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RESEARCH PAPER

BACK TO THE FUTURE: THE ROLE OF INFECTIONS IN PSYCHOPATHOLOGY. FOCUS ON OCD

Alessandra Della Vecchia, Donatella Marazziti

Abstract

Objective: Recently, there has been a resurgence of interest in the relationship between infections and psychopathology, given the increasing data on the neurotropism and neurological/psychiatric morbidity of the SARS-COV2 virus, responsible for the current worldwide pandemic. Although the majority of observations were those obtained in mood and schizophrenic disorders, a few data are also available on the presence of bacterial or viral infections in patients suffering from obsessive-compulsive disorder (OCD). Therefore, given the limited information, the present paper aimed at reviewing the most updated evidence of infections in neuropsychiatric disorders and their possible mechanisms of actions, with a narrow focus on microbes in OCD.

Method: This paper is a narrative review. The databases of PubMed, Scopus, Embase, PsycINFO and Google Scholar were accessed to research and collect English language papers published between 1 January 1980 and 31 December 2021. The data on PANDAS/PANS and those observed during severe brain infections were excluded.

Results: Several pathogens have been associated with an increased risk to develop a broad spectrum of neuropsychiatric conditions, such as schizophrenia, mood disorders, autism, attention-deficit/hyperactivity disorder, anorexia nervosa, and post-traumatic stress disorder. Some evidence supported a possible role of infections also in the pathophysiology of OCD. Infections from Herpes simplex virus 1, Borna disease virus, Group A-Beta Hemolytic Streptococcus, Borrelia spp., and Toxoplasma gondii were actually found in patients with OCD. Although different mechanisms have been hypothesized, all would converge to trigger functional/structural alterations of specific circuits or immune processes, with cascade dysfunctions of several other systems.

Conclusions: Based on the current evidence, a possible contribution of different types of microbes has been proposed for different neuropsychiatric disorders including OCD. However, the currently available literature is meager and heterogeneous in terms of sample characteristics and methods used. Therefore, further studies are needed to better understand the impact of infectious agents in neuropsychiatric disorders. Our opinion is that deeper insights in this field might contribute to a better definition of biological underpinnings of specific clinical pictures, as well as to promote psychiatric precision medicine, with treatments based on altered pathological pathways of single patients. This might be particularly relevant in OCD, a disorder with a high proportion of patients who are resistant or do not respond to conventional therapeutic strategies.

Key words: infectious agents, neuropsychiatric disorders, obsessive-compulsive disorder, immune system, pathophysiology, immuno-neuropsychiatry

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Introduction

Severe infections, especially those occurring in the central nervous system (CNS) such as encephalitis and meningitis, are known to cause brain damage with long-term cognitive and psychiatric symptoms (Kapur et al., 1994; Khanna, 1988; Yaramiş et al., 2009). However, evidence is available that several pathogens might increase the risk to develop neuropsychiatric disorders without causing severe acute infections (Arias et al., 2012; Barichello et al., 2016; Coughlin, 2012; Hornig, 2013; Hornig & Lipkin, 2001; Wang et al., 2014). In the

past, the term "mild (chronic) encephalitis" was coined to referring to these clinical pictures (Müller, 2015).

More recently, there was an upsurge of interest towards the relationships between viral infections and psychopathology given the increasing data on the neurotropism of the SARS-COV32 virus responsible of the current pandemic worldwide (Marazziti & Stahl, 2020)

Although the most consistent data are those gathered in mood and schizophrenic disorders (Asoode et al., 2016; Burgdorf et al., 2019; Chaudhury & Ramana, 2019; Dickerson et al., 2019; Yolken, 2004; Prusty et al., 2018), the obsessive-compulsive symptoms amongst children precipitated after group A beta-hemolytic streptococcus (GABHS) infections are amongst the most robust evidence in this field.

The first studies reported obsessive-compulsive symptoms in subjects affected by Sydenham chorea (SC) (Swedo et al., 1989). In particular, in the late 1980's the National Institute of Mental Health (NIMH, Bethesda, Md., USA) pointed out the high frequency of such symptoms in children and adolescents affected by SC, appear abruptly in the weeks preceding the onset of the chorea, a delayed neurological complication of group A beta-hemolytic streptococcal infection (GABHS) pharyngitis included in the major criteria of acute rheumatic fever, an inflammatory autoimmune disease affecting mainly the heart valves (Swedo et al., 1989). About twenty years later, the NIMH group proposed the term pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) to describe an OCD form characterized by acute prepuberal onset, episodic course, and concomitant neurologic abnormalities – such as choreiform movements – that occur or worsen after exposure to GABHS infection ((Swedo, 2002; Swedo et al., 1998)**.** However, a definite diagnostic temporal window between GABHS infection and the onset of neuropsychiatric in SC and PANDAS has not yet well established (Kurlan et al., 2008; Leckman et al., 2011; Moher et al., 2009; Schrag et al., 2009). In particular, the role of GABHS in PANDAS is questioned (Gilbert & Kurlan, 2009; Kurlan, 2004), since a number of studies failed to find a temporal association between GABHS infection and symptom onset (Kurlan et al., 2008; Leckman et al., 2011; Schrag et al., 2009). Therefore, in July 2010 the NIMH researchers expanded PANDAS to a conceptually broader disorder — the so-called pediatric acute-onset neuropsychiatric syndrome (PANS) — that is characterized by the sudden onset of OCD symptoms that can occur in response to a range of infections and other insults (Chang et al., 2015).

