subject, and the correlation between the disease and its overall impact on the brain, including subcortical structures, has merit. The context for this literature review is to further explore just how substantial the correlation is. The review will primarily focus on the connections found in various scholarly articles and how they apply to trends that are seen in society. The review will be organized by similarity in the concepts. Historical development in the field will also be expounded on since it is imperative to analyze this topic. Though there are a surfeit of recent and older studies that center around how one can best protect themselves from getting infected, the focus of this literature review will primarily be on behavioral changes in individuals infected with *Toxoplasma gondii* and how it impacts an individual and the brain overall.

REVIEW OF THE RELEVANT LITERATURE

If an individual were to extensively research toxoplasmosis, searching for relationships, gaps, contradictions, and common themes, interesting results would be yielded. Throughout the review process, there were some intriguing and somewhat confounding common themes. *Toxoplasma gondii* was first discovered and formally written about by Charles Jules Henry Nicolle, Louis Herbert Manceaux, and Alfonso Splendore (Ajioka & Morrissette, 2009). Some historians have asserted that Samuel Taylor Darling and Alphonse Laveran initially discovered the parasite (Ajioka & Morrissette, 2009). It is possible that Darling and Laveran misidentified *T. gondii* years before its discovery by Nicolle, Manceaux, and Splendore in 1908 (Ajioka & Morrissette, 2009). It was named in 1909 because of its shape, with *Toxoplasma* meaning "arc-like form," and the rodent it was first observed in, the *Ctenodactylus gundi* (Ajioka & Morrissette, 2010, p. 1593). Multiple studies have found that a toxoplasmosis infection greatly impacts rodents' amygdala, an almond-shaped structure that is formed by "many nuclei sorted into five major groups; basolateral nuclei, cortical-like nuclei, central nuclei, other amygdaloid nuclei, and extended amygdala" (AbuHasan et al., 2022, para. 1). The amygdala is a subcortical structure that is a part of humans' limbic system, a system that is vital for an individual's normal functioning and is predominantly involved with emotions, behavior, and memory (AbuHasan et al., 2022). The amygdala lies beneath the uncus situated in the temporal lobe (AbuHasan et al., 2022). One of the principal reasons that damage to the amygdala is so significant is because it can impact how the presence of a threat is perceived. Additionally, the amygdala regulates anxiety, aggression, fear conditioning, emotional memory, and social cognition (AbuHasan et al., 2022). Lesions on the amygdala can block certain unconditioned fear, while "electrical stimulation of the amygdala evokes fear and anxiety responses in humans" (AbuHasan et al., 2022, para. 2). A study conducted on rats that have lesions in the amygdala found that they have "reduced freezing in response to cats, cat hair, attenuated analgesia, heart rate responses to loud noise, and have reduced taste neophobia" (AbuHasan et al., 2022, para. 2). What is particularly interesting is that lesions in the amygdala "do not affect other

