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Chapter 19 *Toxoplasma gondii*, the Immune System, and Suicidal Behavior

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19.1. INTRODUCTION

Each year suicide leads to the tragic and premature deaths of over 1 million individuals around the world with an estimated annual mortality of 14.5 per 100,000 people. This translates to one death occurring every 40 s. Suicide is the 10th leading cause of death, making up 11.5% of all deaths (Hawton and van Heeringen 2009), though this burden is probably underestimated considering many third world countries appear to underreport suicide 9–10 times the actual amount (Hawton and van Heeringen 2009). While suicide rates have remained constant for the last decade, the three greatest causes of death (heart disease, cancer, and cerebrovascular disease) have all seen a decrease in death rates in this time period. Two of the most important risk factors for suicide are history of past suicide attempt (Harris and Barraclough 1997; Mann 2003) and a history of mood disorder. Every suicide is preceded by an estimated 8–25 suicide attempts, and 4% of depressed individuals die from suicide (Hawton and van Heeringen 2009). Additionally, more than half of individuals who attempt suicide had a major depressive episode at the time of the attempt.

For the past 7 years, our team at the University of Maryland School of Medicine Mood and Anxiety Program has been focused on studying triggers and vulnerabilities for suicide originating in the *natural* environment, that is, physical, chemical, and biological. In particular, we have been interested in the highly consistent peaks of suicide (Postolache et al. 2010) during certain seasons and their possible triggers. Specifically, we have identified (1) a relationship between atmospheric peaks of aeroallergens and suicide attempts in women (Postolache et al. 2005), confirmed in Denmark (Qin et al. 2011), (2) a relationship between suicide and allergy (Qin et al. 2011), and (3) an increased expression of allergy-related cytokines in the prefrontal cortex of suicide victims (Tonelli et al. 2008b). We have also reported that intranasal administration of allergens induces animal behaviors that are analogous to certain suicide risk factors such as aggression (Tonelli et al. 2008a) and anxiety (Tonelli et al. 2009). Our intermediate conclusion is that molecular and cellular mechanisms involved in the allergic immune response might attenuate functional capabilities of areas of the prefrontal cortex to act as behavioral breaks via multisynaptic inhibition of infralimbic centers. Following this line of thought, if allergy (a misdirected immune response against innocuous substances that were “misperceived” by the immune system as invasive pathogens) is associated with suicidal behavior, one would expect real neurotropic parasites to also be associated with suicide behavior. This led us to investigate *Toxoplasma gondii* and the anti-*T. gondii* immune response. A possible connection between *T. gondii* and suicidal behavior was suggested by the relatively high seroprevalence, its neurotropism (Flegr 2007), the immune activation involved in the defense against the parasite leading to elevation of cytokines previously found related to suicidal behavior (see Section 19.3.2), the occurrence of induced self-destructive behavior in rodent models (Lamberton et al. 2008; Vyas et al. 2007; Webster 2007), behavioral changes in humans (Flegr et al. 2002), and the parasite’s association with mental illness (Niebuhr et al. 2008; Torrey et al. 2007). We will first briefly review the immune system and the evidence connecting immune activation with suicidal behavior, and then we will describe the immune response to *T. gondii*, followed by a description of the parasite and the evidence associating *T. gondii* infection with suicidal behavior.

19.2. IMMUNE SYSTEM

The immune system is charged with distinguishing self from nonself and attacking and eliminating the nonself. In particular, the immune system protects the individual from pathogenic microbes, their products, and neoplastic cells, while avoiding responses that could produce excessive damage of self-tissues and eliminate beneficial commensal microbes. The microbial defense system is comprised of two domains that include innate immunity and adaptive (or acquired) immunity (Turvey and Broide 2010). These two aspects interact to provide an integrated immune system (Figure 19.1).

19.2.1. Innate Immunity

Innate immunity (Chaplin 2010) includes anatomical and physiological barriers such as epithelial cell layers (e.g., intact skin), mucociliary clearance mechanisms (as seen in the respiratory tract), acidic pH of the stomach, bacteriolytic lysozyme in tears, saliva, and other secretions. Innate immunity also includes a number of soluble proteins and small bioactive molecules that are present in some body fluids or released from activated cells. Examples of soluble proteins and bioactive molecules involved in innate immunity include complement proteins, defensins, chemokines, free radical species, and lipid mediators of inflammation. The remaining aspect of innate immunity involves membrane-bound receptors and cytoplasmic proteins that target conserved microbial components shared by large groups of pathogens (Chaplin 2010).

Innate immunity (like adaptive immunity) has both cellular and humoral components. The various hematopoietic cells (i.e., macrophages, dendritic cells, mast cells, neutrophils, eosinophils, natural killer [NK] cells, and NK T cells) make up the cellular component, while complement proteins, LPS-binding protein, C-reactive protein, and other acute-phase reactants, antimicrobial peptides, and mannose-binding lectin make up the humoral component.

19.2.2. Cellular Components of Innate Immunity

A synoptic review of the principal cellular components of the innate immune system is presented below.

19.2.2.1. Monocytes and Macrophages

Both originate from myeloid stem cells and ingest microbes and particles bound to immunoglobulin, complement, or both (i.e., microbes and particles marked for clearance from the body). They produce nitric oxide, which is very effective in killing microbial pathogens, and are involved in both acute inflammatory responses and granulomatous processes. Activated macrophages produce large amounts of tumor necrosis factor (TNF), interferon gamma (IFN-γ), and interleukins 6 and 12 (IL-6 and IL-12). They play a regulatory role in adaptive immune response via the expression of IL-12 and INF-γ. Additional cells in the monocyte/macrophage lineage include microglial cells in the CNS, Kupffer cells in the liver, and Langerhans cells in the skin.

19.2.2.2. Dendritic Cells

The conventional dendritic cells are derived from myeloid precursor cells and express class I and II major histocompatibility complex (MHC). MHC enables the receptor on T cells to recognize processed antigen. Dendritic cells have the potential to express antigen-presenting cell (APC) function when stimulated. Plasmacytoid dendritic cells (so named because of their morphology) are a second type of dendritic cell capable of producing significant quantities of type I IFN, and possibly play a special role in antiviral host immunity and autoimmunity (Gilliet et al. 2008).

19.2.2.3. Neutrophils

These are important in combating bacterial infection because they are capable of engulfing bacterial pathogens, and produce reactive oxygen species that are cytotoxic to bacteria. They also engulf particulate matter, and have recently been observed to express significant quantities of IL-12, TNF, and certain chemokines (Chaplin 2010).

19.2.2.4. Natural Killer Cells

NK cells are related to both B and T lymphocytes because they are derived from the common lymphoid progenitor cell. They play an important and individual role in antiviral responses, and they also attack tumor cells (Paraskevas 2004).

