INFECTIOUS DISEASES IN MAJOR DEPRESSIVE DISORDER, BIPOLAR DISORDER, AND OBSESSIVE-COMPULSIVE DISORDER

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ABSTRACT

Psychiatric disorders such as major depressive disorder (MDD), bipolar disorder (BD), and obsessive-compulsive disorder (OCD) are among the world's most prevalent and burdensome diseases and involve a complex interaction of environmental and genetic factors that converge on the nervous system to produce psychiatric symptoms. A large and growing body of evidence demonstrates that infectious diseases can constitute a primary cause or significant contributing factor of these neuropsychiatric disorders, particularly through mechanisms involving immune responses and inflammation affecting brain tissue. This chapter summarizes our present understanding of the clinical importance and biological mechanisms of several of the most prevalent and well-studied bacterial (e.g., gram-negative enterobacteria, syphilis, Lyme disease, *Streptococcus*), parasitic (e.g., *Toxoplasma gondii*), and viral (e.g., Borna disease, herpes simplex, Epstein-Barr, human immunodeficiency) infections that contribute to the onset and maintenance of MDD, BD, and OCD as well as some of the key uncertainties and remaining questions for future research.

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INTRODUCTION

Psychiatric disorders are highly prevalent and affect more than 16 percent of people (over 1 billion people) globally each year and are responsible for about 6.8 percent of all disease burden and 18.7 percent of all disability burden (the largest of all disease categories) worldwide {Rehm, 2019 #735}. In addition, the estimated occurrence and impact of psychiatric disorders has been substantially increasing over time throughout the world by about 48.1 percent over a roughly 30-year period, with depressive disorders ranking the highest among most age groups and regions. Unfortunately, the implementation of evidence-based interventions has not generated a detectable, systemic impact on disease burden at the global level {Ferrari, 2022 #573}.

Some investigators have argued that this mental-health crisis supports the need for a paradigm shift that involves reconceptualizing our diagnostic systems to one based on underlying neurobiological mechanisms rather than self-reported clinical syndromes {Cuthbert, 2013 #1562}. Given that patients diagnosed with the same mental disorder can have heterogeneous presentations, identification of biomarkers can help further differentiate subgroups and enhance efforts for prevention, diagnosis, and treatment {García-Gutiérrez, 2020 #1563}. Over the past several decades, investigators have elucidated some of the infectious disease mechanisms that primarily or secondarily affect brain structure or function and thereby produce neuropsychiatric symptoms that can contribute to many major psychiatric disorders, as detailed throughout this book. This chapter summarizes our present understanding of the clinical importance of several of the most prevalent and well-studied bacterial, parasitic, and viral infections that contribute to major-depressive disorder, bipolar disorder, and obsessive-compulsive disorder. Insofar as possible, it also explains the biological mechanisms responsible for the linkage between

infectious diseases and these psychiatric disorders, particularly the mediating role of immune responses, inflammatory reactions, and cytokine signaling.

MAJOR DEPRESSIVE DISORDER

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder with a lifetime prevalence of approximately 20.6 percent {Hasin, 2018 #1564}. It is now considered the leading cause of disability worldwide {Friedrich, 2017 #210} and is responsible for approximately $326.2 billion in economic burden in the United States alone. Its current DSM-5 diagnosis requires the presence of at least five symptoms within a two-week period, including either low mood or anhedonia combined with altered appetite, weight changes, sleep difficulty, fatigue, suicidality, or diminished ability to think or concentrate {American Psychiatric Association, 2022 #1565}. MDD is highly comorbid with other psychiatric disorders, particularly anxiety disorders, and has a lifetime comorbidity rate as high as 60 percent with generalized anxiety disorder {Kaufman, 2000 #229}.

The neural basis of MDD involves a pattern of highly complex neural activity across a large number of brain regions in the cerebral cortex and limbic system {Hamilton, 2012 #612;Miller, 2015 #246;Miller, 2018 #1566}, including the dorsolateral prefrontal cortex (dlPFC) and subgenual anterior cingulate cortex (sgACC), which serve as target regions for emerging therapies such as repetitive transcranial magnetic stimulation {rTMS`; \George, 2010 #1567} and deep brain stimulation {DBS`; \Mayberg, 2005 #241}, respectively. Much of this dysfunctional brain activity also appears to be linked to imbalanced communication between large-scale functional connectivity networks, particularly the default mode, frontoparietal, and salience networks {Kaiser, 2015 #633;Menon, 2011 #244}.