Besides PANDAS/PANS in children, there are scattered data on the presence of bacteria or viral infections in patients suffering from obsessive-compulsive disorder (OCD). Obsessive-compulsive disorder is the core condition of the "obsessive–compulsive and related disorders (OCRDs)", a group of disorders currently classified together in both the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5), (American Psychiatric Association, 2013). It is one of the most prevalent mental disorders (Murray & Lopez, 1997), with lifetime prevalence in the general population of 2-3% (Abramowitz et al., 2009; Ruscio et al., 2010). It is estimated that OCD is as one of the major causes of the global disability, with about 40% of patients who do not respond to standard therapeutic strategies (Fineberg et al., 2018).

Given the controversies in this field, this paper aimed at providing an overview of the most recent evidence of infections in neuropsychiatric disorders and their possible mechanisms of actions. Further, much focus will be given to the available data on microbes and viruses in OCD, excluding pictures falling within SC and PANDAS/PANS and those observed during the course of severe brain infections. Finally, we will discuss and comment on the possible role of these agents in OCD and related therapeutic implications.

Materials and Methods

This paper is a narrative review. The databases of PubMed, Scopus, Embase, PsycINFO and Google Scholar were accessed in order to research and collect English language papers published between 1 January 1980 and 31 December 2021. Free text terms and MeSH headings were combined as follows: "(infections OR bacteria OR viruses) AND (neuropsychiatric disorders OR obsessive-compulsive disorder OR OCD)". The following inclusion criteria were adopted: studies carried out on clinical samples of adults and children/adolescents, reliable diagnosis of psychiatric disorders according to structured interviews and standardized criteria. All the authors agreed to include conference abstracts, posters, and case reports in the review if they were published in indexed journals. The data on PANDAS/PANS and those observed during severe brain infections were excluded.

All the authors equally contributed to identifying potential information specific to this topic amongst the titles and abstracts of the publications

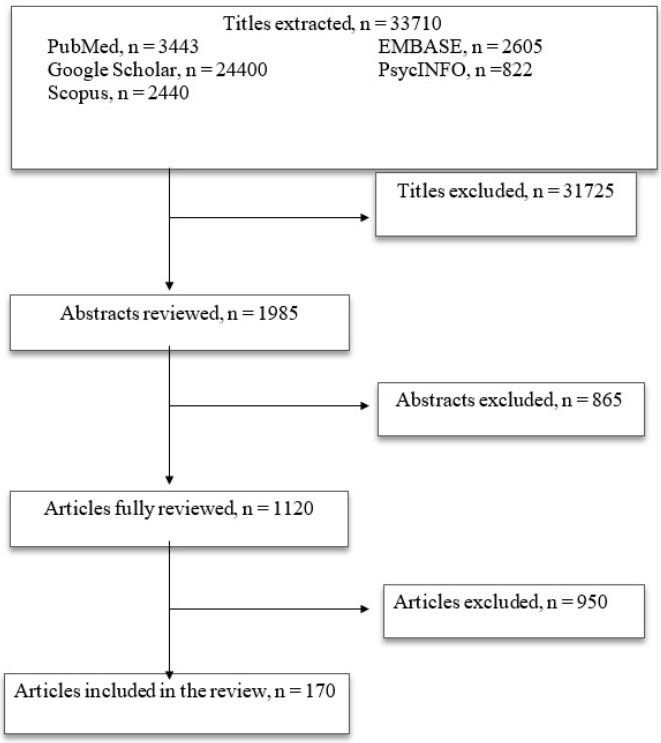
Results

The first selection excluded 31725 titles because they were: a) duplicates; b) not related to the scope of the paper; c) not informative enough. The second selection excluded 865 abstracts after being read and reviewed, as the information reported did not fulfill the scope of our paper and/or the presented information did not seem relevant to the discussed topic. Subsequently, 950 publications were excluded after being completely read and evaluated, as they did not provide enough information and/or were not sufficiently in line with our review. Finally, 170 papers were included in the present review (**table 1**). Among these, 70 are inherent in the relationship between OCD and pathogens, 25 of which highlight a possible association between infectious diseases and the onset of OCD pictures. although most are case reports, cross-sectional or case-control studies on small samples.

Associations between microbes and psychiatric disorders

One of the most fascinating lines of research concerns the intersections between microbes and psychiatric disorders. The first model of mental illness sustained by an infectious agent was that of Neurosyphilis. In the year 1822, the physician Laurent Bayle described a disease currently known as 'general paresis' (Bayle, 1822), characterized, amongst the other symptoms, by mania, delusions, and dementia (for review, see: Washington, 2015). At that time, such a disorder was considered a mental illness, but in the year 1857, Esmarch and Jessen, based on statistical analysis of patients with paresis, suggested syphilis as the cause, so that, since the mid-twentieth century, antibiotics have been successfully used to treat this condition (Esmarch

Table 1. *Article selection flow chart*



& Jessen, 1957).

By the time, in addition to psychiatric pictures due to medical conditions, both early life and adult infections were associated with increased risk of neuropsychiatric disorders (Almanzar et al., 2005; Arias et al., 2012; Brown, 2012; Hornig, 2013; Mufaddel et al., 2014). This notion is supported by animal data, such as those observed in rodents, where fetal infection during the prenatal or perinatal period may cause long-term cognitive damage, including learning, memory, and attention abnormalities (Canetta et al., 2014; Khandaker et al., 2013). In humans, maternal infections during pregnancy were related to an increased risk to develop neuropsychiatric disorders in the offspring, especially schizophrenia and autism spectrum disorders (ADS) (Atladóttir et al., 2010; Blomström et al., 2016; Flinkkilä et al., 2016; Jiang et al., 2016; Kendler, 2020; Lee et al., 2020; Zerbo et al., 2015). Besides SC and PANDAS, other infections during childhood/adolescence seem to increase the chance to develop schizophrenia, non-affective psychoses, mood, eating or anxiety (Breithaupt et al., 2019; Chaplin et al., 2020; Dalman et al., 2008; Goodwin, 2011; Liu et al., 2021). Severe encephalitis and meningitis are now known to cause brain atrophy with long-term cognitive and psychiatric symptoms (Kapur et al., 1994; Khanna, 1988; Yaramiş et al., 2009). Data from a Danish longitudinal register showed that infections requiring hospitalizations were associated with subsequent increased risk of receiving a diagnosis of any mental disorders and of redeeming a prescription for psychotropic medication (Benros et al., 2011). However, several pathogens (**table 2**), including Herpesvirus (HHV), Influenza virus, Measles virus, Borna disease virus (BDV), Borrelia Burgdorferi, Chlamydia spp., Mycoplasma spp., Toxoplasma gondii (T. gondii), Toxocara spp., Helicobacter pylori (H. pylori), seem to increase the risk for subsequent nuropsychiatric disorders without causing no severe acute infections (Arias et al., 2012; Barichello et al., 2016; Coughlin, 2012; Hornig, 2013; Hornig & Lipkin, 2001; Wang et al., 2014).