measures of fear such as an open arm avoidance in an elevated plus-maze in rats or analgesia to shock" (AbuHasan et al., 2022, para. 2). Lesions or trauma to the amygdala can cause the acquisition of active avoidance and passive avoidance of conditioned responses to be disrupted, which is also a significant finding since active avoidance is the escape from fear (AbuHasan et al., 2022). While emotions to fear and aversive stimuli are processed by the amygdala, it also plays a role in conditioning using stimuli of appetite (AbuHasan et al., 2022). There are even more specific functions that the amygdala has. In the dorsal amygdala, there is a cortical-like structure called the basolateral nucleus, or BLA (AbuHasan et al., 2022). The basolateral nucleus's job is to regulate behavioral and physiological responses to stress (AbuHasan et al., 2022). Fearful stimuli, stressful stimuli, and some drug-related stimuli are physiological responses to stressors, something that the central amygdala, or the CeA, plays a significant role in (AbuHasan et al., 2022). Additionally, the extended amygdala is associated with anxiety and stress (AbuHasan et al., 2022). The extended amygdala has also been named the bed nucleus of the stria terminalis, abbreviated to BNST (AbuHasan et al., 2022). In rodents, specifically mice and rats, there is an innate fear or aversion to felines; however, the *Toxoplasma gondii* parasite causes infected rodents to be attracted to the pheromone (Vyas et al., 2007). The "behavioral manipulation" hypothesis might explain how this parasite behaves. The hypothesis states that a parasite can alter the behavior of its host with the purpose of increasing efficient transmission or reproduction (Vyas et al., 2007). The rodents' aversion-turned-attraction supports this hypothesis with rodents' behavior being altered to increase the parasite's transmission. One study's findings suggest that the parasite affects fear memory through dysfunction of the cerebral cortex and the amygdala (Ihara et al., 2016). What is particularly interesting about the findings from this study is that the cerebral cortex suffers from more severe tissue damage than other regions in the brain (Ihara et al., 2016). This study measured neurotransmitter levels in both the amygdala and cortex – these areas were chosen because they are associated with fear memory expression. The researchers found that levels of dopamine metabolites were increased in the cortices of mice that were infected with *Toxoplasma gondii* when compared to the cortices of uninfected mice (Ihara et al., 2016). Contrastingly, serotonin levels were decreased just in the amygdala of infected mice, and norepinephrine levels were decreased in both the amygdala and cerebral cortex of infected mice. The cerebral cortex is the outer layer of compacted neurons on top of the cerebrum (Ihara et al., 2016). The cerebral cortex plays a significant role in intelligence, emotion, the ability to recall memories, reasoning abilities, the ability to make decisions, and the ability to process information (Cleveland Clinic, 2022). The cortex is about half of the brain's total mass (Cleveland Clinic, 2022). The cerebral cortex comprises of six layers of nerve cells, ranging from 14-16 billion nerve cells in the cortex alone (Cleveland Clinic, 2022). An additional article states that the human cerebral cortex contains around 16 billion neurons (Herculano-Houzel, 2009). The cortex is divided into four lobes known as frontal, parietal, temporal, and occipital—each lobe has its own functions and processes (Cleveland Clinic, 2022). Some researchers choose to examine the brain and classify the various areas of the cortex by three of the main functions instead of by the four divided lobes (Cleveland Clinic, 2022). The sensory areas of the cerebral cortex are responsible for receiving sensory information such as taste, flavor, touch, temperature, and pain (Cleveland Clinic, 2022). The motor areas are responsible for muscle movement and complex movement (Cleveland Clinic, 2022). The association areas are present in all lobes and are mainly responsible for personality, emotional behaviors, memory processing, and spatial awareness (Cleveland Clinic, 2022). Damage to the cortex can be caused by tumors, strokes, autoimmune diseases (e.g., lupus), or trauma (Cleveland Clinic, 2022). It is important to be cognizant of these structures, their functions, and their processes because the *Toxoplasma gondii* parasite prefers to embed itself in the neurons found in the cerebral cortex, and this is where significant brain tissue damage occurs (Ihara et al., 2016). Trauma to the cortex can result in memory problems, difficulty with problem-solving and decision-making, aphasia, apraxia, numbness in limbs, agraphia, difficulty generating memories, loss of or no sensation, hearing difficulties, color blindness, hallucinations, or total blindness (Cleveland Clinic, 2022). It would be plausible for an individual infected with the par-