19.2.2.5. Eosinophils,Basophils, and Mast Cells

Eosinophils are prominent in allergic responses. They possess prominent cytoplasmic granules containing toxic molecules and enzymes active against helminthes and other parasites. Basophils and mast cells are important in immediate hypersensitivity responses, and upon contact with selected antigens they release preformed and newly synthetized inflammatory mediators, including histamine, prostaglandins, and cytokines (Stone et al. 2010).

19.2.2.6. Antigen-Presenting Cells

Phagocytic cells of the monocyte/macrophage lineage and dendritic cells are referred to as Antigen-Presenting Cells (APC). They have the ability to "ingest" microbial antigen, process the antigen by proteolysis, and present them in forms (usually 9–11 amino acid peptides) that can activate T cells (see Section 19.2.3.2). Epithelial and endothelial cells may also be stimulated to produce MHC class II in the presence of INF-γ, and therefore act as APC to $CD4^+$ T cells at sites of inflammation (Chaplin 2010). In addition, other host cells that have been invaded by viruses or those that have become tumorous may also produce peptides (bound to MHC) capable of activating T cells.

19.2.2.7. Major Histocompatibility Molecules

MHC molecules are glycoprotein molecules present on the surface of cells and bind peptide fragments of proteins that have either been synthesized locally in the cell (self) or proteolytically processed from protein antigens ingested by phagocytosis (nonself proteins). MHC molecules are involved in the presentation of antigens to T cells (Raposo et al. 1997). If the T cell recognizes the protein as nonself, then a cascade of reactions is triggered, which ultimately results in the killing of the cell expressing the nonself protein (antigen). MHC molecules are also called HLA (human leukocyte antigen) antigens. There are two classes: MHC I (binds endogenous or "self" peptides) and MHC II (binds peptides derived from exogenous or "nonself" antigens).

19.2.3. Adaptive Immunity

The cellular component of the adaptive immune response includes T and B lymphocytes, while immunoglobulins secreted by B cells constitute the humoral component. Both T and B lymphocytes (T: thymus and B: bone marrow) are derived from the common lymphoid progenitor. After a period of development in the primary lymphoid organs (bone marrow and thymus), the lymphocytes migrate to the secondary lymphoid organs (spleen, lymph nodes, Peyer's patches of the gut, tonsils, and adenoids). The secondary lymphoid organs are the site of origin of adaptive immune response, often under the influence of innate immune system signals, resulting either directly from circulating pathogens or indirectly by pathogen-activated APC that have migrated to the secondary lymphoid organs. Lymphocytes that have developed in the spleen and lymph nodes move out and spread to the various parts of the body to initiate immune effector functions (Bonilla and Oettgen 2010).

19.2.3.1. T-Lymphocyte Families

T lymphocytes differ in terms of their effector functions. Those T lymphocytes involved in "helping" other T and B cells by enhancing immunologic cell responses are traditionally referred to as T-helper (T_H) cells. T_H cells express CD4 (cell surface molecules). Based on the predominant cytokines produced by the cells, T_H cells are further subdivided into T_H1, T_H2, and, recently, T_H17. T_H1 cells mainly produce IFN-γ and TNF-β, but not IL-4 and IL-5. T_H1 cytokines promote cell-mediated responses for killing of intracellular microbes. T_H2 cells primarily produce IL-4, IL-5, IL-9, and IL-13, but not IFN-γ. T_H2 cytokines enhance antibody production and allergic immune responses. T_H17 cells express IL-17, a family of six cytokines (IL-17A–F) some of which are proinflammatory and important in immune response to extracellular pathogens (Chaplin 2010).

19.2.3.2. Activation of T and B Cells

T-cell activation is initiated when receptors (T-cell receptors, abbreviated TCRs) on the T cells interact with antigenic peptides (9–11 amino acids) complexed with MHC molecules. The TCRs on $CD8^+$ T cells interact with peptides complexed with MHC class I, while TCRs on $CD4^+$ T cells interact with peptides complexed with MHC class II. Peptides bearing MHC class I are generally derived from proteins produced inside host cells and such proteins are encoded either by the host genome (e.g., cancerous cells) or intracellular pathogens (e.g., viruses). MHC class II peptides reside on APC and can be induced through stimulation of innate immune system (Bonilla and Oettgen 2010). The interaction of the TCRs with the respective MHC/peptide complex triggers a sequence of biochemical events that mobilize the molecular killing machinery in $CD8^+$ T cells (Paraskevas 2004).

Most of the B-cell immune activation and response to antigens involves T cells, but a few antigens are capable of eliciting an antibody response in the absence of T cells. Such antigens are called T-independent antigens (TI antigens). Proteins and glycoproteins that require participation of T cells to generate B-cell antibody response are referred to as T-dependent antigens (Bonilla and Oettgen 2010). T-dependent antigens initiate B-cell activation by first interacting with immunoglobulin receptors on the cells, and making them cross-link. Cross-linking of the receptors triggers intracellular signaling that makes the B cell capable of interacting with a T cell. The peptides can be formed from antigens that were internalized by interaction with the receptors on the B cell. Interaction of the peptide/MHC II with a $CD4^+$ T cell renders the $CD4^+$ T cell capable of aiding the development and differentiation of the B cells to antibody-producing plasma cells or memory cells (that rapidly produce antibodies when rechallenged with the same antigen). The first immune response to an antigen challenge is called the primary response and IgM antibodies of low affinity predominate during this phase. A second presentation of the same antigen results in a stronger and faster response by the immune system, and IgG of high affinity (or IgD and IgE) predominate at this stage (Schroeder and Cavacini 2010).

19.2.3.3. Cytokines

Cytokines are proteins representing molecular signals that the immune cells use to communicate with each other. They help modulate the immune system through their effects on numerous aspects of cell growth, differentiation, and activation (Commins et al. 2010). Cytokines are grossly classified as proinflammatory (Th1) and antiinflammatory (Th2).

19.3. NEUROIMMUNE INTERACTIONS

Interactions between the nervous and immune systems are increasingly being recognized, and neuroimmunology—the synthesis of neurobiology and immunology—is a rapidly evolving discipline (Bhat and Steinman 2009). Until recently, the central nervous system (CNS) was generally believed to be an immunologically privileged anatomical site (Tansey 2010), and this dogma was based on the observation that immune responses are blunted in the CNS. Furthermore, the blood–brain barrier (BBB) does not readily allow the passage of immune cells and molecules into the CNS. In addition, immune cells and other diffusible molecules from the periphery were thought to permeate the BBB only during infection, CNS trauma, and other significant insults. However, recent findings from various biological sciences indicate that regular cellular and molecular cross talk between the immune and nervous systems might occur even in the absence of any CNS pathology. It has also been suggested recently that the BBB becomes relatively more permeable with healthy aging (McAllister and van de Water 2009), as well as in systemic and distant inflammation.

A number of molecules involved in innate and adaptive immunity have been found to have dual roles in the immune system and normal brain physiology. Conversely, some molecules involved in the physiology of the CNS or its neurosecretory appendages have also been found to function as immune modulators. For example, complement molecules that function as opsonins in the immune system also eliminate synapses in the CNS; MHC, involved in antigen presentation, modulates CNS plasticity; and gamma amino butyric acid (GABA), an inhibitory neurotransmitter, also inhibits inflammation triggered by the immune system.