In the past, the term "mild (chronic) encephalitis" was coined referring to these clinical pictures (Müller, 2015). In the most recent meta-analyses, the strongest evidence was reported for T. gondii and HHV, both agents causing latent infection after an acute phase (Burgdorf et al., 2019; Fernandes et al., 2021; Frye et al., 2019; Hamdani et al., 2018; Prusty et al., 2018; Snijders et al., 2019; Wang et al., 2014; Ye et al., 2020). Latent T. gondii infections were related to subtle neurophysiological changes (Tedford & McConkey, 2017; Tomasik et al., 2016) and subsequent severe neuropsychiatric conditions, such as schizophrenia and bipolar disorders (Burgdorf et al., 2019; Chaudhury & Ramana, 2019), increased aggression and impulsivity (Cook et al., 2015), suicide (Sutterland et al., 2019), and Alzheimer's dementia (AD) (Nayeri Chegeni et al., 2019b). Further, growing evidence argues for a potential role of latent HHV infections in CNS diseases, including psychiatric disorders, even in immune-competent individuals. These conditions show heterogeneous courses being monophasic, relapsing-remitting, or even chronic (Ludlow et al., 2016). HHV infection was associated with suicidal behavior and greater risk to have a psychiatric diagnosis (Nissen et al., 2019), including schizophrenia (Dickerson et al., 2019; Yolken, 2004), Recently, abnormally elevated antibody titles in response to Epstein-Barr virus (EBV) virions have been demonstrated in schizophrenic patients in comparison to controls. This exaggerated immune response, combined with an established genetic susceptibility, would lead up to a 8.5-fold increase of a lifelong schizophrenia diagnosis (Dickerson et al., 2019). Evidence also suggested that among patients with schizophrenia or bipolar disorders, infections with Herpes simplex virus (HSV), Cytomegalovirus (CMV), and T. gondii were related to cognitive dysfunctions, particularly with working memory impairment (Hamdani et al., 2017). Even in the prospective Northern Manhattan Study (NOMAS), a high infectious burden (assessed with serological markers for Chlamydia pneumoniae,

Table 2. *Microbes involved in neuropsychiatric disorders*

Viruses	Bacteria	Parasites
Influenza virus	Treponema pallidum	Toxoplasma gondii
Herpes simplex virus 1/2	Borrelia burgdorferi	Toxocara spp.
Epstein-Barr virus	GABHS	
Varicella zoster virus	Chlamydiaceae spp.	
Cytomegalovirus	Mycoplasma spp.	
Human herpes virus-6	Microbiota bacteria	
Rubella virus		
Measles virus		
Mumps virus		
Poliovirus		
Human immunodeficiency virus 1/2		
Endogenous retroviruses		
Borna virus		
Parvovirus B19 and AAV-2		
West Nile virus		
Enterovirus 71		
Coxsackievirus B3		
Polyomaviruses (JC virus and BK virus)		

Note: GABHS = group A beta-hemolytic streptococcus

Helicobacter pylori, CMV, HSV-1 and HSV-2) was related to cognitive decline independently from cardiovascular risk (Katan et al., 2013). The multifaceted relationship between cognition and infection was also highlighted by HIV-associated neurocognitive disorders, that emerge in patients with HIV infection despite highly active antiretroviral therapy (Kamminga et al., 2013), as well as by the association found between infections and increased rate of cognitive decline in AD patients (Perry et al., 2010).

A gender difference associated with infectious agents was also reported, with a greater risk for mood disorders associated with both bacterial and virus infections in women than men (Simanek et al., 2018). This is an interesting, albeit isolated finding that requires to be deepened in future studies

Recent investigations also suggested common genetic vulnerability in psychiatric disorders and infections, while highlighting a tight genetic association for suffering from at least one psychiatric diagnosis and recurrent infections (Nudel et al., 2019). Indeed, psychiatric and chronic autoimmune diseases share several genetic polymorphisms especially in the major histocompatibility complex (MHC) (Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis, 2013).

Furthermore, psychotropic drugs, such as mood stabilizers (i.e., lithium and valproate) (Amsterdam et al., 1990; Ornaghi et al., 2016), antipsychotics (i.e., clozapine and chlorpromazine) (Anderson et al., 2019; Plaze et al., 2020), and antidepressants (i.e., fluvoxamine) (Lenze et al., 2020), showed potential antiviral actions, inhibiting viruses infection and/or reactivation (Golden et al., 2021). On the other hand, some evidence, although controversial suggested a possible therapeutic effect of some antimicrobials agents in psychiatric disorders (Dietrich et al., 2020; Kogelnik et al., 2006; Prasad et al., 2013), at least in the subgroup of patients with signs of infection (i.e., high levels of specific IgG) (Breier et al., 2019, Deakin et al., 2018). Several antibiotics agents, including penicillin, macrolides (i.e., azithromycin), and cephalosporins (i.e., cefdinir), were investigated in PANS/PANDAS patients, reporting efficacy in reducing neuropsychiatric symptoms in such pa population (Sigra et al., 2018). Remarkably, while the use of eradicating antibiotic therapy during active infections in PANDAS/PANS is well established, its effect on ongoing infections is still controversial (Burchi & Pallanti, 2018; Marazziti et al., personal observations).

