



Schizophrenia: The new etiological synthesis

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ABSTRACT

Schizophrenia has been an evolutionary paradox: it has high heritability, but it is associated with decreased reproductive success. The causal genetic variants underlying schizophrenia are thought to be under weak negative selection. To unravel this paradox, many evolutionary explanations have been suggested for schizophrenia. We critically discuss the constellation of evolutionary hypotheses for schizophrenia, highlighting the lack of empirical support for most existing evolutionary hypotheses—with the exception of the relatively well supported evolutionary mismatch hypothesis. It posits that evolutionarily novel features of contemporary environments, such as chronic stress, low-grade systemic inflammation, and gut dysbiosis, increase susceptibility to schizophrenia. Environmental factors such as microbial infections (e.g., *Toxoplasma gondii*) can better predict the onset of schizophrenia than polygenic risk scores. However, researchers have not been able to explain why only a small minority of infected people develop schizophrenia. The new etiological synthesis of schizophrenia indicates that an interaction between host genotype, microbe infection, and chronic stress causes schizophrenia, with neuroinflammation and gut dysbiosis mediating this etiological pathway. Instead of just alleviating symptoms with drugs, the parasite x genotype x stress model emphasizes that schizophrenia treatment should focus on detecting and treating possible underlying microbial infection(s), neuroinflammation, gut dysbiosis, and chronic stress.

1. Introduction

Schizophrenia is a severe mental disorder, which affects about 0.75% of the world's population (Moreno-Kustner et al., 2018), imposing an annual economic burden of more than \$150 billion in the United States alone (Cloutier et al., 2016) and between 0.02% and 1.65% of GDP cross-nationally (Chong et al., 2016). Although schizophrenia is a low-prevalence disorder, it was the 12th most disabling disorder among 310 diseases and injuries globally in 2016 (Charlson et al., 2018).

Schizophrenia is characterized by psychosis, an abnormal condition of the mind, which leads to difficulties determining what is real and what is not. In addition, schizophrenia can include symptoms such as social withdrawal, anhedonia, amotivation, social cognitive impairment, neurocognitive dysfunction (Engelstad et al., 2019; Stratton et al., 2017), and deficits in working memory, processing speed, and executive function (McCutcheon et al., 2020b). A meta-analysis reported that a pooled proportion of 6.48% of all homicide offenders had a schizophrenia diagnosis (Large et al., 2009), which is much higher than the

lifetime prevalence estimates of schizophrenia (0.48–0.75%) (Moreno-Kustner et al., 2018; Simeone et al., 2015). Schizophrenic patients generally have a reduced life expectancy (about 15 years shorter than the general population), lower reproductive rate, and a 22-fold increased lifetime risk of death by suicide compared with the general population (Hjorthoj et al., 2017). The first symptoms of schizophrenia typically appear in late adolescence or early adulthood (Lichtenstein et al., 2009). The prevalence of schizophrenia is higher in men than in women in developed but not in developing countries, and men are also prone to a more severe form of schizophrenia (Aleman et al., 2003). The etiology of schizophrenia has not been understood and there have been no major breakthroughs in the treatment of schizophrenia for 60 years (cf. Akil et al., 2010).

The heritability of schizophrenia has been estimated to be as high as 80% (Hilker et al., 2018). A large Swedish study found that males with schizophrenia had fertility rates that were as low as 23% of the reference population (accounting for age, sex, and family size), while fertility rates in females with schizophrenia were 47% of the reference population

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(Power et al., 2013). Thus, due to its high heritability and substantial decrease in an affected person's reproductive success, natural selection would be expected to have eliminated the genetic variants that make individuals susceptible to develop schizophrenia (Cook et al., 2020). Furthermore, genetic analyses have shown that the total burden of runs of homozygosity is reliably but weakly associated with schizophrenia (Keller et al., 2012). This suggests that causal variants (alleles) that are associated with increased schizophrenia risk are more recessive than expected by chance and are therefore likely to have experienced negative selection over evolutionary time (Zietsch et al., 2015). This negative selection pressure can be inferred from *directional dominance*, that is, deleterious alleles having a higher likelihood of being more recessive while beneficial alleles are more likely to be dominant (Zietsch et al., 2015). Genotype analyses have further shown that people with schizophrenia carry an increased burden of deleterious mutations (Loohuis et al., 2015).

To unravel the evolutionary paradox that arises from these findings, many evolutionary explanations have been suggested for schizophrenia. We present them in Section 5. However, none of them have been able to explain, for example, why chronic stress is often a trigger of psychosis (cf. Howes and McCutcheon, 2017; Nugent et al., 2015). In addition, they have failed to explain why psychosis often occurs in mental disorders such as major depressive disorder, bipolar disorder, and schizoaffective disorder (cf. American Psychiatric Association, 2013). Psychosis may also occur in some other diseases; for example, about half of Alzheimer's patients have psychosis (Murray et al., 2014), and psychosis is sometimes reported in patients with central nervous infections like meningitis (Kumar et al., 2011). Notably, previous evolutionary hypotheses have not facilitated finding better treatments or a cure for schizophrenia.

