# A Systematic Review: *Toxoplasma gondii* infection and Drugs of Abuse

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## Background

***Toxoplasma gondii (T. gondii)*** **is one of the most common parasites that infect humans, existing in approximately 40 million people in the U.S.**

**Chronic *T. gondii* infection has shown to cause behavioral changes in rodents and humans due to presence of cysts diffusely localized throughout the brain, including the ventral tegmental area (VTA), a key player in dopamine transmission.**

***T. gondii*** **can directly or indirectly influence dopaminergic activity in infected cells potentially linking the infection to the development of neuropsychiatric disease, such as schizophrenia, however this mechanism is not fully understood.**

**Likewise, drugs of abuse continues to be a major public health crisis, contributing to neurotoxicity, inflammation, and potentially leading to the development of substance use disorder (SUD).**

## Objective

**Investigate various drugs of abuse and their associations with *T. gondii* infection in the context of dopamine metabolism and inflammation.**

## Methods

**A systematic review of controlled studies on *T. gondii* infection and substance use effects in adults was searched on the electronic databases PubMed, Web of Science, Google Scholar, and Scopus till 30 November 2022.**

**Relevant studies were identified using keywords, "T. gondii infection", "Toxoplasmosis", "T. gondii and drug use", "T. gondii infection, dopamine, and drugs of abuse". The quality of the studies and the results were analyzed.**