19.3.1. Neuroimmune Interactions in Mood Disorders

Through their modulation of neuronal anatomy and function, cytokines and other immune molecules have been found to impact neuropsychiatric functions such as mood and cognition. For example TNF-α and IL-1β, when present at pathophysiologically elevated levels, have the tendency to inhibit long-term potentiation and impair neuronal plasticity (Loftis et al. 2010). Neuronal synaptic plasticity describes the phenomenon whereby postsynaptic neurons are able to vary their response to presynaptic stimulation and long-term potentiation is a long-term increase in synaptic strength. Both synaptic plasticity and long-term potentiation are generally believed to be the basis for learning and memory (Berretta et al. 2008).

An accumulating body of evidence now supports the notion that neuroimmune interactions play a significant role in the pathogenesis of depressive disorders and other psychiatric conditions. An immune (inflammatory) activation

consequence is "sickness behavior," which is characterized by fatigue, sleep disturbance, appetite disturbance, decreased social interaction, and loss of interest in usual activities—all of which are also seen in major depressive disorder (MDD) (Dantzer 2009). Sickness behavior is mediated by proinflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-γ. Several studies have reported elevated levels of proinflammatory cytokines in patients with MDD even without any apparent infection or inflammation (Raison et al. 2006). A corollary to this is the finding that most antidepressant medication as well as electroconvulsive therapy (ECT) inhibit the production of proinflammatory cytokines (Müller et al. 2009).

In MDD, cellular, molecular, and morphological studies in animals and human subjects have demonstrated an imbalance between neuroprotection and neurotoxicity in favor of the latter (Duman 2009). Neuroimmune interactions are involved in the neurotoxic mechanisms of depressive disorder. Proinflammatory cytokines such as IL-2, IFN-γ, and TNF-α increase the activity of indoleamine 2,3-dioxygenase (IDO) and kynurenine monooxygenase (KMO), two enzymes involved in the metabolism of tryptophan. Tryptophan is an amino acid that serves as "raw material" for the synthesis of serotonin (a neurotransmitter). IDO catalyzes the breakdown of tryptophan to kynurenine, thus resulting in a relative tryptophan depletion. The shunting of tryptophan toward production of kynurenine makes tryptophan unavailable for serotonin synthesis ultimately resulting in low serotonin levels in the brain. Low serotonin has been implicated in the pathogenesis of depression (Dursun et al. 2001). In addition, suicide attempters (especially those with violent attempts) have been found to have significantly lower cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA), a key metabolite of serotonin, relative to healthy volunteers (Träskman et al. 1981). Kynurenine crosses freely from the periphery to the brain and from the brain to the periphery. It has recently been implicated in depression and depressive-like behaviors (Dantzer et al. 2011; Raison et al. 2010). Kynurenine metabolites are potent immunomodulators (Schwarcz and Pellicciari 2002); specifically under the influence of KMO, kynurenine is catalyzed to 3-hydroxykynurenine (3-OH-kynurenine) and quinolinic (QUIN) acid in a two-step process. Both 3-OH-kynurenine and QUIN can induce neurodegeneration through the induction of excitotoxicity and generation of neurotoxic radicals (Müller et al. 2009). These pathways have specific cellular substrate. For instance, the microglia are the cells responsible for the rate-limiting pathway of transformation of kynurenine via kynurenine 3-monooxygenase (KMO) to QUIN. Astrocytes are responsible for the transformation of kynurenine via kynurenine aminotransferases (KAT) I and II to kynurenine acid (KA) (Wonodi and Schwarcz 2010).

19.3.2. Immune Activation and Suicidal Behavior

In contrast to the number of published studies on immune dysregulation and mood disorders, only a few studies have identified a possible link between immune mechanisms and suicidal behavior. In one study (Nassberger and Traskman-Bendz 1993), the plasma concentrations of soluble interleukin-2 receptor (S-IL-2R) in medication-free suicide attempters were significantly higher than those found in healthy controls. Most recently, Janelidze et al. (2010) evaluated blood cytokine levels in 47 suicide attempters, 17 non-suicidal depressed patients, and 16 healthy controls, and found increased levels of IL-6 and TNF-α in suicide attempters relative to non-suicidal depressed patients and healthy controls. While this cytokine activation was found in the "periphery," IL-6 levels have also been reported to be elevated in the CSF of suicide attempters relative to controls (Lindqvist et al. 2009). Another study found elevated levels of Th2 cytokine mRNAs in postmortem brain tissue samples within the orbitofrontal cortex of suicide victims (Tonelli et al. 2008b). Microglia cells in the brain are capable of expressing cytokines, and significant microgliosis has been observed in the brains of patients who committed suicide (Steiner et al. 2008).

19.4. *Toxoplasma gondii* AND SUICIDE

T. gondii, a widespread neurotropic protozoan parasite (Ajioka and Soldati 2007), affects approximately one-third of all humans worldwide. Symptoms of infection range from none to minimal depending on the host's immune response adequacy. Congenital infection, occurring if a mother has a primary infection during pregnancy and passes it to the fetus, is relatively rare. Within the animal world, felids have been identified as the definitive host to *T. gondii*. It is within the cat's gut that the parasite can sexually reproduce and spread via oocysts. Humans may be infected by *T. gondii* via ingestion of the parasite's oocysts, which can spread from the feces of infected cats. Other routes of transmission include consumption of undercooked meat that has been infected with *T. gondii* cysts or ingestion of contaminated water. When

ingested by an intermediate host, the parasite spreads from the intestine to other organs, finally localizing in muscle and brain. In the brain, the parasite will hide within neurons and glial cells, intracellularly, ultimately in cystic structures. These structures have minimal exposure to cellular and molecular mediators of the immune system that contain the infection successfully, but fail to eradicate it. Previous research in rodents has revealed that *T. gondii* localizes in multiple structures of the brain, including the prefrontal cortex and predominantly the amygdala (Vyas et al. 2007). These areas have a primary role in emotional and behavioral regulation, and they show major histopathological changes in suicide victims (Mann 2003). It is possible that because *T. gondii* occupies these areas, *T. gondii* infection may disrupt the balance of affective and behavioral modulation and in turn elevate risk of suicide.

19.4.1. Immune Responses to *T. gondii*: Innate Resistance

Production of IFN-γ by T cells and NK cells is critical to resistance to *T. gondii*. In addition, IL-12 production is also critical as the absence of IL-12 incapacitates replication, probably via a reduced production of IFN-γ. Both IL-12-deficient as well as IFN-γ-deficient animals succumb to infection. The major source of IL-12 *in vitro* appeared to be the macrophages (Gazzinelli et al. 1993a,b), but more recent work *in vivo* points toward dendritic cells (which synthesize it) and neutrophils (which have it prestored in vacuoles to be released upon contact); thus, multiple cells types are involved in resistance (Pepper and Hunter 2007).