Investigators also now increasingly recognize significant relations between infectious diseases and MDD, which are often mediated through mechanisms of inflammation. The following sections provide examples of prevalent and well-studied bacterial, parasitic, and viral infections that appear to contribute to the onset and maintenance of depressive symptoms, with a particular emphasis on the currently known epidemiology and biological mechanisms linking these infectious disease and disorders.

GRAM-NEGATIVE ENTEROBACTERIA

Gram-negative enterobacteria, which exist inside the human intestinal tract, have been implicated in a number of diseases when these toxic bacteria escape gastrointestinal isolation, referred to as leaky gut syndrome. This condition appears to contribute to the onset and maintenance of MDD as well as ulcerative colitis and Crohn's disease, collectively referred to as inflammatory bowel disease {IBD`; \Yu, 2022 #811}. Comorbidity and bidirectional associations between MDD and IBD are high, with MDD and IBD each contributing substantial bidirectional risk, after adjustment for potential confounders, of 1.87 (odds ratio; $p < 0.028$) and 9.43 (odds ratio; $p < 0.001$) relative to controls, respectively {Zhang, 2022 #815}.

In healthy individuals, the intestinal tract contains toxic enterobacteria containing liposaccharides in the cellular walls that are mainly ingested through contaminated food or water. The typical immune system does not show a response to these enterobacteria because the bacteria are quarantined within the gastrointestinal tract and isolated from the rest of the body through selective mucosal barriers, tight junction proteins, and mesenteric lymph nodes {Maes, 2012 #238;Yu, 2022 #811}. However, if the barriers are compromised, the enterobacteria may escape the isolation of the gut and enter the lamina propria and the bloodstream through bacterial

translocation and, once outside the outside the intestines, the liposaccharides in the cells walls of the gram-negative bacteria activate the immune system {Yu, 2022 #811}.

Interestingly, patients with chronic MDD have higher levels of immunoglobin antibodies targeting gram-negative bacterial liposaccharides relative to healthy controls, which suggests higher rates of bacterial translocation {Maes, 2008 #671}. Moreover, injection of liposaccharides into animal models induces depressive symptoms, including anhedonia, reduced exploratory behavior, fatigue, and reduced social interactions {Arling, 2009 #1568;Dantzer, 2008 #199;Leonard, 2012 #652;Maes, 2012 #238}. In addition, these depressive symptoms have been shown to be ameliorated by immunosuppressant treatment of IBD {Guloksuz, 2013 #1569;Horst, 2015 #624}, and treatment of Crohn's disease with anti-tumor necrosis factor (TNF)-α antibodies reduces depressive symptoms {Rook, 2008 #742}.

A leaky gut may be a primary trigger of depression for individuals at risk or could be a secondary reaction to existing depressive symptoms {Leonard, 2012 #652;Maes, 2012 #238}. If a leaky gut is a primary trigger of depression, the underlying mechanism responsible may involve inflammation of brain tissue following a sustained immune response to leaking enterobacteria that causes elevation of cytokine levels in the body. In particular, cytokines, which are released by immune cells such as macrophages in the body or microglia in the central nervous system (CNS), promote an inflammatory response to intracellular pathogens, including gram-negative bacteria liposaccharides {Beurel, 2020 #494;Chen, 2015 #1570;Kim, 2016 #644}. Proinflammatory cytokines are depressogenic molecules inducing sickness behaviors such as fatigue, weight loss, and disrupted sleep patterns {Dantzer, 2008 #199;Maes, 2008 #671}. Indeed, a large-scale meta-analysis found elevated TNF-α and interleukin (IL)-6 cytokine concentrations in depressed individuals, though other cytokine levels were not significantly

different in MDD individuals {Dowlati, 2010 #204}, and there is much heterogeneity among individual studies on the relationship between cytokine levels and depression {Köhler, 2017 #1571}.