Although inferences based on family and twin studies have assumed that schizophrenia is largely a genetic disorder, with environmental factors playing a limited role, this seems not to be the case (Torrey and Yolken, 2019). For example, based on six national twin register studies, Torrey and Yolken (2019) calculated that schizophrenia concordance rate in monozygotic twins was only 28% (and 6% for dizygotic twins). In other words, of all the monozygotic twin pairs (i.e., those with identical genes; $n = 268$), both twins ($n = 74$) developed schizophrenia only 28% of the time, whereas only one of the monozygotic twins became affected 72% of the time—despite having identical genes (Torrey and Yolken, 2019). In addition, there is no individual gene or allele that causes schizophrenia; instead, thousands of gene variants comprise risk factors for schizophrenia, each having a small effect, while many of them are also associated with bipolar disorder and other mental disorders (Anttila et al., 2018; Hindley, 2021; Legge et al., 2021). The risk profile scores constructed from alleles associated with schizophrenia explain only about 7.7% of the variation in the liability to develop schizophrenia (Legge et al., 2021). Thus, genetic factors comprise only a minor part in the etiology of schizophrenia, and the contribution of various environmental factors needs to be explored in greater detail (Torrey and Yolken, 2019). If we want to understand the etiology of schizophrenia, the most important questions are: What are the environmental factors that cause schizophrenia? And why do they cause it?

Schizophrenia is characterized by heterogeneity in etiology, clinical presentation, and prognosis (Seaton et al., 2001; Xiao et al., 2022), which has been a thorny issue in the psychiatric literature. In this article we provide an explanation for this heterogeneity. We also present a novel evolutionary explanation for schizophrenia, integrating it with the proximate mechanisms behind this mental disorder. In doing so, we answer research calls to explore biological phenomena on two different but complementary levels of analysis: (1) what are the proximate mechanisms underlying the trait: how does it work?; and (2) what is the ultimate reason it evolved: what fitness benefit, if any, does it provide for the organism? (Luoto et al., 2019a; Rantala et al., 2019; Zietsch et al., 2021). In the final section of the article, we critically review previous hypotheses about the evolutionary origins of schizophrenia, showing

how they have provided inadequate and/or poorly supported accounts of this mental disorder.

2. The parasite x genotype x stress interaction model

Progress in explaining the etiology of schizophrenia has been partially hindered by the lack of integrative approaches that synthesize different strands of research and bring together different parts of the etiological puzzle, including evolutionary, parasitological, and psychoneuroimmunological perspectives. The parasite x genotype x stress interaction model addresses this lack of integrative approaches and forms the backbone of the new etiological synthesis for schizophrenia.

2.1. The role of neuroinflammation in schizophrenia

There is a substantial body of evidence from both in vitro and in vivo studies implicating dysregulated immunity in schizophrenia (Müller, 2021; Ozaki et al., 2021). For example, signs of neuroinflammation have been found in postmortem brain tissue of schizophrenics, although different methods to measure neuroinflammation have produced mixed results, and many findings have been inconsistent probably due to heterogeneity in study design and medication, which can affect neuroinflammation (reviewed in Trepanier et al., 2016; van Kesteren et al., 2017). Despite heterogeneity in the findings, microarray analyses from post-mortem brain samples have consistently indicated elevated inflammatory markers such as SERPINA3 (a protease inhibitor, which is involved in inflammatory processes and connective tissue turnover) and interferon-induced transmembrane protein (IFITM) in schizophrenia patients (Trepanier et al., 2016). Ultra-resistant schizophrenia (UTRS) is characterized by chronic low-grade peripheral inflammation (OR = 2.6) even after adjustment for age, sex, current daily tobacco use, metabolic syndrome, and antidepressant consumption (Fond et al., 2019).

Meta-analyses have found that patients with schizophrenia have higher levels of proinflammatory cytokines in the blood and in cerebrospinal fluid than healthy controls (reviewed in Mongan et al., 2020; Muller et al., 2015). In addition, patients with schizophrenia have decreased anti-inflammatory cytokine levels compared with healthy controls (Boerrigter et al., 2017). Nevertheless, increased cytokine levels in blood are not evident in all instances of schizophrenia: approximately 48% of people with schizophrenia belong to the high cytokine biotype as determined by increased levels of IL-6, IL-8, and TNF- α (Boerrigter et al., 2017), with UTRS being characterized by elevated C-reactive protein, a marker of low-grade systemic inflammation (Fond et al., 2019).