Two proximal signaling events are involved in the production of IL-12—first(Luangsay et al. 2003) is via the chemokines receptor CCR5 (and G protein–coupled signaling) and the second (Medzhitov 2001) is via toll-like receptors (TLRs). Downstream from TLRs, signaling involves MyD88 and TRAF-6, and from there it branches to either MAPK or IKK and NF-κB both signaling production if IL-12.

NK cells-mediated resistance of *T. gondii* has been clearly demonstrated by the successful resistance to *T. gondii* of SCID mice that have normal NK cells but lack T and B cells. IFN- γ derived from NK or T cells plays the major role in controlling *T. gondii*, with multiple downstream pathways including (a) priming phagocytes to produce leukotrienes and reactive oxygen intermediaries that kill the parasite and (b) depriving the parasite of tryptophan via activating IDO. There is evidence that TNF-α also plays a role, and the two cytokines act synergistically to increase activity of enzyme inducible nitric oxide synthase (iNOS) and nitric oxide production (Pepper and Hunter 2007).

In addition to the innate immunity mechanisms described earlier, adaptive immunity mechanisms including nongermline-encoded clonal receptors BCR and TCR are essential for long-term resistance. A major expansion of B cells results in high levels of IgM (acute infection) and IgG (chronic infection; Montoya and Liesenfeld 2004). These antibodies opsonize extracellular parasites and induce complement activation and lysis, as well as phagocytosis by macrophages. μMT mice, that lack B cells, are able to survive the acute phase of infection to *T. gondii* only to die from fatal toxoplasma-caused encephalitis <1 month postinfection. The role of T cells in *T. gondii* resistance is illustrated by the reactivation of infection in AIDS patients, as well as immunosuppressive therapies and cancers that lead to T cells deficiency in number or function (Israelski and Remington 1993; Israelski et al. 1993).

Initiation of the adaptive immune response is dependent upon presentation by accessory cells, of peptides derived from the parasite in the context of MHC molecules. The parasite-derived MHC class I molecules could be presented to $CD8^+$ T cells by any cells but most commonly by infected cells, while MHC class II molecules can be presented to $CD4^+$ cells by dendritic cells (predominantly), macrophages, and B cells (Pepper and Hunter 2007).

After priming, T cells acquire cytolytic properties against infected cells. However, in toxoplasmosis the main role of T cells is to produce IFN-γ for which controls parasite replication. In addition to Major Histocompatibility Complex/T-cell Receptor (MHC/TCR) interactions, co-stimulatory molecules such as CD28, ICOS (Inducible T-cell co-stimulator) and IL-2 production by $CD4^+$ cells all appear to contribute to adequate IFN-γ production.

19.4.2. Immune Manipulation of the Parasite

T. gondii uses the immune system to facilitate its spread. The manipulation of the immune system by the parasite starts in the small intestine, where *T. gondii* starts replicating in the lamina propria (Speer and Dubey 2005). Immature dendritic

cells are recruited by the chemokine-like activities of the parasite (Diana et al. 2005) in the small intestine (Luangsay et al. 2003), further amplified by inflammatory cells attracted at the site of infection. Dendritic cells and monocytes that cross the lamina propria in the intestine act as Trojan horses to safely disseminate *T. gondii* to its final tissue destination, including the brain (Courret et al. 2006). In order to survive, *T. gondii* must ensure not only its own survival, but also the survival of its host (it is unlikely that cats will eat corpses). Thus, *T. gondii* plays a sophisticated balancing game between signaling, allowing itself to be kept in check by the immune system, and also avoiding complete elimination by the immune system. From a molecular standpoint, one of the most important mechanisms is interference of the parasite with NF-κB and STAT1 signaling and activates STAT3, resulting in reduced production of IL-12 and inhibition of proinflammatory events (Pepper and Hunter 2007).

19.4.3. Pathological Immune Responses

Systemic inflammation, high levels of inflammatory cytokines, and flu-like symptoms occur during the acute infection (Liesenfeld et al. 1996). While replicating parasites may have a role, the immune-mediated (particularly $CD4^+$ cells) bystander effect is to the greatest extent the culprit (Mordue et al. 2001). Anti-inflammatory mechanisms involving TGF-β, IL-4, IL-10, and IL-5 are necessary to tune down or prevent hyperinflammation (Buzoni-Gatel et al. 2001; Gazzinelli et al. 1996; Nickdel et al. 2004). Other more recently discovered breaking mechanisms are MHC CD1 and the γδ T cells (Egan et al. 2005; Smiley et al. 2005). In fact, elevations of self-targeting antibodies (for instance, antithyroid antibodies) are also observed in chronic "latent" toxoplasmosis in contrast to other chronic or latent infections (Wasserman et al. 2009).

19.4.4. Toxoplasma in the Brain

T. gondii transforms from tachyzoite to bradyzoite forms under the pressure of the adaptive immune response. The bradyzoite live in cystic structures that persist for the life of the individual, occasionally release bradyzoite that are able to infect other cells and transform into tachyzoites for a brief time, considering the immediate pressure from the adaptive immune system. Immunodeficiency may result in toxoplasmic encephalitis. The ability to control *T. gondii* in the brain is a paradox for those who still believe in the brain as an immunoprivileged organ, considering the BBB that limits access to molecular and cellular mediators of inflammation, the small constitutive expression of class I and II molecules, and the absence of a lymphatic system. In mice models, dendritic cells, macrophages, $CD4^+$, and $CD8^+$ cells migrate to the brain and produce Th1 cytokines (Fischer et al. 2000; Hunter and Remington 1994). Prior to T-cell infiltration, astrocyte activation has been observed (Hunter et al. 1993). Astrocytes infected with *T. gondii* produce the proinflammatory cytokines IL-1, IL-6, and TNF-α (Fischer et al. 1997) as well as additional cytokines with a possible role in resistance, IL-12 and IL-10.

Essentially, the production of IFN-γ by T cells, in combination with TNF-α, is probably the most important factor for the control of *T. gondii* in the CNS, via activation of microglia and infiltrating macrophages and their production of NO controlling replication (Chao et al. 1993). Mice that lack TNF-α develop toxoplasma encephalitis, consistent with a recent report in a patient treated with anti-TNF who developed toxoplasma encephalitis (Young and McGwire 2005).

Thus, the immune response in the brain involves activation of immune mechanisms previously implicated in suicide and suicide risk factors—some involved in protection against *T. gondii* invasion, such as TNF-α (Janelidze et al. 2010), IL-6 (Janelidze et al. 2010), and microglia activation (Steiner et al. 2008), and others to minimize immune pathology, such as IL-4 and IL-5 (Tonelli et al. 2008b).