In addition, clinical studies show that elevated levels of cytokines in physically ill patients can induce MDD {Dantzer, 2008 #199}, that elevated cytokine levels have been observed in MDD patients and suicide victims {Canli, 2014 #190}, and that treatment of hepatitis and cancer patients with proinflammatory cytokines such as interleukin-2 and interferon (IFN)-α can induce depression {Beurel, 2020 #494;Rook, 2008 #742}. Basic science studies also show that production of proinflammatory cytokines by microglia, which are critical for neuroplasticity, learning, and memory {Beurel, 2020 #494;Kim, 2016 #644} at normal basal levels, becomes harmful when produced at chronically high levels and negatively impacts neurotransmitter signaling as well as the synthesis, reuptake, and release of neurotransmitters {Beurel, 2020 #494}. Other investigators have found that high concentrations of interleukin-6 and TNF-α followed by microglial activation decreases neurogenesis within the hippocampus and is associated with reductions in hippocampal volume, including in first-episode and drug-naïve patients with MDD {Kakeda, 2018 #1572}, and likely contribute to the onset and maintenance of depression {Kim, 2016 #644;Roohi, 2021 #1573}.

Alternatively, if a leaky gut is a secondary symptom of depression, the inflammatory factors associated with depression may cause damage to the mucosal barriers and tight junctions of the gut, thereby triggering bacterial translocation {Maes, 2012 #238}. Stressful or negative life events have been shown to increase proinflammatory cytokine production in humans {Maes, 2008 #671}, and this response is exaggerated in depressed individuals {Rook, 2008 #742}. Furthermore, depression is associated with increased production of corticotropin-releasing

hormone and glucocorticoids, which are both involved in the permeability of the mucosal barrier in the gut {Maes, 2012 #238}. Hence, leaky-gut symptoms may be a primary trigger or a secondary complication of depression—or, most likely, these two complex disorders and their underlying mechanisms may exert reciprocal influences on each other.

In any case, bacterial translocation should be of increasing concern for human health. Rates of IBD are curiously much greater in industrialized, Western countries than in developing countries {Molodecky, 2012 #695}, which is likely due in part to the increased sterilization of the environment in industrialized nations that has reduced human exposure to many microorganisms, including the symbiotic bacteria that form our healthy gut microbiota. Evolutionary exposure to these tolerogenic bacteria may have previously served to calibrate our immune system to respond appropriately to differing pathogen threat levels. With significantly reduced exposure to these "old friend" microorganisms, the human immune system may now overreact when exposed to leaking enterobacteria, which may contribute to the rising incidence of chronic inflammatory disorders and MDD in industrialized nations {Raison, 2010 #1574}.

TOXOPLASMA GONDII

The parasite *Toxoplasma gondii* (*T. gondii*) is an obligate intracellular protozoan parasite and lives primarily in the feline intestinal tract {Wang, 2014 #1575}. *T. gondii* often infects humans through undercooked meat or exposure to water, garden soil, or a child's sandbox that has been contaminated by cat feces {Montoya, 2004 #251} and is estimated to have infected approximately one-third of the human population worldwide. When rats encounter the *T. gondii* eggs in cat excrement, the parasite forms cysts within the rats' amygdala, which reduces corticosterone levels and activates sexual arousal pathways and decreases capacity for memory and learning {Arling, 2009 #1568}. Some studies have found that *T. gondii* infection is

associated with behavioral changes and various diseases as well as psychiatric disorders in humans, including MDD and suicidality {Bak, 2018 #1576;Soleymani, 2020 #1577}; however, other studies have not found a significant link between *T. gondii* infection and MDD {Gale, 2021 #1578}.

Investigators have identified multiple mechanisms through which *T. gondii* may contribute to depressive symptoms. First, humans typically experience an acute initial reaction to *T. gondii* infection, which can be followed by a chronic latent intracellular infection in the form of cysts in various brain regions {McConkey, 2013 #1579} that may contribute directly to depressive symptoms. Typically, this chronic cyst infection is suppressed by T helper (Th) and natural killer (NK) cells that allow the host to remain immunocompetent. However, if these cysts are not contained, parasitic *T. gondii* cells may be released back into circulation in the body, and the metabolites from within the broken cyst may directly alter neurotransmitter concentrations {Groer, 2011 #218}.

Alternatively, infection by *T. gondii* may indirectly influence human depressive symptoms via a prolonged immune response by the host. Humans infected with *T. gondii* have higher concentrations of cytokine proteins, due to the long-term efforts by Th cells to suppress *T. gondii* cysts {Canli, 2014 #190}. These cytokine proteins are necessary to fight off the original infection by *T. gondii* but have depressogenic side effects, as discussed previously.