Positron emission tomography (PET) studies that use radioligands, which target the microglial cell marker 18 kDa translocator protein (TSPO) (which is thought to be a biomarker of glial activation, therefore playing a potential role in neuroinflammation), have led to mixed and even contradictory results for schizophrenia (for a meta-analysis, see Plaven-Sigra et al., 2021). However, these PET studies targeting TSPO might be unable to produce reliable information about neuroinflammation given that a recent postmortem study found no relationship between TSPO and cell- and activation-specific markers of neuroinflammation (Sneeboer et al., 2020).

Mongan et al. (2021) tested whether plasma proteomic biomarkers could predict if a person at risk for psychosis is likely to develop a psychotic disorder years later. The method was able to correctly identify those who would go on to develop a psychotic disorder in 67.8% of high-risk cases, and it correctly identified those who would not in 75.8% of cases. Importantly, inflammation was involved in many of these proteomic biomarkers (Mongan et al., 2021). The hypothesis that neuroinflammation plays a role in schizophrenia is further supported by a meta-analysis which found that anti-inflammatory drugs help to improve psychotic disorders when used as an add-on to antipsychotics compared to antipsychotics plus placebo (Jeppesen et al., 2020).

During neuroinflammation, overactivated microglia cells release proinflammatory cytokines and free radicals which cause neuronal

degeneration, abnormalities in white matter, and decreased neurogenesis (Monji et al., 2009). This neuronal damage may explain many of the negative symptoms of schizophrenia, such as deficits in working memory, processing speed, and executive function. However, although there is clear evidence for the role of neuroinflammation in schizophrenia, existing psychiatric literature does not provide a convincing explanation for why a person with schizophrenia has neuroinflammation, and why neuroinflammation would cause symptoms such as hallucinations and delusions which are defining features of schizophrenia. Current evidence indicates that neuroinflammation occurs in major depressive disorder (Rantala et al., 2018), bipolar disorder (Rantala et al., 2021), and anorexia nervosa (Rantala et al., 2019), but only a small proportion of patients with depression and eating disorders experience psychosis (Jaaskelainen et al., 2018; Miotto et al., 2010). It therefore appears that neuroinflammation alone is not an adequate explanation for psychosis, although it may explain many negative symptoms in schizophrenia (that are shared with depression: see Rantala et al., 2018), and it may also explain why the majority of patients with first-episode psychosis would fulfill the diagnostic criteria of major depressive disorder (e.g., 80% in Uptegrove et al., 2010). However, it has also not been clear whether neuroinflammation is the cause or the effect of schizophrenia.

In the next sections, we review evidence which suggests that psychosis might be caused by pathogens. We then explain why they cause the symptoms of schizophrenia. Owing to the global geographic variation in the prevalence of different pathogens, the pathogen hypothesis of schizophrenia can also explain the inconsistency of previous immunological research on schizophrenia, as well as its phenotypic heterogeneity.

2.2. The role of pathogens in the etiology of schizophrenia

2.2.1. Toxoplasmosis

Toxoplasmosis is a parasitic disease caused by a single-celled protozoan called *Toxoplasma gondii* (Dubey, 2010). It plays an important role in schizophrenia (see Section 2.2.2 for a detailed review). To understand this role, it is necessary to consider how *T. gondii* operates in non-human animals. This protozoan can reproduce sexually only in the digestive tract of cats or other felids. In other animals, it can reproduce only asexually by cloning itself.

The problem that the protozoan faces is how to transfer its offspring to the intestines of other cats. It has harnessed intermediate hosts for this task. The protozoan is able to spread its offspring into its environment as oocysts for 1–3 weeks with cat feces, after which the cat recovers from the infection. When rodents eat food contaminated with cat feces or drink water contaminated with feces, they develop a *Toxoplasma* infection. In the intermediate host such as humans, the parasites form a tissue cyst in the muscles, brain, and other tissues as a result of the activation of the host's immune system. These tissue cysts are an inactive form of the parasite surrounded by a protective shell, where the parasites wait to end up in the intestines of felines (Dubey, 2010).

Normally, a protozoan is not very likely to end up in a cat's gut because rodents instinctively fear cats. In *Toxoplasma*-infected rodents, however, the fear of cats disappears (Vyas et al., 2007). The mere smell of a cat normally makes rodents flee, but rodents infected with *Toxoplasma* experience the smell of cat as sexually attractive (Berdoy et al., 2000; House et al., 2011). This makes them seek out cats, making *Toxoplasma*-infected rodents more likely to end up as cat food. These rodents still avoid other predators as before (Berdoy et al., 2000; House et al., 2011). The reversal of this innate fear reaction helps the protozoan reach its definitive host, a cat, and to propagate its genes to future generations.