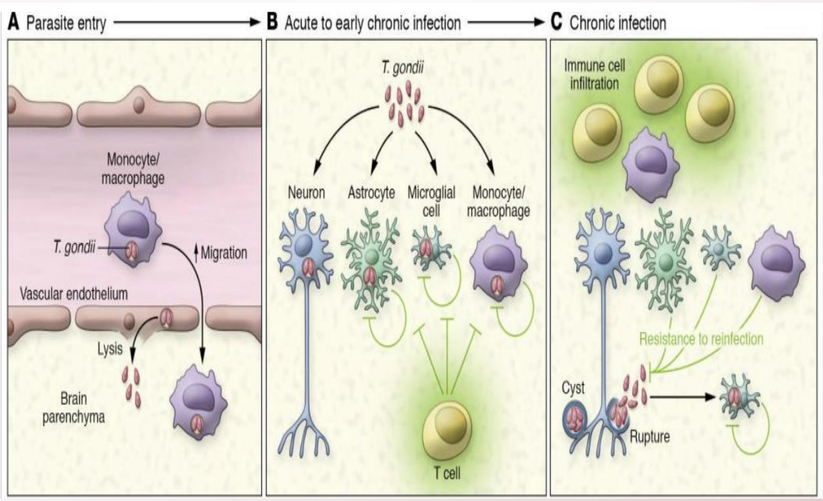
## Results

### Drugs of abuse and the brain

| DRUG OF ABUSE | INFLAMMATORY EFFECTS | NEUROPHYSIOLOGICAL EFFECTS |
|---|---|---|
| AMPHETAMINES, COCAINE, AND OTHER PSYCHOSTIMULANTS | Chronic amphetamine use and cocaine use results in neurotoxicity marked by activated microglia and astrocytes respectively, causing secretion of proinflammatory cytokines. However, a decrease in proinflammatory cytokines has been shown in active cocaine users as well.<br><br>Chronic cocaine use is implicated in HIV-1 associated neurological complications through enhanced replication, increased blood brain barrier permeability, and secretion of cytokines that decline CD4+ T cell counts. | These drugs act on the brain by increasing the availability of norepinephrine, dopamine, and serotonin at the synapse thus changing behavior and providing a sense of euphoria, alertness, agitation, and hyperactivity.<br><br>Additionally, the inhibition of dopamine and monoamine reuptake can result in imbalanced free radical accumulation leading to oxidative stress and neuroinflammation. |
| ALCOHOL | Alcohol demonstrates increased NF-kB activation leading to upregulation of proinflammatory cytokines in the brain.<br><br>Chronic alcohol consumption induced microglia activation and peripheral macrophage infiltration in the CNS. | Alcohol acts on the brain by exerting inhibitory or excitatory effects on dopaminergic, NMDA, and GABAergic systems, with chronic use increasing tolerance and addiction.<br><br>Alcohol abuse alters neuroplasticity and neural circuitry thus accelerating cognitive decline, and further causing brain injury making the brain more susceptible to foreign toxins. |
| OPIOIDS | Heroin abusers have lower levels of proinflammatory cytokines after immune cells *in vitro* were stimulated by LPS.<br><br>Opioids alter blood brain barrier permeability through the upregulation of pro-inflammatory cytokines and tight junction protein disruption. | Opioids provide analgesic properties by acting as agonists primarily on the mu opioid receptors distributed throughout the central and peripheral nervous system. |
| HALLUCINOGENS | LSD has shown the ability to suppress the proliferation of B cells and the production of pro-inflammatory cytokines IL-2, IL-4, and IL-6 in in vitro splenic lymphocytes derived from female rats.<br><br>A human study looking at ayahuasca effects in healthy volunteers observed a decrease in CD4 and CD3 cells and an increase in natural killer (NK) cells compared to placebo group and subjects treated with D-amphetamine. | Hallucinogens primarily function through the serotonergic pathways by binding to and activating the 5-$HT_2$ serotonin receptors.<br><br>Long term users can develop persistent psychosis or hallucinogen persisting perception disorder (HPPD) both of which are often seen in people who have a history of mental illness. |
| MARIJUANA | Cannabinoids obtain immunosuppressive properties exhibited by the decrease in TNF-a, IFN-y, and GM-CSF levels. | Marijuana acts by activation of cannabinoid receptors located throughout the central and peripheral nervous system., with chronic use resulting in emotional lability, anxiety, insomnia, hyperreflexia, and diaphoresis. |

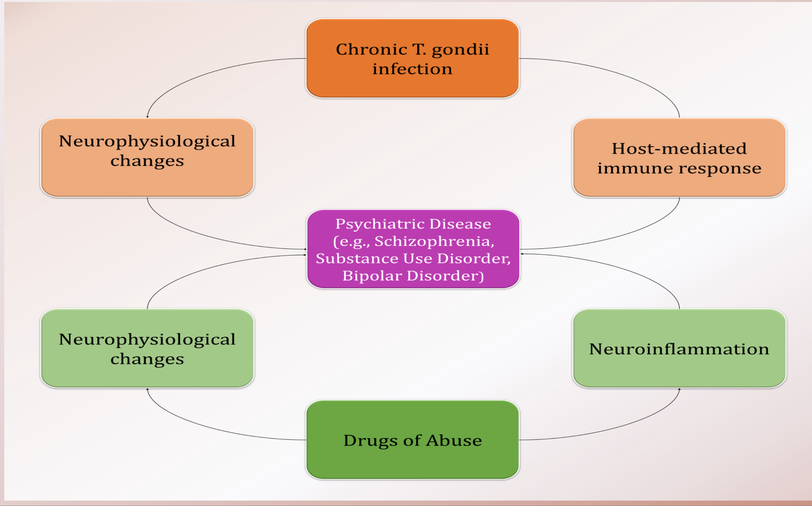
### T. gondii infection in the brain

Figure 1: Toxoplasma gondii infection from acute stage to chronic stage of infection




### Key Findings

Figure 2: Mechanisms of T. gondii infection and drugs of abuse linked to psychiatric disease




## Future Directions

**These preliminary findings pose the question of whether SUD is a potential risk factor for the development of behavioral and psychiatric complications associated with *T. gondii* infection.**

**Further research is necessary to understand the mechanisms associated with dopamine metabolism and inflammation regarding drug dependence in the context of *T. gondii* infection.**