asite to experience any one of these results of trauma to the cerebral cortex. Recent studies have placed an emphasis on how the parasite behaves once it has completed the final infectious stage in its life cycle. In immunocompromised individuals, toxoplasmosis may merely be a reactivation of quiescent parasites (Ajioka & Morrissette, 2009). Immunocompromised individuals are also more likely to suffer from blindness or death if infected (Seizova et al., 2022). However, little was known about how the parasite manipulates host cells until recently. A recent research study found that *Toxoplasma gondii* does have the ability to lay dormant while inside neurons and muscle cells by exporting proteins to the host cell that then suppress immune signals (Seizova et al., 2022). These exported proteins play a significant role in limiting interferon signaling—this explains why infected individuals are asymptomatic but seropositive if tested in certain cases. Interferon is a protein released to aid in the fight against a disease or virus, and the parasite needs to turn the signal off to survive (Seizova et al., 2022). This means that the parasite can remain undetected through manipulation of the host cell. Prior to this study, it was known that the parasite makes its own molecules and proteins during the stage to protect itself (Seizova et al., 2022). Perhaps one of the most interesting findings from numerous studies is the behavioral changes found in individuals infected with the parasite. Intermittent explosive disorder, suicidal behavior, and many psychiatric disorders are all associated with a *Toxoplasma gondii* infection (Coccaro et al., 2016). This study found that a *Toxoplasma gondii* seropositive status is associated with higher levels of aggression and impulsivity (Coccaro et al., 2016). Toxoplasmosis has been linked to impaired brain functioning and a spectrum of behavioral and neuropsychiatric disorders (Samojłowicz et al., 2018). One study sought to find the correlation between parasites in the brain and risky behavior, and the results indicated a positive correlation (Samojłwicz et al., 2018). In addition to causing brain damage and impairments in cognitive functioning, this virulent, adaptable, and highly transmissible parasitic disease is linked to several other diseases (Samojłowicz et al., 2018). The discussion of this study included the finding that there is a strong correlation between *Toxoplasma gondii* presence and an individual's propensity for risky behavior that could potentially lead to death (Samojłowicz et al., 2018). The findings of multiple research studies indicate that the parasite may be responsible for hundreds of thousands of deaths, including those that died in car accidents, work accidents, and suicides (Samojłowicz et al., 2018). Yet another study found that significant behavioral changes can occur after becoming infected. This study reports that *Toxoplasma gondii* is associated with schizophrenia, suicide attempts, and aggressive driving (Desmettre, 2020). This is another relationship and common theme found in previous articles cited. A more positive finding is that infection with the parasite is a consistent and positive predictor of activity pertaining to starting and maintaining one's own business (Desmettre, 2020). This is quite an interesting finding because it relates to what is known about damage to the amygdala. When toxoplasmosis infection occurs, it impacts the amygdala, which controls responses to fearful stimuli—those that are infected may be more willing to engage in behaviors they would not otherwise engage in (Desmettre, 2020). A literature review cited the strong correlation found between long-lasting *T. gondii* infections and behavioral changes, as well as the onset of neuropsychiatric disorders (e.g., schizophrenia) (Wohlfert et al., 2017). Another study included in this review used Cattell's 16-personality factor questionnaire and Cloninger's Temperament and Character Inventory personality test to test students and faculty at Charles University (Flegr, 2007). This study found that the personality of infected men led them to disregard rules and be more jealous and suspicious (Flegr, 2007). The researchers also wanted to examine the relationship between age/years of infection and personality factors. After examining the relationship, they found that superego strength significantly decreased in men and increased in women regarding the length of infection (Flegr, 2007). The same researchers tested psychomotor performance and found that those with latent infection had significantly poor performance and could not focus on the task at hand (Flegr, 2007). Additionally, traffic incidents and a higher incidence of *Toxoplasma gondii* antibodies have been associated with one another (Flegr, 2007). This study posits that the parasite alters not only one's behavior but also one's personality (Flegr, 2007). It is known how the zoonotic disease interacts and