Of particular interest is how *T. gondii* manages to modify the behavior of its host (Borráz-León et al., 2021). *T. gondii* is able to penetrate into the brains of all mammals (including humans) through the blood–brain barrier (Ross et al., 2022). It specifically targets the forebrain and amygdala, but *Toxoplasma* cysts can be found all over the

brain (Del Grande et al., 2017). The protozoan increases the production of dopamine by the cells it infects (Prandovszky et al., 2011) and modifies the serotonin and GABA signaling systems (Del Grande et al., 2017). Toxoplasmosis also increases the production of the neurotransmitter glutamate. Glutamate regulates messaging between nerve cells. If too much glutamate is excreted, nerve cells will no longer be able to communicate with each other but wither away. Astrocytes remove excess glutamate so that it does not damage nerve cells. Astrocytes convert glutamate to glutamine, which can be processed for energy production. *Toxoplasma* has been shown to inhibit the function of astrocytes in the brain (David et al., 2016). As a result, too much glutamate accumulates in the nerve cells and they begin to wither away. *Toxoplasma* can infect up to 30% of brain microglial cells and 10% of astrocytes, and can cause central nervous system inflammation (Cowan et al., 2022; Flegel, 2013; Matta et al., 2021), chronic inflammation (Egorov et al., 2021), and intestinal inflammation (Couturier-Maillard et al., 2018; Watanabe et al., 2018).

2.2.2. Toxoplasmosis and schizophrenia

The association between latent toxoplasmosis and various mental health problems has been investigated in tens of studies around the world. In a recent meta-analysis of 54 studies, *Toxoplasma*-IgG seropositivity increased schizophrenia risk (OR = 1.91) (Contopoulos-Ioannidis et al., 2022). However, with increased understanding of the biology of the *Toxoplasma* parasite, it seems that these estimates of the magnitude of the association might be flawed. *Toxoplasma* occurs in genetically distinct strains, and their proportions vary geographically (Su et al., 2012). It appears that the standard method of detecting *Toxoplasma* antibodies is not sufficiently sensitive to detect all strains: recent studies suggest that many individuals who are “seronegative” using standard enzyme-linked immunosorbent assay (ELISA) nevertheless have evidence of reactivity to *Toxoplasma* proteins visualized by Western blotting techniques (Xiao et al., 2018). Thus, standard assays may substantially underestimate toxoplasmosis prevalence (Xiao et al., 2018). In addition, there are differences in virulence between *Toxoplasma* strains, and all strains are not associated with mental health problems (Xiao et al., 2009). Since the prevalence of different *Toxoplasma* strains varies between countries (Su et al., 2012), it is to be expected that studies on the relationship between schizophrenia and toxoplasmosis have been inconsistent. The true magnitude of the association between schizophrenia and toxoplasmosis will only be known after conducting studies that use more sensitive methods that are able to detect all *Toxoplasma* strains and to determine which strain a person suffers from. Furthermore, cyst location in the brain seems to be widely and randomly spread in the brain. Thus, cysts may be located in different brain areas in different patients, which may explain why symptoms differ between patients. Other reasons for individual variation in symptoms may arise from differences in parasites strains, infection state, the timing of first exposure, and the manner of exposure (Xiao et al., 2018).

Meanwhile, the strongest evidence for a link between toxoplasmosis and schizophrenia comes from brain imaging studies. Changes in brain gray matter, typical of schizophrenia, have been found only in schizophrenics with toxoplasmosis (Horacek et al., 2012), and schizophrenia and toxoplasmosis induce similar, often discrete changes in brain morphology, including gray matter atrophy, ventricle system enlargement, and microscopic presence of inflammatory cells in perivascular spaces (Fuglewicz, Piotrowski, and Stodolak, 2017). Unfortunately, a cause-and-effect relationship cannot be inferred from these studies, as it may be that schizophrenics may be more susceptible to toxoplasmosis than controls. However, research in U.S. soldiers using blood samples collected years before the onset of schizophrenia has been able to show that schizophrenics were not more susceptible to toxoplasmosis; instead, toxoplasmosis infection preceded the onset of schizophrenia (Niebuhr et al., 2007).

At a neurobiological level, schizophrenia has been found to be

associated with dysfunction in dopamine and glutamate systems (reviewed in McCutcheon et al., 2020a), while many antipsychotic drugs have dopamine-antagonist effects (Brisch et al., 2014; Sonnenschein et al., 2020). Mice chronically infected with *Toxoplasma* have excessive activation of inflammation in the brain, an excessive secretion of cytokines and chemokines, higher activation of the dopamine signaling pathway, and increased dopamine production (Omidian et al., 2021; Wang et al., 2019). It seems that while genetic factors may directly underlie glutamatergic dysfunction, only a few genetic risk variants of schizophrenia are associated with the dopamine system, implicating that dysfunction in dopamine signaling in schizophrenia is likely predominately caused by other factors than genetics (McCutcheon et al., 2020a). Genome-wide analyses of human cells infected with *Toxoplasma* have, however, found that the parasite influences epigenetic regulation of host dopamine pathways (Syn et al., 2018). In vitro experiments have revealed that *Toxoplasma* in petri dish increases dopamine production in mammalian cells and that *Toxoplasma* cysts in brains release dopamine into surrounding tissue (Prandovszky et al., 2011). The genome of *Toxoplasma* contains two genes for tyrosine hydrolase, the key enzyme for dopamine synthesis (Gaskell et al., 2009). These genes are not found in *T. gondii*'s close relatives that do not live as parasites, suggesting that the genes might be selected as an adaptation to manipulate host behavior (Gaskell et al., 2009). The central question is: why does toxoplasmosis cause elevated dopamine levels and why is *T. gondii* infection associated with schizophrenia?