19.4.5. Fatal Attraction to Cats in Rodents

Normally, rodents display an instinctual avoidance of feline odors. However, infection with *T. gondii* induces not only a reduction in avoidance of, but also attraction to feline odors (Berdoy et al. 2000; Vyas et al. 2007). The attraction appears rather specific for felids and is not present for odors of other predators. The infected rodents therefore become more vulnerable to predation and correspondingly contribute, albeit unwittingly, to *T. gondii* reproduction. This striking phenomenon appears to be consistent with many well-documented examples of "behavioral manipulation" of the host

by parasite. In addition to the specific changes in behavior related to attraction to cats, nonspecific effects of decreasing neophobia (Hay et al. 1984; Webster 2007) have also been reported, though unconfirmed by other studies (Vyas et al. 2007). A decrease in neophobia might be a consequence of the functional impairment of fear circuits in the amygdala, where *T. gondii* predominantly localize (Vyas et al. 2007).

19.4.6. Toxoplasma and Suicide Attempts: First Reported Association in Patients with Mood Disorders

The first report of a relationship between *T. gondii* infection and suicidal behavior was reported by our group at the Mood and Anxiety Program at the University of Maryland School of Medicine (Arling et al. 2009).

Two hundred and eighteen individuals classified as having MDD or bipolar disorder by the Structured Clinical Interview for DSM-IV Disorders (SCID) (First 2003) along with 39 healthy controls had *T. gondii* IgG antibodies measured through solid-phase enzyme immunoassay as was previously described (Leweke et al. 2004). Titers of anti-*T. gondii* antibodies greater than 10 international units per individual sample were considered to be positive for seropositivity analysis purposes. Quantitative analysis for antibody levels (serointensity) was also performed using a ratio of the sample's optical density (OD) and a standard with 10 international units of anti-*T. gondii* antibody.

If patients failed to meet the criteria for either bipolar disorder or MDD or if they met criteria for cognitive disorders, psychotic disorders, or substance dependence, they were excluded from the study. A semistructured questionnaire, The Columbia Suicide History Form, was used to collect the history of suicide attempt (Oquendo et al. 2003). An individual's diagnosis or suicide attempt status was unknown to the laboratory staff.

Chi-square tests and one-way analysis of variance were used to compare demographic characteristics and *T. gondii* serointensity values of the three groups (i.e., mood disorder patients with and without history of suicide attempt and controls), which, because of their positive skew, were log transformed. Log-transformed *T. gondii* antibody titers were compared among groups using linear regression analyses, with adjustments for race (white or other), gender, and age. Geometric means with 95% confidence intervals were calculated by exponentiation of the mean log-transformed titers of *T. gondii* antibody, and are given for the comparison of adjusted and non-adjusted values of the three groups. Finally, logistic regressions were carried out with attempt status as dependent variables. SAS 9.1 (SAS Institute Inc., Cary, NC) was used to perform all statistical analyses, with $p < 0.05$ as a level of significance.

Patients with recurrent depression who previously attempted suicide had mean values for antibodies to *T. gondii* higher than either the patients with recurrent depression and no history of suicide attempts ($p = 0.04$), or the normal control group ($p = 0.12$). When adjusted for race, age, and gender, the suicidal patients with recurrent depression versus non-suicidal patients with recurrent depression had a greater mean IgG titer of 0.51 versus 0.37 ($p = 0.017$) (Figure 19.2). Logistic regression models revealed that serointensity predicted suicide attempts with OR of 1.55 (1.14–2.12), $p = 0.006$. However, there was a nonsignificant relation of seropositivity with suicide attempt, OR = 1.62 (0.72–3.65).

No significant difference was found between *T. gondii* positive and *T. gondii* negative patients when compared using Pearson's *chi-square* test in relation to proportion with versus without recurrent mood disorder ($p = 0.62$), proportions having MDD versus having bipolar ($p = 0.82$), or proportion with compared to without psychotic symptoms ($p = 0.66$). *T. gondii* antibody levels showed no difference in regard to subjects with versus without a mood disorder ($p = 0.22$), having MDD versus having bipolar disorder ($p = 0.55$), or with in comparison to without psychotic symptoms ($p = 0.34$).

Limitations of this study included the cross-sectional design, as well as an unmeasured difference among socioeconomic groups, which could explain the variations in suicidality and titers of *T. gondii* antibody.

19.4.7. Toxoplasma and Suicide Attempts: A Replication

An independent group in Turkey (Yagmur et al. 2010), 1 year after the Arling et al.'s report, published a study confirming the association between *T. gondii* IgG (but not IgM) antibodies and suicide attempts. They compared 200 psychiatric inpatients who had attempted suicide and 200 controls recruited from "case workers" and family members/visitors of patients, matched for age, gender, and urban versus rural residence. The IgG seroprevalence was

41% in the patient group and this was significantly higher than in the control group with a seroprevalence of 28% (p = 0.004 by chi-square test). This study, performed in a country with a higher seropositivity for *T. gondii*, identified not only serointensity but also seropositivity as related to suicidal behavior. All limitations of the Arling's (2009) study are also present in the Yagmur et al.'s (2010) study. In addition, the Yagmur et al.'s study does not have diagnostic information, and the patient group is likely more heterogeneous. If one would look solely at the Yagmur et al.'s study, it would be impossible to rule out the possibility that mental illness is in fact associated with *T. gondii* seropositivity. It has already been established that there is an increased rate of *T. gondii* seropositivity in psychotic disorders (see Torrey et al. 2007 for meta-analysis), and thus it might be possible that the individuals with psychotic illness present only in the suicide group "drove" the observed association. Teasing apart suicidality from psychosis requires a study comparing psychotic attempters and psychotic nonattempters. Some of these limitations are addressed in the next study.

19.4.8. *Toxoplasma gondii* IgG Antibodies and Suicide Attempts in Patients with Psychotic Disorders

Supported by a grant from the American Foundation for Suicide Prevention (PI Postolache, CoPI Rujescu), the project involved comparing suicide attempters with nonattempters in 950 schizophrenia patients (aged 38.0 ± 11.6 years) recruited in the greater Munich area of Germany (Okusaga et al. 2011). All the subjects in the study underwent the SCID (First 2003) and they provided written informed consent after the study procedures were explained to them in detail. Toxoplasma IgG antibodies were measured using methods previously described earlier (Arling et al. 2009). Logistic regression was used to determine whether *T. gondii* seropositivity and serointensity are associated with a history of suicide attempt, after adjusting for potential confounders such as age, sex, illness duration, illness severity, education, and plate. The logistic regression analysis revealed that in the schizophrenia patients younger than 38 years, the median age of the sample, *T. gondii* serointensity (p = 0.02) was associated with a history of suicide attempt (Figure 19.3). In the same younger age group (i.e., <38 years), *T. gondii* seropositivity was also associated with suicide attempt history (odds ratio 1.57; CI 1.03–2.38, p = 0.03). Finding the association in the younger subpopulation is particularly relevant considering that suicide-related mortality is relatively elevated early after the diagnosis of psychotic illness (Osborn et al. 2008). It is also important to note that the association of *T. gondii* with history of suicidal behavior is unlikely to have been mediated through symptom severity since *T. gondii* was not associated with symptom severity in this sample of schizophrenia patients.