Possible mechanism of actions of microbes in psychiatric disorders

Most of the current evidence would indicate inflammation as an intermediate pathway between infectious agents and different neuropsychiatric conditions. Several pathogens have been hypothesized to trigger inflammatory processes that would lead to CNS functional/structural damage in vulnerable subjects (Pape et al., 2019). Transient low-grade inflammation after an infection might modify mental processes up to the onset of a broad range of neuropsychiatric symptoms, including change in mood, social behavior, and cognitive abilities – clinical pictures also known as sickness behavior (D'Mello & Swain, 2017; Kelley et al., 2003; Pape et al., 2019). These manifestations are usually related to the release of pro-inflammatory cytokines, such as interleukin of type 1β (IL-1β), IL-6 and tumor necrosis factor (TNF), outside the CNS, that would affect the brain via neural (mainly vagal) pathways, interaction with cytokine receptors on cerebral endothelial cells, and/or microglial activation (D'Mello & Swain, 2017). Similarly, treatment with some cytokines, as interferon (IFN) used for chronic viral hepatitis or multiple sclerosis, was associated with neuropsychiatric symptoms as an adverse effect (Aarab et al., 2018; Malek-Ahmadi, 2001; Neilley et al., 1996), although it should be noted that this transient response is absolutely physiological and can help the organism fight against pathogens (Kelley et al., 2003). Beside transient low-grade inflammation, infectious agents

may also provoke a chronic low-grade inflammation, associated to the development of neurotoxicity, neurodegeneration, and persistent neuropsychiatric symptoms over time (Larochelle et al., 2016). The chronic secretion of pro-inflammatory cytokines may provoke neurotoxic effects by increasing production of reactive oxygen species, activating microglia, reducing monoamine transmission, and potentiating glutamatergic transmission (Hanisch, 2002; Müller & Schwarz, 2007; Gertig & Hanisch, 2014; Lively & Schlichter, 2018; Pacheco et al., 2007). Some microbes might also act via epigenetic pathways to modulate the immune responses, thereby influencing the risk profile for neuropsychiatric disorders (Wendeln et al., 2018). Indeed, the exposure to T. gondii is supposed to modulate the influence of toll-like receptor (TLR)-2 genetic variation in bipolar disorders (Oliveira et al., 2016).

Conversely, other pathogens could act predominantly through the direct induction of cytotoxicity and neurodegeneration, as in the case of HSV-1 infection in AD (Fülöp et al., 2018; Lövheim et al., 2015; Wozniak et al., 2009). HSV-1 proteins impair neuronal autophagy and, consequently, antigen presentation (O'Connell & Liang, 2016). In mice, recurrent asymptomatic activation of HSV-1 leads to upregulation of markers of neuroinflammation and early neurodegeneration (Martin et al., 2014). HHV may induce apoptosis, autophagy, and cellular oxidation alterations (Brunson et al., 2016; Duarte et al., 2019; Ludlow et al., 2016), even in other neurodegenerative and perhaps neuropsychiatric disorders (Abdoli et al., 2020; Duarte et al., 2019).

Autoimmunity is another important mechanism that can be sparked by infectious agents, mainly through molecular mimicry phenomena (Hornig, 2013; Pape et al., 2019). Increased prevalence of autoimmune and atopic disease (Benros et al., 2011; Benros et al., 2012; Bilbo et al., 2012; Eaton et al., 2010; Elamin et al., 2013; Keil et al., 2010; Mostafa & Shehab, 2010; Pedersen et al., 2012; Swedo, 1994, 2002), as well as the presence of autoantibodies (Dickerson et al., 2011; Cascella et al., 2013; Fox et al., 2012; Najjar et al., 2012; Rossi et al., 2011; Rout et al., 2012; Severance et al., 2012) in individuals with psychiatric disorders and their first-degree relatives, suggested a strong association between these conditions and autoimmunity. However, while the evidence is more robust for some of these conditions – as in the case of SC and PANDAS – for others remains weak. Both innate and adaptive immune mechanisms play a role in autoimmunity. The autoimmune psychosis is a sort of paradigm in this sense, as symptoms occur because of the presence of autoantibodies against neuropil that can develop spontaneously in neoplastic diseases or after viral infections, particularly HSV encephalitis (Armangue et al., 2015). In the latter, cytotoxic T cells are supposed to be responsible for much of the neuronal damage associated with neuropsychiatric symptoms (Bien et al., 2012). Autoantibodies against extracellular antigens involved in synaptic transmission also seem involved, including antibody against the gamma aminobutyric acid receptor of type A (GABA-A), the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, and the N-methyl-d-aspartate (NMDA) glutamate receptor, although disagreement do exist (Dalmau et al., 2011; Haselmann et al., 2018; Hughes et al., 2010; Petit-Pedrol et al., 2014). Patients with anti-NMDAR encephalitis can show symptoms like sleep disorders, anxiety, paranoia, mania, agitation, catatonia, but also memory impairment, disintegration of language, abnormal movements, and autonomic instability (Dalmau et al., 2011). Antibodies that cross-react with the NMDA receptor have been also found in patients with neuropsychiatric systemic lupus erythematosus (DeGiorgio et al., 2001; Nestor et al., 2018), with pure psychotic symptoms, and even in healthy subjects (Hammer et al., 2014). Similar results have been reported for a variety of brain antigens, challenging the pathological relevance of CNS-specific autoantibodies (Dahm et al., 2014).