impacts both rodents' and humans' behavior, with significant behavioral/personality changes in rodents and humans due to a toxoplasmosis infection; however, the research on the behavioral changes and symptoms in felines is relatively preliminary. There are virtually no articles that address the specific behavioral changes caused by toxoplasmosis in felines, with most articles focusing on the felines being vectors. Though it is not featured in a scholarly journal, the Cornell University College of Veterinary Medicine (2016) published an article on toxoplasmosis in felines. It addressed some of the symptoms that can be found in infected felines. Cases where symptoms are present are considered rare and this article also addressed how these unique cases are diagnosed. In most cases, an infected feline will have no symptoms or show any signs of disease. In the rare instance that they do, toxoplasmosis occurs when a feline's immune response cannot suppress the tachyzoites from spreading. Felines with suppressed immune systems are more likely to have symptoms of the disease, similar to how the disease interacts with immunocompromised individuals. An example would be a kitten or cat with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV). The common symptoms found in felines that show symptoms include fever, loss of appetite, and lethargy. Symptoms do depend on an acute or chronic infection and the location of the parasite. If the infection is targeting the liver, then jaundice may be present in the skin and mucous membranes—this can be described as a yellowish discoloration or tinge to the skin. Pneumonia may develop if the infection is in the lungs, resulting in difficulty breathing and a gradual decline in breathing ability. The feline's central nervous system and eyes might also be affected. Additional symptoms that can be concomitant with a *T. gondii* infection are inflammation of the uvea (uveitis), the retina, abnormal pupil size and responsiveness to light, blindness, hyperesthesia or an increased sensitivity to touch, difficulty staying coordinated, changes in personality, frequent circling and head pressing, ear twitching, difficulty masticating and swallowing, seizures, and a recent lack of control over urination and defecation (Cornell University College of Veterinary Medicine, 2016). This paragraph is interesting because it mentions how a feline might experience personality changes but does not elaborate on the changes. It can be inferred that the researchers are referring to changes in a feline's playfulness, decreased or increased grooming habits, changes in litter box use, increased vocalization, and/or changes in their social interactions (e.g., a usually friendly cat hissing at other pets and caretakers). Increased aggression may be common in felines and humans, and decreased levels of fear are typically only seen in the rodents studied, though damage to the amygdala can be found in most, if not all, hosts. A test is warranted when there are signs of the illness in the feline. A veterinarian will measure the presence of IgG and IgM, two types of antibodies to *Toxoplasma*, and high levels of IgG antibodies signify that a feline has been infected previously. High IgM levels indicate an active infection in the feline. If no antibodies are detected in a healthy feline, then this suggests it is susceptible to future infection and would shed oocysts for several days after. Clindamycin is the main antibiotic used to treat toxoplasmosis in felines, and corticosteroid may be required if the eyes are significantly inflamed. Another interesting connection between the impact of the disease on felines and humans pertains to the most severe and serious effects. Infected infants are likely to develop signs of the infection as they age; some signs are a loss of the ability to see and hear, intellectual disabilities, and possibly death (Cornell University College of Veterinary Medicine, 2016). According to the CDC (2018), poor coordination, fever, seizures, headaches, and death are common in immunocompromised individuals. Permanent structural changes are common in rodents and likely humans. One study induced latent toxoplasmosis in rats to investigate if the parasite genotype impacts the distribution, location, size of the tissue cysts, and/or lesions. They found that tissue cysts were located in all areas of the brain, and the cerebral cortex, thalamus, and cerebellum had higher tissue cyst densities (Dubey et al., 2016). Additionally, two of the eleven *T. gondii* strains displayed tropism for the colliculus and olfactory bulb (Dubey et al., 2016). The attraction to the pheromones present in the urine of felines might be partially imputed to the displayed tropism for the olfactory bulb. Interestingly, ocular and brain lesions were detected. The ocular lesions were located in twenty-three of the rodents' eyes two months post-inoculation. The sclera, optic nerve,

and retina were the areas where the lesions were predominately found (Dubey et al., 2016). The findings from a study conducted by Loeuillet et al. (2019) provide more parallels between the infection in humans and rats. They conducted a study similar to the one by Dubey et al. (2016) and assessed the hypervirulence of various strains of *T. gondii*. Rats that were infected with the Prugniad strain presented clinical signs and survived until two months after they were initially infected (Loeuillet et al., 2019). Another strain that was intraperitoneally inoculated in the rats was GUY008-ABE which presented no clinical signs during the first week post-infection; however, respiratory distress, asthenia, emaciation, and orbital hemorrhage were all symptoms that developed after ten days post-infection (Loeuillet et al., 2019). This study also found that damage to the liver, heart, brain, and lungs were also caused by infection. The researchers found a reaction of lymphohistiocytic vessels in the liver, focal inflammatory reactions in the heart and brain, and parasite granuloma in the liver and brain as a response to infection (Loeuillet et al., 2019). Additionally, there were an average of 482 cysts per brain in the rats that were more susceptible to hypervirulent strains (Loeuillet et al., 2019). The findings from this article are particularly interesting because they indicate that the hypervirulence in the rat model does parallel human infection. There already were a surfeit of studies conducted that examined precisely how this parasite groups felines, rodents, and humans together, but this article cements the relationship between those three groups and the significance of the correlation. Studies on this subject over the years have very similar findings and/or common themes. The relevant literature shows that the current state of research indicates that significant advancements have been made to better understand how this parasite behaves and interacts with its intermediate hosts and definitive hosts while still illustrating the need for far more research to be conducted on the subject. These studies have significant relationships, with many of them reporting similar findings. Toxoplasmosis is an overlooked parasitic disease that relates to behavior, personality, and the brain in more intriguing ways than one. The studies reviewed also orient the relationship between felines, toxoplasmosis, and humans by providing more background and insight into the parasitic disease. The studies that examined infected individuals' ages and the duration of their infection helped provide more insight into the long-term effects of the disease and how it impacts one's body and brain.