According to the “behavioral manipulation hypothesis,” the dopamine production and other symptoms of schizophrenia caused by *T. gondii* are adaptations of *T. gondii* to enhance the odds that its mammalian host ends up as a prey of its definitive host, which are feline species (Tong et al., 2021). For example, *T. gondii* infection blocks the innate aversion of rats for cat urine; instead, infected rats find the urine sexually attractive, increasing the likelihood of a cat preying on a rat (Berdoy et al., 2000). Subsequent research on mice has found that *T. gondii* infection lowers general anxiety and increases explorative behaviors. Importantly, the strength of these behavioral changes is linked with the level of inflammation in the mice (Boillat et al., 2020). In chimpanzees (*Pan troglodytes troglodytes*), which are prey for leopards (*Panthera pardus*), it has been shown that *Toxoplasma*-infected chimpanzees lose their innate aversion towards leopard urine and find its odor attractive (Poirotte et al., 2016). Furthermore, *Toxoplasma*-infected men are more attracted to cat odor than non-infected men are (Flegr et al., 2011).

Antipsychotic medication treatment (haloperidol), antimicrobial medication (dapson), and an anticonvulsant and a mood stabilizer (valproic acid) also restore antipredatory behavior in *Toxoplasma*-infected rats (Webster et al., 2006). These drugs—known to be effective in schizophrenia—also inhibit cell invasion and replication of *T. gondii* tachyzoites (Webster et al., 2006).

Toxoplasma infection is associated with an increased risk of suicide in humans. For example, women with *Toxoplasma* infections were 81% more likely to attempt violent suicide and twice as likely to succeed than women without *Toxoplasma* infection (Pedersen et al., 2012). In particular, these women were more likely to attempt violent suicides (for example, using a knife or a gun, instead of overdosing on pills). In addition, suicide attempt risk is positively correlated with the level of infection. Those with the highest levels of antibodies were 91% more likely to attempt suicide than uninfected women. The association between *Toxoplasma* infection and suicide risk held even for women who had no history of mental illness: among them, infected women were 56% more likely to commit self-directed violence than non-infected women (Pedersen et al., 2012). The findings of two meta-analyses have provided further support for the connection between toxoplasmosis and suicide, with latent *T. gondii* infection being associated with a higher suicide risk (OR = 1.39) in Sutherland et al. (2019) as well as in Amouei et al. (OR = 1.57) (2020).

Although nowadays humans are no longer common prey of big

felines, it is possible that in the evolutionary history when our ancestors lived in Africa, *T. gondii* manipulated hominid behavior to make them easier prey for big felines (Borráz-León et al., 2021; Flegr, 2013). Almost all wild lions, leopards, and hyenas are *Toxoplasma* seropositive in Africa (Ferreira et al., 2019; Penzhorn et al., 2002). The suicidal behavior caused by toxoplasmosis in humans might have also increased the probability that the parasite ends up in the intestines of the definitive host in the evolutionary environment, since carnivorous mammals like hyenas and lions eat carrions too. It is therefore possible that the behavioral changes induced by *Toxoplasma* in humans, including suicidality, are a part of its adaptations to increase the probability that our ancestors were eaten by lions or leopards (Brune, 2019; Del Giudice, 2019). Alternatively, these behavioral changes in humans may be byproducts of similar mechanisms that *T. gondii* uses to manipulate its other mammalian hosts, having similar neurobiological and behavioral effects in humans despite not necessarily resulting in similar outcomes. According to this view, the “proper domain” (Sperber and Hirschfeld, 2004) of these *T. gondii* adaptations consists of mammalian hosts that facilitate the parasite's reproduction; nevertheless, the parasite may have similar behavioral effects in other contexts, such as contemporary domesticated *Homo sapiens*, where *T. gondii* parasitizes mammals other than those which it evolved to parasitize, resulting in a poor outcome for the parasite inasmuch as (contemporary) human hosts do not facilitate its ultimate parasitic lifecycle.