A question arises: Could this relationship be an artifact, the result of a general immune activation, or antibody elevation in patients at risk for suicide? We tested this hypothesis by analyzing antibodies to a number of neurotropic viruses as well as a food antigen, gliadin, and found no differences, using identical methods with those used for *T. gondii* antibodies analysis, for the cytomegalovirus (p = 0.22), herpes 1 virus (p = 0.36), and gliadin (p = 0.92). Thus, the increase in *T. gondii* IgG antibodies in patients who attempted suicide is unlikely to be attributed to a general nonspecific increase in antibody production.

All these results presented so far are cross-sectional associations. The following study will have a model of predictive association, as the determination of *T. gondii* antibodies will precede (often by many years) suicidal behavior.

19.4.9. Predictive Association between *T. gondii* Seropositivity and Suicidal Behavior in Women

Participants in this study (Pedersen et al. 2012) were women living in five counties in Denmark from 1992 to 1995 and were originally recruited for a project on *T. gondii* neonatal screening. In order to test for phenyl ketonuria and other metabolic abnormalities, a heel stick blood sample was obtained 5–10 days after birth. Only the first birth was included in the study. Two 3.2 mm disks were obtained from the children whose mothers agreed to participate in the *T. gondii* study and analyzed using an enzyme immunosorbant assay (EIA) for *T. gondii* IgG antibodies (Lebech and Petersen 1995). The level of those antibodies was then given as a percentage of the OD obtained for the World Health Organization (WHO 1994) international standard serum. The IgG titer was calculated as the mean of the titers for the two disks. Mothers with children that had an IgG titer above 24 were defined *T. gondii* positive at the time of delivery. As IgG passes through the placenta, and furthermore an infected newborn will only begin producing the antibodies at an estimated 3 months of age (Wilson and McAuley 1999), the *T. gondii* IgG antibodies in child's blood were 100% of maternal origin.

The titers for IgG antibodies were cross-linked with information from the Danish Civil Registration System (Pedersen et al. 2006), the Danish National Hospital Register (Andersen et al. 1999), computerized version of the Danish Psychiatric Register (Munk-Jorgensen and Mortensen 1997), the Danish Cause of Death Register (Juel and Helweg-Larsen 1999), and the Danish Psychiatric Central Register (Munk-Jorgensen and Mortensen 1997). ICD 8 and 10 codes for deliberate self-harm and suicide attempts, as well as suicide, were analyzed.

Relative risk of deliberate self-harm after delivery was higher in seropositive women: Among 45,271 mothers, 488 had a first episode deliberate self-harm with 595,306 person-years at risk, corresponding to an incidence rate of 8.20 per 10,000 person-years. *T. gondii* seropositive women had a 1.53-fold (95% CI, 1.27–1.85, $p = 0.002$) significant relative risk of deliberate self-harm compared to *T. gondii* seronegative mothers. The risk of deliberate self-harm increased with increasing IgG level—stratified as quartiles (women with an IgG level above 71 had a relative risk of 1.89 [95% CI 1.42–2.46] compared to seronegative women). Contrary to our expectations, the association was stronger in women without a diagnosis of a psychiatric illness than in those with a psychiatric illness. There was no significant increase in repeated attempts in women who attempted suicide prior to testing in *T. gondii* positive women.

Relative risk of violent suicide attempt was higher in seropositive women: Seventy eight of 45,745 women had a violent suicide attempt during 603,876 person-years at risk (incidence rate of 1.29 per 10,000 person-years). The risk was 1.81 (95% CI, 1.13–2.84, $p = 0.014$) higher in *T. gondii* positive women when compared to *T. gondii* seronegative women.

Suicides (total 18) were too few to be analyzed with satisfactory statistical power. Nevertheless, the relative risk appeared to be nonsignificantly higher in women who were *T. gondii* positive, as compared to women who were *T. gondii* negative 2.05 (95% CI, 0.78–5.20, $p = 0.142$).

The major strength of this study is that, for the first time, it connects *predictively T. gondii seropositivity* with suicide attempts. Limitations include insufficient coverage for medical illness, not including women who did not give birth, and the potential-limited generalizability from Denmark to the rest of the world. Finally, this study was not powered to study suicides, but only attempts. It is unclear if associations with attempts would translate to associations with suicide. Our next study, even if preliminary, is a first connection of *T. gondii* with suicide.

19.4.10. National Suicide Rates Positively Correlate with Seroprevalence Rates for *T. gondii* in Women

Very recently, an abstract reported that seroprevalence for 20 European countries was significantly correlated with increased suicide rates (Lester 2010). Due to the fact that blood samples were taken from women only, we retested this association in women only, stratified by age (Ling et al. 2011, Figure 19.4). In women 60 years and older, simple correlations between ranked *T. gondii* seropositivity and suicide rate identified were significant ($p < 0.05$); adjusting for GDP, positive relationships also occurred in the 45 and above age group. After adjustment for GDP, the relationship ($p = 0.007$) resisted Bonferroni adjustment for multiple comparisons only in the 60–74 age-group (Figure 19.4). In conclusion, the results confirm a relationship between suicide and *T. gondii* seropositivity, especially in the postmenopausal age group. As the methodology is ecological, and thus prone to inherent fallacies, individually linked methodologies and prospective studies are necessary to further confirm the association.

In conclusion, cross-sectional studies in mood disorders (Arling et al. 2009), psychiatric inpatients (Yagmur et al. 2010), schizophrenic patients (Okusaga et al. 2011), a prospective cohort study in mothers (Pedersen et al. 2012), and an ecological study in Europe (Ling et al. 2011) strongly support an association between *T. gondii* and suicidal behavior.

What are possible mechanisms mediating the relationship between T. gondii *and suicidal behavior?* In addition to reactivation of the latent parasite (i.e., a direct effect), one of the important potential mechanisms is the host's immune system activation in response to *T. gondii* infection. Previous studies have demonstrated that the production of proinflammatory cytokines (Aliberti 2005; Miller et al. 2009) is an integral part of containing *T. gondii*. It is possible that the elevation of inflammatory cytokines IL-6 in the CSF (Lindqvist et al. 2009) and IL-6 and TNF in the plasma (Janelidze et al. 2010) that have been found previously elevated in those who attempt suicide may mediate the association of *T. gondii* and suicide behavior. The growth of *T. gondii* is blocked by the production of inflammatory cytokines, particularly IFN-γ resulting in activation of macrophages and lymphocytes (Denkers and Gazzinelli 1998) as

well as activation of the enzyme IDO. This results in relative tryptophan depletion (Miller et al. 2009) stemming from the IDO activation that starts a degradation tryptophan toward kynurenines. Local depletion of tryptophan decreases both the proliferation of *T. gondii* and the synthesis of serotonin, which may affect a number of suicide risk factors such as anxiety, impulsivity, and affective lability. Furthermore, IDO activation leads to production of kynurenine that further generates antagonists (kynurenic acid) or agonists (e.g., quinolinic acid) of the *N*-methyl-d-aspartate (NMDA) receptors and therefore alterations of glutaminergic neurotransmission (Dantzer et al. 2008). Recent findings on the activation of kynurenine pathways in suicidal behavior support this idea. Namely, violent suicide attempts, history of major depression, and IL-6 levels (Lindqvist 2010) have been found to be associated with kynurenic acid concentrations in the CSF. Our collaborative study with Dr. Mann's group at Columbia University has found that patients with mood disorders who have a history of suicide attempt relative to those without a history of attempts had an elevated level of kynurenine in plasma (Sublette et al. 2011) (Figure 19.5).