Microbes and OCD

Some evidence supported a possible role of infections in the pathophysiology of OCD, at least in a subgroup of patients. The first description of OCD symptoms in patients with lethargic encephalitis and basal ganglia lesions after viral infections dates back to the end of the last century (Cheyette & Cummings, 1995), however this report was mostly ignored for the interest mainly focused on OCD pictures precipitated by GABHS at that time. Other pathogens, including bacteria, virus and parasites, have been associated with OCD in a few cases of both children and adults (**table 3**). Most of them are neurotropic pathogens that after acute infection may establish a latent infection in the CNS.

Group A beta-hemolytic streptococcus is a gram-positive bacterium involved in the etiology of a variety of diseases, including streptococcal pharyngitis, rheumatic fever, and scarlet fever, more recently associated with SC, PANDAS, and OCD as well. Beside SC and PANDAS, some data suggested a potential role of streptococcal infection even in OCD subjects without SC and without PANDAS (Mell et al., 2005; Wang et al., 2016). A higher frequency of OCD and related disorders was observed in subjects with present or previous history of RF without SC (Alvarenga et al., 2006; Alvarenga et al., 2009; Ashfaq-U-Rahaman et al., 2007; Hounie et al., 2004; Mercadante et al., 2000), suggesting that GABHS can trigger psychiatric conditions that may persist throughout life regardless of GABHS reinfections. As such, RF seems to increase the risk for OCD spectrum disorders, even in the non-acute phase (Hounie et al., 2004; Mercadante et al., 2000; Mercadante et al., 2005). A cross-sectional study found that the rate of clinical OCD and subclinical OCD was 10% and 3% respectively (a rate much higher than the 1-3% rate reported in general population) in adult subjects with RF history, even in the absence of frank chorea (Ashfaq-U-Rahaman et al., 2007). Family

Table 3. *Microbes implicated in obsessive-compulsive disorder.*

Viruses	Bacteria	Parasites
Herpes simplex virus 1	GABHS	Toxoplasma gondii
Borna disease virus	Borrelia spp.	
	Microbiota bacteria	

Note: GABHS = group A beta-hemolytic streptococcus.

studies also indicated that this relationship could be familial, based on findings that OCD-related disorders aggregate more frequently in first-degree relatives of RF probands, when compared with controls (Hounie et al., 2007; Seixas et al., 2008). A population-based cohort study using data from the nationwide Danish registers found that individuals with a positive streptococcal test result had an increased risk of any mental disorder, particularly of OCD and tic disorders compared with individuals with a negative streptococcal test (Orlovska et al., 2017). Some case reports revealed the development of obsessions and compulsions in adult subjects after severe sore throat and fever opening the question of the possible existence of PANDAS-like clinical pictures in adults (Bodner et al., 2001; Pfizer & Andrade, 1999).

Borrelia burgdorferi is a spirochete known to cause Lyme disease (LD), a bacterial infection spread through ticks that, weeks or months after a migrant erythematous rash, can cause damage to the joints, heart, and nervous system if untreated. Individuals with LD showed higher rates of any mental disorder, particularly affective disorders, suicide attempts, and death by suicide compared with those without it (Fallon et al., 2021). A self-report study on adults subjects with a previous LD diagnosis, recruited from online supporting groups, highlighted a high rate (84%) of OCD symptoms (Johnco et al., 2018). In most cases, OCD symptom onset was reported to be gradual and responded to psychological and drug treatment including antibiotic treatment (Johnco et al., 2018).

Toxoplasma Gondii is a ubiquitous intracellular parasite that, after a brief acute infection, forms infectious cysts in the brain, muscle, and other tissues, establishing a lifelong latency. Although latent infections are traditionally considered to be silent, mounting evidence points to their association with neurological deficits and neuropsychiatric disorders (Egorov et al., 2018). A few MRI studies examined the location of T. gondii cysts in the human's brain, mainly on AIDS patients who, as being immunocompromised, have active infections, and they showed that frontal and parietal lobes, basal ganglia, and cerebellum are the preferred grafting sites (McConkey et al., 2013).

Some researchers investigated the association of T. gondii with OCD on the basis of the preferential neurotropism of this parasite for the same areas involved in OCD pathophysiology. Case control studies reported higher T. gondii seroprevalence in OCD patients, as compared with controls. A recent meta-analysis of eight case-control and three cross-sectional studies reported a higher risk to develop OCD in subjects seropositive to T. gondii and with a history of toxoplasmosis (OR = 1.96) (Nayeri Chegeni et al., 2019a). In agreement with this findings, an ecological study revealed a tight correlation between incidence of toxoplasmosis and OCD-related burden in both European ($p = 0.02$) and non-European countries (Flegr, 2015). Recently, another Internet-based cross-sectional survey using a Facebook-based snowball method found that seropositive patients for T. gondii have a greater probability of a previous diagnosis of OCD (OR = 2.5) and elevated scores on OCD scales (Flegr & Horáček, 2017). Interestingly, anti-protozoan medications in children with toxoplasmosis and OCD showed to decrease both T. gondii antibodies and OCD symptoms (Brynska et al, 2001):

Borna disease viruses are negative-strand RNA viruses able to establish a non-cytolytic persistent CNS infection, with preferential neurotropism for CSTC circuits regions. They infect a variety of warm-blooded animals worldwide, like horses, sheep and cattle, in which cause a wide spectrum of neurological disorders, including immune-mediated diseases and behavioral alterations without inflammation resembling symptoms observed in human psychiatric diseases such as schizophrenia, mood disorders, and autism (Amsterdam et al., 1985; Carbone, 2001). In 2005, Dietrich et al. (Dietrich et al., 2005) reported an association between BDV-specific circulating immune complexes and dysfunction in the cingulate cortex of OCD patients. However, this finding resulted unspecific, as BDV antibodies were also detected also in patients with other psychiatric conditions and in healthy individuals (Ludlow et al., 2016).