Toxoplasma infection is known to cause microglia activation and neuroinflammation in humans (Li et al., 2019) and nonhuman animals (Boillat et al., 2020; Carrillo et al., 2020; Shinjyo et al., 2021; Wang et al., 2019). In addition to its association with schizophrenia in humans, persistent *Toxoplasma* infection in animal models leads to seizures (Brooks et al., 2015; David et al., 2016). Studies in humans and mouse models suggest that both seizures and schizophrenia are caused by a loss or dysfunction of inhibitory synapses (Carrillo et al., 2020). Persistent *T. gondii* infection alters the distribution of glutamic acid decarboxylase 67 (GAD67), an enzyme that catalyses GABA synthesis in inhibitory synapses. Persistent infection not only leads to a significant loss of perisomatic synapses, but also induces the ensheathment of neuronal soma by myeloid-derived cells, as found by using serial block face scanning electron microscopy (Carrillo et al., 2020). These myeloid-derived cells include activated microglia cells, which actively displace or phagocytose synaptic elements (Carrillo et al., 2020). These results suggest that activated microglia contribute to perisomatic inhibitory synapse loss following parasitic infection, providing a mechanism for the way in which persistent *T. gondii* infection may contribute to both seizures and psychiatric illness.

2.3. Parasite x genotype x stress interaction

The primary shortcoming of the toxoplasmosis hypothesis of schizophrenia is its inability to explain why only a small minority of people with toxoplasmosis have schizophrenia or psychosis. One way to address this shortcoming is to acknowledge that there are substantial individual differences in response to *Toxoplasma* infection. Only infections that lead to cyst formation in the brain lead to behavioral changes caused by *Toxoplasma*. For example, *Toxoplasma*-exposed rats tested positive for serum anti-*Toxoplasma* IgG, but only a subset of *Toxoplasma*-exposed rats developed chronic infection with cysts in the forebrain (Evans et al., 2014), and only infection with cyst in brains causes behavioral changes typical to *Toxoplasma* infection (Afonso et al., 2012). Studies in humans further suggest that only a subpopulation of *Toxoplasma*-seropositive individuals develop the active form of toxoplasmosis that results in cyst formation (Xiao et al., 2018, 2013).

Genetic factors play an important role in susceptibility to *T. gondii* (El Mouhawass et al., 2020; Kano et al., 2020). For example, an important gene related to susceptibility to mental illness, *Disrupted-in-Schizophrenia 1* (DISC1), is involved in altered host immune responses against *T. gondii* infection (Kano et al., 2020). The gene is also associated with alteration

in the dopaminergic system (Dahoun et al., 2017). Kano et al. (2020) found that individuals who are homozygous for the DISC1 Phe607 variant showed more than a 3-fold elevation in serum anti-*T. gondii* IgG levels compared to others. Studies in DISC1 animal models have reported that behavioral abnormalities appear only in the presence of psychosocial isolation stress (in animals where *T. gondii* infection is not controlled for) (Goldwasser et al., 2021; Howes et al., 2017; Niwa et al., 2013). This is consistent with observations in humans which have shown that stress is often a triggering factor of psychosis (Schifani et al., 2018). Thus, it seems that there is a parasite x genotype x environment interaction that influences whether a person will develop schizophrenia or not (Fig. 1).

Chronic psychosocial stress is a well-known trigger for psychosis and schizophrenia (Aas et al., 2020; Howes et al., 2017; van Winkel et al., 2008). For example, a study on urban Tanzanians reported that experiencing two or more stressful life events in the past year was associated with a much higher risk of developing schizophrenia (aOR = 6.43) (Jenkins et al., 2010). In light of the parasite hypothesis of schizophrenia and psychosis, it would seem very likely that latent toxoplasmosis or other pathogen-related infections are activated as a result of impaired immunity caused by chronic stress, beginning to interfere with the functioning of the dopaminergic system of the brain in those with a genetic predisposition to schizophrenia. It is well known that traumatic life events during childhood increase sensitivity to social threat and adversity in adulthood, leading to higher susceptibility to chronic stress (Agorastos et al., 2019; Fogelman and Canli, 2019). This increased sensitivity to stress would explain why traumatic life events in childhood increase the risk of psychosis and schizophrenia later in life (Popovic et al., 2019; Varese et al., 2012) if chronic stress leads to a higher likelihood of activation of latent microbial infection in the brain. This hypothetical mechanism is predicated upon the effects that chronic stress has on immune function: long-term stress suppresses or dysregulates innate and adaptive immune responses by inducing low-grade systemic inflammation, altering the Type 1–Type 2 cytokine balance, and suppressing numbers, trafficking, and function of immunoprotective cells (Dhabhar, 2014) and can therefore make individuals more susceptible to the effects of pathogenic infections.

One of the best pieces of evidence showing that environmental factors play an important role in the risk of schizophrenia and non-affective psychosis comes from a study on 13,163 children born in Sweden between 1955 and 1984, reared in Swedish adoptive families (Wicks et al.,

2010). The risk of schizophrenia was two times higher among adoptees (without biological parental history of psychosis) reared in families with disadvantaged socioeconomic position than in families with a better socioeconomic position. Likewise, in the adopted individuals who had a genetic liability for schizophrenia (with parental history of psychosis), the risk was 4.7 times higher than in others. Among those who had both genetic liability and were adopted into families with parental unemployment, the risk of psychosis and schizophrenia was 15.0 times higher than in others, suggesting strong genotype by environment interaction (Wicks et al., 2010).