In addition, previous research has suggested that infection with *T. gondii* may elevate testosterone levels (Flegr 2007), and in turn that elevation in testosterone may lead to an increase in aggression, which has been identified as an intermediate phenotype in suicide (Kovacsics et al. 2009; Mann et al. 2009). Testosterone has been linked to the suppression of neural circuitry that is related to both impulse control and emotional regulation (Mehta and Beer 2010). This could help explain why the association between *T. gondii* and suicide is observed in older women, but not in younger women, whose androgens are balanced by endogenous estrogen and progesterone.

T. gondii infection may have the potential to heighten the risk factors that lead to attempting suicide. Joiner et al. (2009) presents a two-factor theory that states that there are two components that lead to attempting suicide when occurring simultaneously. The first domain is psychological, and it is expressed as a desire to die. This commonly results from a lack of the feeling of belongingness and a perception that one is a burden. The second domain is behavioral and is expressed as an acquired capability to attempt suicide through the habituation to the fear of death, dying, and the beyond; it is sometimes a result of witnessing or experiencing violence, or having painful and fearful occurrences.

T. gondii infection may contribute to the *capability* to engage in self-injurious behavior rather than just the increased *wish* to commit suicide. In experimentally infected immunocompetent rodents, *T. gondii* cysts are predominantly found in the amygdala, an area implicated in the expression of fear, of its host (Vyas et al. 2007), leading to a degree of atrophy of the dendritic tree and deafferentation. Furthermore, *T. gondii* contains two genes encoding tyrosine hydroxylase producing L-DOPA (Gaskell et al. 2009), which in turn may lead to an increase in dopamine and the ability to act on suicidal impulses and overcoming an innate fear of death. In additional to increased localization in the amygdala and olfactory bulb, *T. gondii* is localized in the prefrontal cortex (Vyas et al. 2007). Histopathological changes in certain areas of the prefrontal cortex, namely, the ventrolateral prefrontal cortex, have been implicated in suicidal behavior (Mann 2003). It is also possible that the ability of the prefrontal cortex to act as a behavioral "braking mechanism" on impulses and emotions produced in the subcortical structures of the limbic system is inhibited.

19.5. CONCLUSION

T. gondii is one of the most widespread parasites affecting approximately one-third of the population of the world (Montoya and Liesenfeld 2004), and ~60 million individuals in the United States (CDC 2010). Its unique ability to alter immune responses, to manipulate the immune system, and to alter behavior of the host could mediate an increased vulnerability to suicide attempts in those harboring the parasite. Not all individuals infected with *T. gondii* are at risk for suicide; most likely, a combination of predispositions, triggers, availability of means, and absence of protective factors and deterrents would be necessary. The intermediate mechanisms may include heightening of risk factors for suicide such as depression, impulsivity, aggression, arousal, and reduction of fear (especially fear of death). Considering the potential for new prognostic paradigms and etiological preventative interventions, this predictive association deserves future larger, longitudinal, and interventional studies.

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Figures

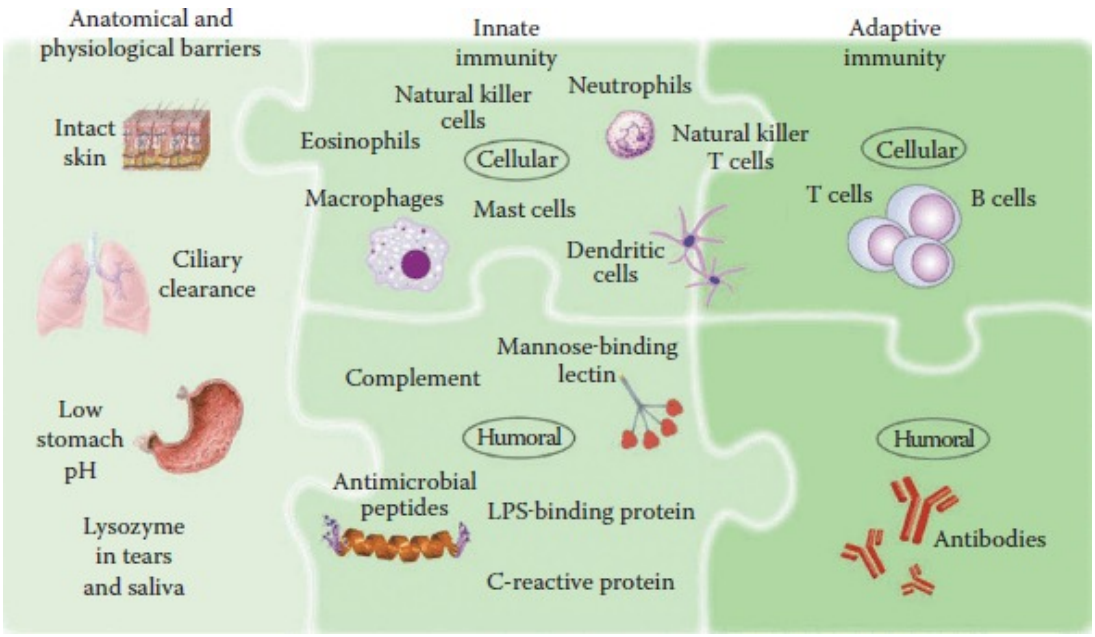

FIGURE 19.1

(See color insert.) Various subdivisions of the human immune system. (From Turvey, S.E. and Broide, D.H., *J. Allergy*, 25, S24, 2010. With permission.)

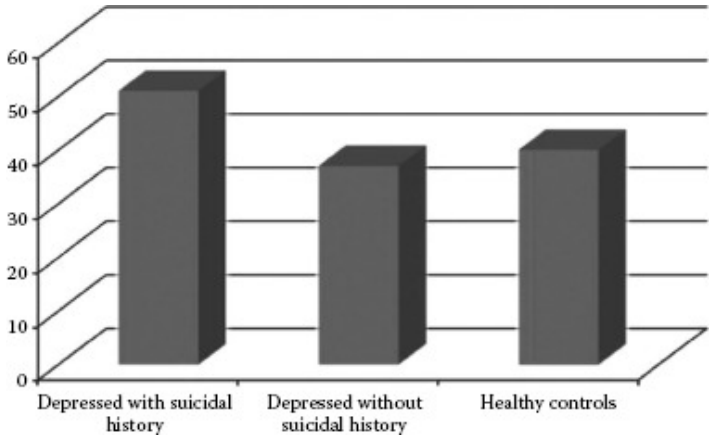

FIGURE 19.2

Increased antibody titers in patients with history of depression and suicide attempt than in patients with history of depression without suicide attempts and healthy controls (geometric means × 100). (From Arling et al. 2009. With permission.)