Herpesviruses are large, enveloped viruses possessing a linear double-strand DNA. Similarly, to T. gondii, after a primary lytic phase, HHVs establish life-long latent infections in specific type cells that can occasionally be reactivated (Ludlow et al., 2016). Acute HHV infections, particularly HSV encephalitis, are known to be associated with neuropsychiatric pictures, including OCD symptoms (Torrey, 1986). Similarly, a case report study reported an OCD secondary to a lesion in lentiform nuclei associated with a history of recent Varicella Zoster virus (VZV-) infection in a child (Yaramiş et al., 2009). Attention deficit and tic disorders were also observed after varicella encephalitis localized in basal ganglia (Dale et al., 2003). Noteworthy, CSTC loop areas (especially basal ganglia, frontal, and temporal lobes) are involved in both HSV encephalitis (Damasio & Van Hoesen, 1985; Ludlow et al., 2016) and OCD pathophysiology. On the contrary, to date a few studies investigated the possible link between HHV latent infections and OCD development. A study reported higher titers of blood and CSF IgG anti-HSV-1 in group of OCD patients, but these findings were no longer replicated (Khanna et al., 1997a, 1997b).

Possible role of microbes in OCD

Obsessive-compulsive disorder is currently considered a mental illness with a complex etiology and pathogenesis possibly involving a variety of molecular, genetic, epigenetic, cellular, and distinct brain networks. This would explain the heterogeneous phenotypes of the patients possibly due to specific alterations in different molecular pathways and processes. Beside the biological domain, simultaneous alterations in other individual organization areas might contribute to the OCD development, including psychological, social, cultural, cognitive, emotional, and behavioral domains, where changes in an area might trigger modifications in other ones. Moreover, although the pathophysiology of OCD is still unclear, mounting evidence indicates that dysfunctions in specific neuronal circuits might explain a major part of the OCD typical symptoms.

Studies in animal with stereotypical and grooming behaviors (considered reliable animal models of OCD) (Burguière et al., 2015; Kalueff et al., 2016), as well as advanced functional and structural brain imaging techniques, highlighted alterations of specific neural networks in OCD, especially cortico–striato–thalamo–cortical (CSTC) loop, thus suggesting a disrupted integration of sensorimotor, cognitive, affective, and motivational information in this disorder (Baxter et al., 1992; Fineberg et al., 2018; Kwon et al., 2009). These circuits include direct (positive feedback) and indirect (negative feedback) pathways projecting from specific cortical areas to the corresponding subregions of the striatum and thalamus with recurrent projections to the cortex. The direct pathway facilitates striatal-thalamic

transmission, promoting the actuation of procedural strategies. By contrast, the indirect pathway inhibits thalamic activity, allowing the cortex to respond to different stimuli. These pathways are involved in a variety of activities, including reward processing, action selection, habit formation, and motor control (Robbins et al., 2012). Moreover, they play an important role by using complex feedbacks in the recognition of significant behavioral stimuli (and error detection) and in the regulation of targeted responses (Lovinger, 2010). The first evidence that OCD symptoms may be mediated by CSTC circuits included research showing an association between parkinsonian post-encephalitis, obsessive-compulsive symptoms, and striatal lesions (Reghunandanan et al., 2015). Later, OCD symptoms have also been observed in other neurological disorders involving striatal pathology, including Tourette's syndrome, SC, Huntington's disease, Parkinson's disease, and neuroacanthocytosis (Chacko et al., 2000; Laplane et al., 1989; Laplane, 1994; Maia et al., 2008; Rapoport, 1989). The main neurotransmitters underpinning OCD symptoms correspond to key neurotransmitters of CSTC circuits (Stein et al., 2019). Noteworthy, besides functional and structural anomalies of CSTC circuits (Maia et al., 2008; Rasgon et al., 2017), emerging evidence suggests also the involvement of widespread associative networks in OCD, including regions of the frontal, parietal and temporal cortex, limbic areas, and cerebellum (Hazari et al., 2019).

Although different mechanisms have been hypothesized on how pathogens might contribute to the OCD development, it is generally agreed that they would converge to cause functional/structural alterations of CSTC circuits, with direct or indirect neurotransmitter dysfunctions.

Based on the high rate of anti-basal ganglia antibodies detected in SC and PANDAS cases (Kirvan et al., 2003; Williams & Swedo, 2015), it was proposed that some pathogens could act by triggering autoimmune processes against brain regions involved in OCD pathophysiology. This autoimmunity would be unleashed by molecular mimicry, whereby the antibodies produced against the pathogen cross-react with neuronal antigens, producing both antibody– and/or cell-mediated neural damage (Kapadia & Sakic, 2011). In SC and PANDAS antibodies produced against GABHS components cross-react with endogenous proteins, mainly represented by human lysoganglioside GM1 (a ganglioside expressed in the brain (Kirvan et al., 2003)), neuronal surface glycolytic enzymes (Dale et al., 2006), tubulin (Kirvan, et al., 2007), and D1 and D2 receptors (Ben-Pazi et al., 2013; Dale et al., 2012). However, in a prospective study of children with post-streptococcal neuropsychiatric symptoms, no correlation was found between clinical symptoms and a change in autoimmune markers, such as anti-neural antibodies or inflammatory cytokines (Singer et al., 2008). Since these cross-reactive antibodies showed to bind basal ganglia components and induce CaMKII activity of Cam Kinase II (CaMKII) – a protein kinase involved in multiple signaling cascades (Kirvan et al., 2006) – other authors hypothesized that they may directly stimulate or block the receptors expressed in basal ganglia. In particular, it has been proposed that antibodies against the D1 and D2 receptor may be pathologically relevant in SC and PANDAS, as they can affect dopaminergic neurons in the basal ganglia and in the cortex contributing to the development of movement and behavioral disorders observed in these conditions (Williams & Swedo, 2015). Notably, in most cases the success of the animal models in PANDAS was based on the possibility of autoantibodies to breach the BBB (Hornig, 2013). This hypothesis could explain why healthy individuals often harbor antineuronal antibodies in their serum (Levin et al., 2010). Plausibly these autoantibodies failed to induce disease due to the absence of additional pathological factors – such as proinflammatory cytokines and molecules associated with stress responses – that compromise the integrity of the blood brain barrier, necessary to allow the autoantibodies to access the SNC (Levin et al., 2010). It is also possible that, although immunoassays may detect such autoantibodies in healthy individuals, their relevant features, that correlate with pathogenicity might not be captured through such assays, including differences in IgG subclasses, presence of additional immunoglobulin isotypes differences in specificity (Maes et al., 2011) and in binding ability in response to the local environment (i.e., regional differences in redox/oxidative stress conditions (McIntyre et al., 2007).