2.4. Other pathogens associated with schizophrenia

Not every schizophrenic patient has toxoplasmosis, and not every patient with schizophrenia presents with the same set of symptoms. The most probable explanation for the existence of different subtypes of schizophrenia is that they are caused by different kinds of pathogens.

For example, in general paresis, which is one form of neurosyphilis, patients have clinical symptoms of schizophrenia such as delusions, hallucinations, cognitive impairment, emotional problems, personality changes, and abnormal behavior. Patients with general paresis are often misdiagnosed as having schizophrenia or bipolar disorder (Wang et al., 2016). Neurosyphilis is caused by the invasion of *Treponema pallidum* into the central nervous system, which occurs in people who have had untreated syphilis for many years. Treatments with antibiotics alleviate the symptoms (Sarkar et al., 2019; Seo et al., 2018).

Another notable pathogen associated with schizophrenia is the bacterium *Chlamydia psittaci*, which causes chlamydial venereal disease and significantly increases the probability of developing schizophrenia (OR = 29.5) (Arias et al., 2012). This bacterium is spread by birds and can be transmitted to humans via birds. *C. psittaci* is known to remain in the body at rest until it is activated by stress (Tolba et al., 2019). *C. psittaci* has been found in autopsies in the forebrain segments of schizophrenia patients (Fellerhoff and Wank, 2011). In a small study in Germany with five schizophrenia patients, adoptive immunotherapy of *C. psittaci* infection resulted in a marked reduction in the symptoms of schizophrenia, leading to remission in all patients, with only two patients relapsing later (Fellerhoff et al., 2005). There seems to be a strong parasite x genotype interaction also in schizophrenia induced by *C. psittaci*. Fellerhoff et al. (2007) found a dramatic influence for a persistent infection with *C. psittaci* for carriers of HLA-A10 (a human

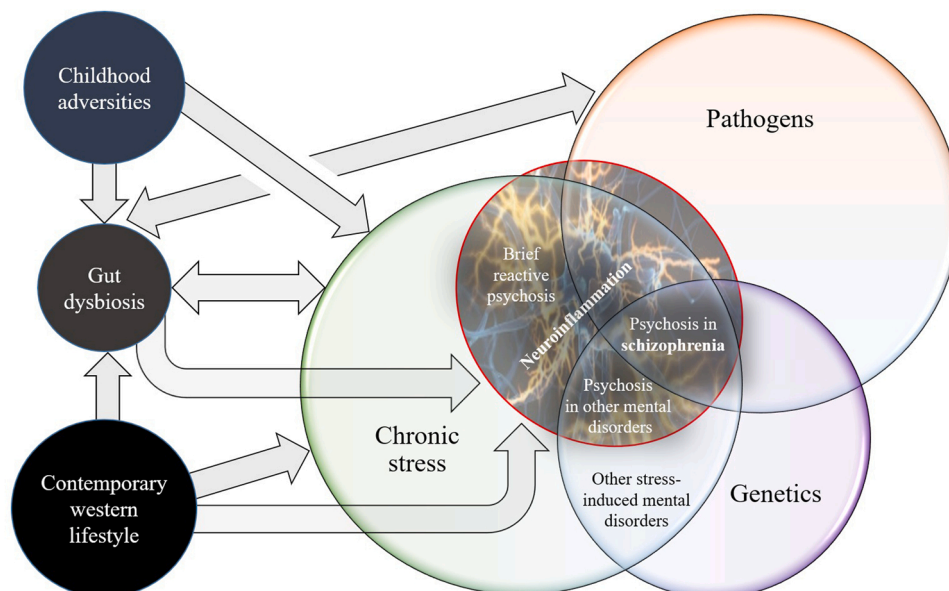


Fig. 1. The parasite x genotype x stress interaction model of schizophrenia.

lymphocyte antigen genetic polymorphism), which has previously been associated with a three-fold increased odds ratio of developing schizophrenia (OR = 3.07). For carriers of HLA-A10, infection with *C. psittaci* constitutes a 50-fold increased odds ratio for schizophrenia (OR = 50.00), representing the highest known risk factor to be associated with schizophrenia (Fellerhoff et al., 2007). Stress seems to be the triggering factor in *C. psittaci*-induced schizophrenia as *C. psittaci* has also been shown to be activated as a result of stress (DeLano and Mallery, 1998).

Chlamydia pneumoniae is another potential etiological agent of schizophrenia when it enters into the central nervous system. A meta-analysis found that *C. pneumoniae* infection was more common in patients with schizophrenia than in controls (OR = 5.96) (Gutierrez-Fernandez et al., 2015). A study using brain biopsy derived from frontal cortex reported that four schizophrenia patients out of 34 had *C. pneumoniae* DNA in the blood while only one out of 35 control participants had *C. pneumoniae* DNA in their brain tissue (OR = 5.08) (Fellerhoff and Wank, 2011).