T. gondii may also indirectly influence depressive symptoms of its host through tryptophan withdrawals. Tryptophan, which is an essential amino acid for human hosts (and for *T. gondii*), is ingested through dietary proteins {Mittal, 2017 #691}. The human immune response to *T. gondii* infection includes increasing the enzymatic activity of indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan in the body and starves the parasite. However,

tryptophan is also used to synthesize serotonin in humans {Chen, 2015 #1570}; without the building block of tryptophan, serotonin levels would presumably decrease, which some investigators have argued could induce depressive symptoms {Beurel, 2020 #494;Dantzer, 2008 #199;Leonard, 2012 #652}. Notably, the activation of IDO also creates other neurotoxic metabolites through the kynurenine pathway, which may contribute to depressive symptoms. In particular, the degradation of tryptophan by IDO forms quinolinic acid (QA), which is an N-methyl-D-aspartate (NMDA) receptor agonist, and kynurenic acid (KA), which is an NMDA receptor antagonist {Dantzer, 2008 #199}. Some evidence indicates that the ratio between these metabolites of tryptophan, which have opposing functional roles, is associated with depression {Dantzer, 2008 #199;Guloksuz, 2013 #1569;Leonard, 2012 #652;Mittal, 2017 #691}.

BORNA DISEASE VIRUS

Borna disease virus (BDV), which is well-known for inducing fatal encephalitis in infected sheep and horses, also infects the nervous system of humans {Murray, 2021 #286} and appears to be linked to higher rates of psychiatric disorders such as MDD. Indeed, a meta-analysis of infectious agents and depression found a statistically significant correlation (p=0.026) between BDV infection and depression and an odds ratio of 3.25 for exposure to BDV among MDD patients compared to healthy controls {Wang, 2014 #1575}.

Interestingly, when MDD patients infected with BDV are treated with the antiviral drug amantadine, both their BDV symptoms and depression symptoms improve {Canli, 2014 #190;Dietrich, 2008 #554}. One study found a response rate of 68 percent in depressive symptoms in treating BDV-infected MDD patients with amantadine after an average of 2.9 weeks {Dietrich, 2000 #203}. The success of amantadine in treating both BDV and MDD symptoms may provide insight into the biological mechanism linking BDV and depression. As

discussed above, the activation of IDO in MDD patients increases QA levels, which increases glutamate production {Müeller, 2007 #1580}. Amantadine is an antagonist of the NDMA receptor, which suggests it may counteract the imbalance in MDD between QA and KA and serve as a link between depression and glutaminergic receptor activity {Müeller, 2007 #1580;Dantzer, 2008 #199;Guloksuz, 2013 #1569}.

HERPES SIMPLEX VIRUS TYPE 1

Herpes simplex virus type 1 (HSV-1) is extremely common, with an estimated global prevalence of approximately 66.6 percent for individuals 0 to 49 years of age {James, 2020 #630}. A large-scale meta-analysis found a significant association between depression and HSV-1 based on a pooled analysis of 28 primary studies {Wang, 2014 #1575}. In addition, a recent analysis of the UK Biobank, a vast biomedical database, found higher HSV-1 antibody serum concentrations was associated with an increase occurrence of depression {Ye, 2020 #810}.

After initial infection, HSV-1 often becomes a chronic latent infection in nerve ganglia of human hosts, with sporadic reactivation most commonly in the form of cold sores or genital herpes {Curanovic, 2009 #537}. This chronic latent infection may cause prolonged cytokinetic inflammation {Ye, 2020 #810}, which may contribute to depressive symptomatology, as discussed above. The UK Biobank study also suggested several potential single nucleotide polymorphisms (SNPs) involved in nerve development and immune function, which may serve as genetic vulnerabilities for developing MDD following HSV-1 infection {Ye, 2020 #810}. Nerve development is particularly relevant to herpes viral infection, as HSV-1 can enter the CNS of the host and subsequently spread transneuronally {Curanovic, 2009 #537}.