CONCLUSION

Toxoplasma gondii has the ability to effectively manipulate its host to ensure transmission and survival (de Medeiros Brito et al., 2022; Seizova et al., 2022). The review of relevant literature has substantiated many postulations regarding just how significant the impact of toxoplasmosis on the brain and other cognitive functions is. In addition to increasing aggression levels, suicidal ideation, suicide attempts, and aggressive driving, *Toxoplasma gondii* has been linked to the impairment of perineuronal nets, which control plasticity as one of its primary functions (de Medeiros Brito et al., 2022). Research studies have also found that the cerebral cortex and amygdala are predominately negatively impacted by *Toxoplasma gondii* (Cerebral Cortex, 2022; Ihara et al., 2016). Some recent studies have found that driving accidents are more likely to occur in those that have been formally diagnosed with toxoplasmosis (Flegr, 2007). One of the most interesting correlations is the parasite and the development of neuropsychiatric disorders, such as schizophrenia (Cocarro et al., 2016; Desmettre, 2020). There does not appear to be literature available that specifically focuses on the development of schizophrenia after becoming infected with toxoplasmosis; however, multiple research studies and literature reviews have reported on the correlation. This begs the question: Does *Toxoplasma gondii* cause schizophrenia to develop in those already predisposed to it? This idea might have merit considering these preliminary findings and because damage to certain areas in the brain can contribute to the development of many other neuropsychiatric disorders. Another interesting avenue to explore would be delving deeper into intermittent explosive disorder and how it relates to toxoplasmosis. It is known that rodents will become attracted to the urine of cats after they have contracted the disease, which is believed to be caused by damage to the amygdala and olfactory bulb (AbuHasan et al., 2022). Given that there is increased aggression and an increased risk of neuropsychiatric disorders in individu-

als that have been diagnosed with toxoplasmosis, research on rises in crime and toxoplasmosis could be the foundation for future study. The CDC (2018) have stated that more than forty million individuals in the United States carry the parasite, and the percentages are rising yearly. This trend could be moving in the same upward direction as current crime rates. However, it is important to mention that correlation does not imply causation. It is possible that they could be correlated but without causality. An additional future study could examine whether or not certain predispositions might increase one's risk of aggression after contracting the parasite. This could explain why certain individuals exhibit more negative signs or appear more aggressive than others. How the disease impacts the way humans act toward other humans is a future study that would also likely yield interesting results. Since rodents have decreased response to fearful stimuli after infection and become attracted to the pheromones of felines, it would be interesting to further examine how humans react to the scent of felines and how they react when in a situation that would customarily cause fear. One limitation requiring further research pertains to the regions where the cysts have been observed. Currently, with the available research and studies in mind, the regions in the brain that are impacted the most by the parasite are the amygdala and the whole cerebral cortex; however, further research is warranted to be able to definitively declare this. The focus on new research could surround observing the areas in which region the parasite is most frequently found and why. There do not appear to be any significant gaps or critical flaws in the existing literature base, just some unanswered questions that can be answered by future studies on the subject. The findings from these studies have applications that span multiple disciplines, such as forensic psychology, neuroscience, and biology. The findings from research on this subject illustrate the need for regular screening and more resources dedicated to preventing and treating toxoplasmosis before it results in brain damage or neuropsychiatric disorders.

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