The raised levels of immuno-inflammatory markers in significant subsets of OCD patients (Gerentes, et al., 2019; Marazziti et al., 1999; Marazziti et al., 2018), led to infer that some infection might initiate chronic inflammation that activates microglial inflammasome that, in turn, causes an increase in pro-inflammatory mediators (Pape et al., 2019). In addition, cytokines can also influence neuronal apoptosis (Hu et al., 1997; Mousa & Bakhiet, 2013), neurogenesis, neuroplasticity, and neurotransmission (Borsini et al., 2015; Levin & Godukhin, 2017). Particularly, they may modulate serotoninergic and glutamatergic systems, involved in OCD (Müller & Schwarz, 2007). Such an explanation, proposed for LD, might also fit with T. Gondi and HHV infections (Johnco et al., 2018). Indeed, T. gondii infections were associated with elevated biomarkers of chronic inflammation and vascular injury (El-Sayed et al., 2012; Egorov et al., 2018, 2021; Tomasik et al., 2016), as well as with subtle neurophysiological changes (Tedford & McConkey, 2017; Tomasik et al., 2016). Beside the cytotoxic action typical of acute infections, HHV latency may induce immune dysregulations with secretion of several immune-modulatory cytokines, platelet activation, and vascular dysfunctions (Brunson et al., 2016; ; Duarte et al., 2019; Ludlow et al., 2016).

Given the neurotropism for areas involved in OCD pathophysiology, a mechanism of direct or immune-mediated damage at the level of the implant site was proposed for other infectious agents. This pathogenetic model was also called “tuberculosis model”, since, as in the tuberculosis, the disease arises from the interaction between the pathogen, that preferentially settles in some organs, and the immune processes acting to contain it (Szechtmane et al., 2014). It was first proposed for OCD (Rotge et al., 2010), by noting that BDV infection associated with OCD symptoms (Bode et al., 1995), had preferential neurotropism for CSTC circuits areas. Therefore, they speculated that BDV infection grafting into CSTC circuits could cause immune-mediated alterations of CTCS networks producing OCD symptoms. However, it was also proposed that BVD could elicit glutamate excitotoxicity (Rotge et al., 2010), since genetic association were reported between glutamate transporter gene variants and OCD onset (Arnold et al., 2006). Indeed, according to these authors, genetic alterations of the glutamatergic system would facilitate pathogens-induced immunopathological reactions in the OCD-relevant brain regions, with consequent hyperactivity of basal ganglia loops (Wu et al., 2012). It was also observed that BDV specifically

interferes with the activity-dependent enhancement of synaptic vesicle recycling, one component of neuronal communication together with synaptic transmission (Volmer et al., 2006). In addition, in rats, BDV infection may induce expression of key enzymes of the kynurenine pathway, shunting tryptophan from the production of 5-HT towards that of the neurotoxic quinolinic acid. This pathogenetic hypothesis can be speculated for all neurotropic pathogens, including T. Gondii and HHV, and it would be responsible for the decreased functioning of the serotonergic system in OCD, that is the core abnormality in this condition and still represents a sort of paradigm for current anti-obsessive drugs, i.e., 5-HT reuptake inhibitors (Müller & Schwarz, 2007).

Finally, infectious agents could trigger OCD pictures through a sensitization-related mechanism leading to the CSTC circuit hyperactivity. This phenomenon may occur in both physiological and pathological conditions. An example is what is labeled as the "compensatory behavioral prophylaxis" during the menstrual cycle (Fessler, 2001). At times of relatively high progesterone levels, women seem more susceptible to infections because of the immune system suppression. During these periods, OCD symptoms, like cleaning rituals, may be a behavioral compensation to prevent contamination (Woolf, 2011; Szechtman et al., 2014). Unfortunately, these are just suggestions that would require to be corroborated by specific studies.