EPSTEIN-BARR VIRUS

Epstein-Barr virus (EBV) is another member of the herpesvirus family (HHV-4) and frequently manifests as infectious mononucleosis in human hosts. It is also very common, with an estimated 90 percent of adults being exposed to the virus before the age of 30 years {Vindegaard, 2021 #787}. Despite its broad distribution, EBV infection has been found to be nearly twice as prevalent among individuals with MDD as in the general population {Wang, 2014 #1575}, and individuals afflicted with infectious mononucleosis have a 40 percent increased risk of depression more than one year following the initial EBV infection {Vindegaard, 2021 #787}. During viral replication, EBV produces the protein EBV-encoded deoxyuridine triphosphate nucleotidohydrolase, which induces the production of proinflammatory cytokines, including TNF-α and IL-6, which can induce depressive symptoms {Vindegaard, 2021 #787}.

HUMANIMMUNODEFICIENCY VIRUS

Human immunodeficiency virus type 1 (HIV-1) is a retrovirus that causes acquired immunodeficiency syndrome (AIDS) in humans. Approximately 1.2 million people in the United States {U.S. Department of Health & Human \Services, 2022 #1581} and 38.4 million people worldwide {U.S. Department of Health & Human \Services, 2022 #1582} are infected with HIV-1. The chronic activation of the immune system from the presence of HIV-1 increases enzymatic activity of IDO and reduces tryptophan levels {Moreau, 2005 #1583}. As discussed above, chronic activation of IDO is associated with human depressive behavior, and this link between IDO activation and depressive behavior has been demonstrated experimentally in animal models {Dantzer, 2008 #199}. Similarly, the chronic activation of the immune system in response to HIV-1 is also thought to activate microglia in the brain and cause neuroinflammation {Beurel, 2020 #494}, both of which have been identified as significant correlates of depression {Yu, 2022 #811}.

BIPOLAR DISORDER

Bipolar I disorder (BD-I) is a common psychiatric disorder with a lifetime prevalence of approximately 4.4 percent {Harvard Medical \School, 2007 #1584}. It involves alternating episodes of major depression and mania, or distinct periods of elevated, expansive, or irritable mood along with abnormal and persistent goal-directed behavior and energy as well as three or more symptoms such as inflated self-esteem, decreased need for sleep, increased talkativeness, flight of ideas, distractibility, psychomotor agitation, and high-risk behavior for at least one week {American Psychiatric Association, 2022 #1565}. BD-I has high comorbidity with multiple other disorders, including lifetime prevalence of 61.0 percent with substance-use disorder, the highest comorbidity rate within any psychiatric disorder, and 52.8 percent with anxiety disorders {Simon, 2004 #765}.

The neural basis of BD closely resembles that of MDD in many ways, though structural and functional imaging studies have found subtle differences between the two disorders in brain regions such as the caudate, anterior cingulate, and habenula {Almeida, 2013 #472;Almeida, 2013 #1598;Sacchet, 2015 #749}. In addition, BD appears to have a strong genetic basis, with a heritability index of 0.7 to 0.8, and genome-wide association studies (GWAS) have implicated hundreds of candidate genes, many of which are involved in voltage-gated calcium and glutamate signaling and are shared with schizophrenia {Harrison, 2018 #613;Nurnberger, 2014 #1585}.

Investigators have also identified a number of associations between infectious diseases and BD, including several that are shared risk factors for MDD and are discussed above, such as gram-positive bacterial infection {McGuinness, 2022 #461}, toxoplasmosis {Oliveira, 2017 #256}, and BDV infection {Oliveira, 2017 #256}. Some investigators have proposed that the

multiple sources of these infections and the pronounced but varied psychiatric symptoms as well as consistent immunological findings suggest a common underlying mechanism linking infectious diseases and BD that involves immune activation and inflammation of the brain or surrounding tissue {Oliveira, 2017 #256;Rosenblat, 2014 #743}. In addition, infectious exposure to these pathogens, as well as to others such as influenza {Parboosing, 2013 #724}, that occurs around the perinatal period may elevate risk of BD in offspring, though results of this effect remain inconclusive {Barichello, 2016 #184}. The following sections discuss several additional viral and bacterial infections that appear to contribute to neuropsychiatric symptoms that include mania.