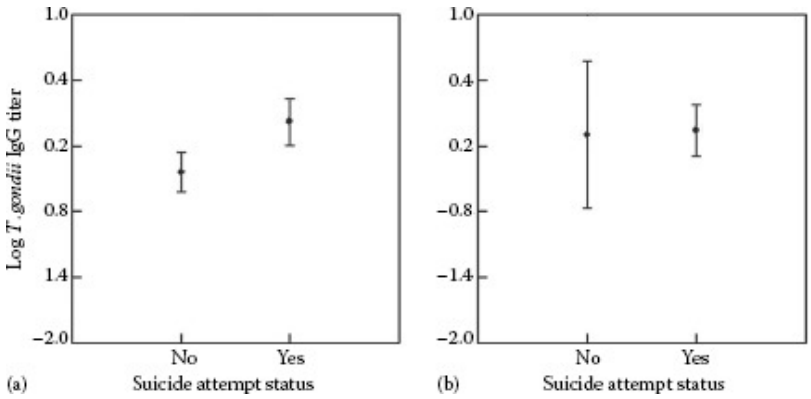

FIGURE 19.3

Comparison of *T. gondii* IgG antibody titers in schizophrenia patients with and without history of suicide attempt. (a) Difference is significant in the subgroup younger than 38 years (the median of the sample). $F = 10.607$, $p = 0.001$. (b) Difference is not significant in patients 38 years and older. $F = 1.141$, $p = 0.258$. (From Okusaga, O. et al., *Schizophr. Res*., 133, 150, 2011. With permission.)

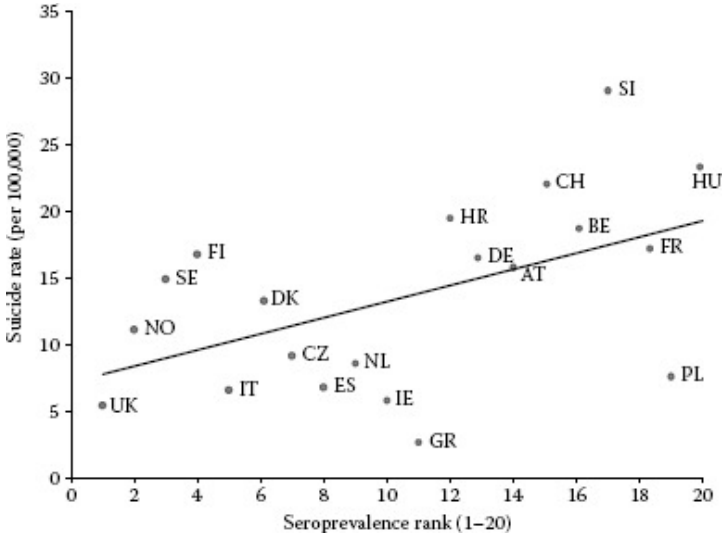

FIGURE 19.4

Relationship between suicide rates and *T. gondii* seroprevalence rank across 20 European countries in women aged 60–74 years old. Linear regression ($t = 2.54$, standardized coefficient = 0.51, $p = 0.020$; after adjustment for GDP rank: $t = 3.02$, standardized coefficient = 0.33, $p = 0.008$). Rank order is reversed. AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; GR, Greece; HU, Hungary; IE, Ireland; IT, Italy; NL, the Netherlands; NO, Norway; PL, Poland; SI, Slovenia; ES, Spain; SE, Sweden; CH, Switzerland; UK, United Kingdom. (From Ling, V.J. et al., *J. Nerv. Ment. Dis*., 199, 440, 2011. With permission.)

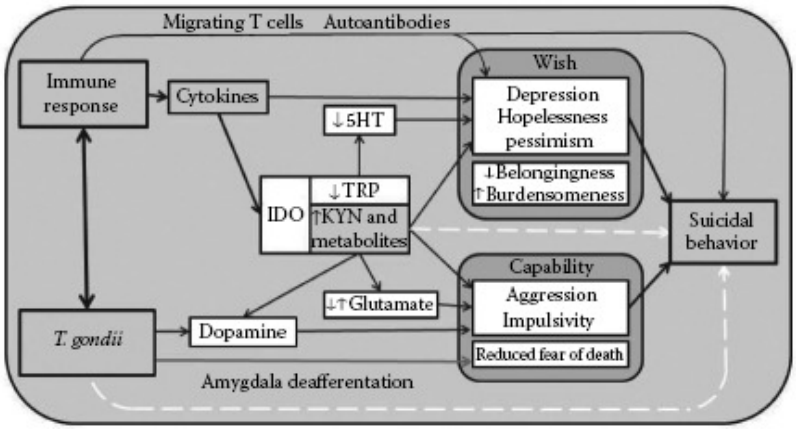

FIGURE 19.5

Hypothesized relationship between *T. gondii* and suicidal behavior and possible mechanisms. White dashed lines mark available preliminary evidence for the relationships between *T. gondii*, kynurenine, and suicidal behavior. The model integrates hypothesized molecular impact of *T. gondii* infection in an immunocompetent host with elements of Joiner's Interpersonal (Joiner 2009) and Mann's Stress Diathesis (Mann 2003) theories of suicide. The immune response to *T. gondii* releases cytokines that may directly or indirectly affect the brain and induce depression, elevating hopelessness and pessimism (diathesis) or desire to die (in Joiner's theory). In addition to cytokines, migrating T cells and autoantibodies could affect the centers involved with emotional regulation and dysregulation and lead to suicidal behavior. *T. gondii* has the enzymatic capacity to produce its own dopamine, and thus lead to potential increased aggression, arousal, and changes in impulsivity. In addition, activation by interferon-γ and TNF-α of the enzyme idolomine-2, 3-deoxygenase (IDO) results in the stealing of tryptophan from the synthesis of serotonin toward kynurenine and its metabolites. Kynurenine's metabolites, kynurenic acid and quinolinic acid, modulate glutaminergic and dopaminergic neurotransmission, further leading to changes in impulsivity and aggression. Decreased tryptophan may lead to decreased serotonin turnover and depression, hopelessness, and increased pessimism. Neuroanatomically, *T. gondii* parasitizes brain structures involved in behavioral regulation, the predominant site being the amygdala. The *T. gondii* infestation of the amygdala may result in deafferentation and the shrinkage of neurotic processes (Vyas et al. 2007). This may be contributory, hypothetically, to a reduced fear in general and potentially a reduced fear of death, an important factor in Joiner's theory for *acquired capability* to commit suicide. Important factors such as availability of means and deterrents are omitted. Also omitted is the reported elevation of testosterone in individuals harboring *T. gondii*, with potential for increased aggression.

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