Conclusions

The findings discussed in this review would suggest a possible involvement of infectious agents in the development of primary neuropsychiatric conditions, such as schizophrenia, mood disorders, ASD, ADHD, tic disorders, anorexia nervosa and PTSD (McCusker & Kelley, 2013; Pape et al., 2019). Several mechanisms have been proposed through which microbes or viruses could contribute to CSN dysfunctions. However, most of the evidence suggested immune alterations and inflammation as intermediate pathways. Several pathogens could act by triggering immune-inflammatory processes that, in turn, would lead to CNS functional/structural damage (Pape et al., 2019). Indeed, infectious agents may provoke a chronic low-grade inflammation, associated to the development of neurotoxicity, neurodegeneration, and persistent neuropsychiatric symptoms over time (Larochelle et al., 2016). The chronic secretion of pro-inflammatory cytokines my induce neurotoxic effects by increasing production of reactive oxygen species, activating microglia, and altering neurotransmission (Hanisch, 2002; Hanisch & Gertig, 2014; Lively & Schlichter, 2018; Müller & Schwarz, 2007; Pacheco et al., 2007). Some microbes could also act via epigenetic pathways to modulate the immune responses, thereby influencing the risk profile for neuropsychiatric disorders (Wendeln et al., 2018). In addition, molecular mimicry, anti-neuronal autoantibodies, pro-inflammatory cytokines, microglial activation, neuroinflammation, and BBB disfunctions may be all involved in such conditions. It is currently known that the interaction between neurons, glial cells, and immune system contributes to the proper functioning of the CNS (Pape et al., 2019), so that the disturbance of this balance by external agents is likely to modify mental processes. However, several questions remain unresolved, such as whether immunological dysfunctions are a cause or a consequence of certain disorders, or why the same infectious agent can lead to clinically distinct disorders. For example, previous infections and/or reactivations by CMV, EBV, and T. Gondii are associated with different psychiatric disorders, possibly sharing common neuro-inflammatory patterns and/or neurotransmitter system dysfunctions. Latent T. gondii infections, was related to schizophrenia and bipolar disorders (Burgdorf et al., 2019; Chaudhury & Ramana, 2019), increased aggression and impulsivity (Cook et al., 2015), suicide (Sutterland et al., 2019), and AD (Nayeri Chegeni et al., 2019b). The HHV infection was associated with suicidal behavior and greater risk to have a psychiatric diagnosis (Nissen et al., 2019), including schizophrenia (Dickerson et al., 2019; Yolken, 2004), bipolar disorder and depression (Asoode et al., 2016; Prusty et al., 2018). Evidence also suggested a possible relationship between infections with HSV, CMV, and T. gondii and cognitive dysfunctions, particularly of working memory amongst patients with schizophrenia or bipolar disorders (Hamdani et al., 2017). Therefore, the variability of outcomes after infections would suggest that these pathogens could be related to symptom clusters or dimensions rather than to distinct nosological entities, by non-specifically increasing the risk for CNS dysfunctions (McAlonan et al., 2010; McCusker & Kelley, 2013).

In addition, the available evidence would indicate that exposure to some infectious agents could represent a possible environmental risk factor even for the onset of primary OCD. Several studies associated infectious agents with pediatric OCD forms, characterized by an abrupt onset and an episodic course, currently globally known as PANS. In PANS the OCD onset is typically acute – triggered by infection, reinfection, or reactivation from an infectious agent – and the OCD course is typically episodic, with symptoms resolving as the infection cleared. Findings in adult patients with OCD are more limited to a few, albeit intriguing studies investigating the presence of seropositivity for bacteria, viruses, or parasites with primary OCD. Taken as a whole, these studies suggested that OCD symptoms triggered by infectious agents might show a gradual onset and persist life-long regardless of acute infection or reinfection. The variability in CNS outcomes after infection can reflects differences in both exposure timing or in type or severity of host immune responses to the agent (McCusker & Kelley, 2013). Autoimmunity and latent infections by neurotropic pathogens could be a plausible explanation (Bechter, 2013; Flegr & Horáček, 2020; Watson et al., 2013). Some evidence also indicates that co-or-multiple infections might synergically augment the level of inflammatory reactions and induce more severe outcomes than a single infection (Abdoli et al., 2020).

Different mechanisms have been hypothesized on how pathogens and related immunological and inflammatory processes could contribute to the OCD development. Agreement does exist that they would ultimately converge to cause functional/structural alterations of areas involved in OCD pathophysiology (i.e., CSTC networks), with cascade dysfunctions of several other mechanisms. As with other neuropsychiatric disorders, microbes seem to act predominantly through immuno-inflammatory pathways, given the raised levels of immuno-inflammatory markers in a significant subset of OCD patients (Gerentes et al., 2019; Marazziti et al., 2018). The associations between OCD and infections were mainly investigated by measuring pathogen-specific IgG, a rather generic parameter, reflecting previous exposure to infectious agents, whether it is infection, reinfection, or reactivation. The limited

findings on the possible temporal relationship between pathogenic infections and OCD development are also controversial, particularly in prospective clinical studies (Luo et al., 2004; Leckman et al., 2011; Murphy & Pichichero, 2002). The demonstration of a reliable temporal association between these two events is lacking, although it would be fundamental to prove a cause-effect relationship.

Several limitations of the reviewed studies should be emphasized since they lessen the conclusions about the association between infections and OCD. Indeed, the currently available literature is meagre and mainly represented by case reports, cross-sectional or case-control studies on small samples. The different studies are heterogeneous in terms of population characteristics and methods used. Variations in the sensitivity and specificity of assay kits and the different cut-off values are also factors affecting the prevalence of infections. Furthermore, except for studies on T. Gondii, most of these results have not been replicated. Finally, the lack of evaluation of different associated factors in eligible studies can be considered as basic gap.

In conclusion, further studies on large homogeneous samples and with a standardized prospective design are needed to investigate the possible links between infectious agents and neuropsychiatric disorders. If accurate and controlled, they might shed new light on this field that has significant potential pathophysiological, clinical and therapeutic implications. Therefore, together with the infectious agent Ig profiles, fluid and imaging immuno-inflammatory biomarkers, as well as functional/structural neuroimaging studies, should also be evaluated. Again, new insights into the role of infections and the immune system in psychiatric disorders might contribute to the development of new and more tailored drugs for psychiatric disorders, as well as to psychiatry precision medicine, in which treatment would be based on altered pathological pathways detected in single patient. This seems particularly relevant in patients suffering from OCD that, in the real-life clinical practice, result particularly resistant to currently employed therapeutic strategies.

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