HERPESVIRUSES

Herpesvirus is a genus-level classification that includes nine virus types categorized by host range, genetic organization, and replication strategy that infect humans and can cause a range of diseases. Although nearly all humans become infected by one or more of these viruses, severe disease from most herpesviruses in immunocompetent individuals is rare, except for cytomegalovirus (CMV; HHV-5), which more frequently invades the nervous system in healthy individuals {Sehrawat, 2018 #759}. Several herpesviruses, including HSV-1, HSV-2, EBV (HHV-4), and CMV (HHV-5) have been associated with significant risk for BD {Oliveira, 2017 #256}, although evidence for these links remains limited and the mechanisms are nonspecific {Dickerson, 2004 #553;Tucker, 2019 #782}.

SYPHILIS

Syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum (T. pallidum)* that typically appears as a lesion at the site of sexual contact and then quickly spreads to distant bodily tissues through a series of stages. Without treatment, *T. pallidum*

infection can advance to a tertiary stage and invade brain tissue, a condition referred to as *neurosyphilis* {Ghanem, 2020 #1586}. This neurologic syndrome can produce pronounced and varied clinical symptoms, often including general paresis, cognitive impairment, delirium, hallucinations, and mania. MRI examinations of neurosyphilis patients with psychiatric manifestations tend to show pronounced but nonspecific and varied findings, including cerebral atrophy, demyelination, hydrocephalus, hippocampal sclerosis, and cerebral hemorrhage {Lin, 2014 #658}.

LYME DISEASE

Lyme disease is an infection caused by the bacterium *Borrelia burgdorferi* (*B. burgdorferi*) and is typically transmitted through the bite of an infected deer tick. Typically, the infection first manifests as a skin lesion around the site of the tick bite and then spreads to other body systems {Sanchez, 2016 #754}. In a minority of cases, Lyme disease may become a chronic disease that is highly difficult to manage and treat {Marques, 2022 #676}. *B. burgdorferi* can also invade the peripheral and central nervous systems and cause a variety of neurologic symptoms, including facial palsy, radiculopathy, and lymphocytic meningitis {Sanchez, 2016 #754}. There is also increasing evidence that Lyme disease can cause a wide spectrum of gradually developing neuropsychiatric symptoms, including mania, depression, anxiety, sleep disturbance, substance abuse, dissociation, and depersonalization in addition to cognitive impairment {Bransfield, 2018 #186}.

OBSESSIVE COMPULSIVE DISORDER

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder with a lifetime prevalence of 1 to 3 percent {Stein, 2019 #1587}. It is characterized by intrusive and persistent obsessions, such as worries about contamination, symmetry, and sex or aggression, as well as

compulsions, or repetitive behaviors such as handwashing, ordering, checking, mental counting, or superstitious touching of objects {American Psychiatric Association, 2022 #1565}. OCD shows a high comorbidity with other psychological disorders, including a lifetime probability of 76 percent of being diagnosed with an anxiety disorder, 41 percent of being diagnosed with MDD, and 39 percent of being diagnosed with a substance-use disorder. OCD also shows high comorbidity with some motor disorders, such as Tourette syndrome and tic disorders, with a comorbidity rate as high as 35 percent between these disorders {Kumar, 2016 #648}.

The neural basis of OCD involves, in part, aberrant activity in the basal ganglia and dysfunctional brain circuits between the basal ganglia, thalamus, and cortex in the cortico-striatal-thalamic-cortical circuitry {Levy, 2011 #234;Moreira, 2017 #700}. Neurochemically, serotonergic and dopaminergic systems tend to be most disrupted in individuals with OCD, though dysfunctions in GABA and glutamate systems also appear to contribute to symptoms {Goodman, 1990 #1588;Karthik, 2020 #1589;Zohar, 2000 #819}.

Numerous factors that contribute to the etiology of OCD have been identified, ranging from complex risk associated with serotonin, dopamine, and glutamate genetics {Browne, 2015 #189} as well as trauma exposure {Dykshoorn, 2014 #560}, pregnancy and birth {Russell, 2013 #746}, arsenic poisoning {Wu, 2017 #803}, and several types of pathogens {Endres, 2022 #1590}. In this section, we examine the link between well-studied or highly prevalent protozoa and bacterial pathogens and OCD and discuss how exposure to these pathogens is understood to affect brain cells in the basal ganglia directly or indirectly through an autoimmune response, which occurs most frequently during childhood and early adolescence.

TOXOPLASMA GONDII

T. gondii is a geographically widespread parasitic protozoan that can directly infect neurons and glial cells in the central nervous system {Carruthers, 2007 #191}, including in the basal ganglia {Miman, 2010 #1591}. *T. gondii* infection may also be a risk factor for developing OCD, especially in particular regions {Threat, 2014 #1592;Flegr, 2015 #208}. In a meta-analysis, {Chegeni, 2019 #1593@@author-year} found a statistically significant odds ratio of 1.96 when examining the chance of *T. gondii* infection in OCD patients compared to healthy controls.

The mechanism of *T. gondii* in promoting OCD may involve interactions of many factors, including genetic susceptibility to *T. gondii* {Carter, 2013 #522}, infection of neurons and glial cells in the basal ganglia {Miman, 2010 #1591}, and modification of neurotransmitter activity {Endres, 2022 #1590}. Some investigators have found that *T. gondii*-infected neurons increase dopamine release by several factors, and this increased dopamine may exacerbate OCD symptoms in humans {Denys, 2004 #551;Akaltun, 2018 #1594}. In addition, *T. gondii* infection appears to initiate an autoimmune response and inflammation that may secondarily contribute to the onset and maintenance of OCD symptoms {Endres, 2022 #1590}.

STREPTOCOCCUS

Group A *Streptococcus* (GAS) is a bacterium that almost exclusively infects humans and causes a strong inflammatory response that is responsible for a broad spectrum of invasive and autoimmune diseases {Dale, 2005 #539;Liu, 2019 #662}, including rheumatic fever and various neuropsychiatric syndromes such as pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS), which is characterized by symptoms that resemble OCD. Indeed, several large-scale studies have found a high level of lifetime comorbidity (43

percent) and significantly higher risk (adjusted hazard ratio = 1.85) for OCD among individuals with autoimmune disorders {Wang, 2019 #794;Mataix-Cols, 2018 #1595}.

Converging evidence from multiple fields and many studies indicates that autoimmune processes and inflammation in the basal ganglia following infection from pathogens such as *Streptococcus* can produce OCD symptoms {Gerentes, 2019 #214}. Structural neuroimaging studies indicate that the basal ganglia appear to be highly vulnerable to inflammatory changes following GAS infection and that these changes are associated with clinical and behavioral abnormalities {Giedd, 2000 #216;Zheng, 2020 #816}. Immunological studies also demonstrate that immunoglobulin G (IgG) antibodies from GAS-infected human children can bind to cholinergic interneurons and inhibit functioning of the basal ganglia in mice {Frick, 2018 #209;Xu, 2021 #805}.

Although many investigators and clinicians have demonstrated that post-streptococcal autoimmunity plays a causal role in many cases of OCD, there have been some mixed results in studies looking at the relationship between streptococcal infection and PANDAS {Wilbur, 2019 #801}, and the clinical extent of and guidelines related to PANDAS remain somewhat controversial {British Paediatric Neurology \Association, 2021 #1596; PANS PANDAS UK, 2021 #722}. Indeed, while some investigators have found a statistically significant increased risk between streptococcal infection and OCD using a large Danish registry on over 1 million children {Orlovska, 2017 #257}, other researchers have raised concerns regarding research designs and possible biases {Harvey, 2018 #614;Sigra, 2018 #764}. Some critics have also raised concerns that administering prophylactic antibiotics or anti-inflammatories to treat PANDAS may cause unwanted side effects such as a weakened immune response {Brown, 2017 #188;Sigra, 2018 #764}.

CONCLUSIONS

Psychiatric disorders such as MDD, BD, and OCD are highly prevalent and burdensome diseases that involve a complex interaction of genetic and environmental factors that converge on the nervous system to produce psychiatric symptoms. A large and growing body of evidence demonstrates that bacterial, parasitic, and viral infections can constitute a primary cause or contributing factor of these neuropsychiatric disorders, particularly through mechanisms involving immune responses and inflammation affecting brain tissue. Future research should continue to investigate associations between infectious diseases and the biological mechanisms that mediate infectious disease and neuropsychiatric disorders, as well as to develop clinical diagnostics and therapeutics designed to target those disease processes to improve treatment outcomes for patients suffering from these disorders.

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