Toxocarosis is a zoonotic disease occurring worldwide in humans. It is transmitted via infection by *Toxocara canis* and *Toxocara cati*, which are common roundworms in canids and felids. Infection in humans occurs mainly through diet by ingesting *Toxocara* eggs from contaminated vegetables, food, or soil, or *Toxocara* larvae in undercooked or raw meats from cows, sheep, or chicken, which (together with humans) are paratenic hosts to *Toxocara*. The rate of *Toxocara* seroprevalence in humans varies between world regions, being relatively high in African countries (20.2–49.4%) and somewhat less common in the Americas (19.7–26.0%) and Europe (8.5–12.8%) (Taghipour et al., 2021). A meta-analysis of six studies on *Toxocara* infection/exposure found that schizophrenia patients (15% prevalence) had higher pooled seroprevalence (pooled OR: 4.06) of *Toxocara* infection/exposure than a control group (3.3% prevalence) (Taghipour et al., 2021). *Toxocara* spp. larvae can cause neurotoxocarosis by crossing the blood–brain barrier and invading the central nervous system. Larvae migration in the body can also induce local or generalized inflammation, mainly because of eosinophilia or increased production of pro-inflammatory cytokines and specific antibodies (Taghipour et al., 2021).

Cat ownership increases schizophrenia risk due to an increased risk of infection with toxoplasmosis (Torrey et al., 2015), and childhood cat scratches and bites increase the risk of developing mental disorders, including schizophrenia spectrum disorders (Bedwell et al., 2020; Kolkpava and Bedwell, 2013). *Bartonella* bacterium, which is associated with cat-scratch disease, might also play a role in the etiology of some cases of schizophrenia. For example, in a case study, a human patient diagnosed with rapid onset schizophrenia was found to have a *Bartonella henselae* infection, which was transmitted by being scratched by a cat. A combination of antimicrobial chemotherapy led to full recovery (Breitschwerdt et al., 2019). A study on 17 people with stable, medically managed schizophrenia or schizoaffective disorder, and a control group of 13 healthy adults, found that of the 17 patients with schizophrenia, 11 had *Bartonella* infection, compared to only one of 13 in the control group (Lashnits, 2021). These small-scale studies await replication in other, larger samples.

Influenza viruses have been associated with psychosis and psychotic disorders since the eighteenth century (Kepinska et al., 2020). In addition to influenza virus, many other viral infections have also been associated with the occurrence of psychosis or an increased risk of schizophrenia spectrum disorders. These include cytomegalovirus (CMV) (Yolken and Torrey, 2008), Epstein–Barr virus (Dickerson et al., 2021), herpes simplex virus type 1 (HSV-1) (Dickerson et al., 2021), and SARS CoV-2 infection (DeLisi, 2021) (though prenatal maternal infections with HSV-1 and CMV have not been found to be associated with increased schizophrenia risk: Khandaker et al., 2013). The most likely explanation for why viral infection causes psychosis or an increased risk of schizophrenia spectrum disorders is that they cause neuroinflammation when crossing the blood–brain barrier and entering the central nervous system. However, to our knowledge, there have been no

studies on whether latent toxoplasmosis or infection with other pathogens are required in order for these viruses to cause psychosis or schizophrenia, or whether viral infection by itself is able to cause neuroinflammation that is strong enough to lead to psychosis. Future studies on the connection between viral infections and psychosis should therefore analyse potential interactive effects with *T. gondii* and other pathogens known to be causal agents in schizophrenia.

Studies in which CMV-seropositive patients with schizophrenia received medication to suppress CMV replication have reported significant improvements in overall symptoms of schizophrenia (Dickerson et al., 2003; Muller et al., 2002). Genital herpes is known to end up in the central nervous system and, in the worst case, to cause severe encephalitis, accompanied by psychotic symptoms (Whitley, 2006). Herpes has also been shown to be activated as a result of stress (DeLano and Mallery, 1998) across multiple species (Sebastiano et al., 2016), supporting the parasite x genotype x stress model.

Another piece of evidence for the hypothesized association between brain microbial infection and psychotic symptoms comes from patients with meningitis. Altered sensorium has been reported in 13–75% of patients with the cryptococcal meningitis, and sometimes psychosis may occur even without fever or other symptoms (reviewed in Kumar et al., 2011; see also Lofgren et al., 2017). Interestingly, antifungal treatment with amphotericin B leads to full recovery from psychotic symptoms (Kumar et al., 2011). Psychoses are also known to occasionally occur in bacterial diseases such as typhoid fever, tuberculosis, syphilis, and diphtheria (Yolken and Torrey, 2008), supporting the hypothesis that pathogen invasion in the brain may trigger neuroinflammation, which causes psychotic symptoms. It is an open question whether these bacterial diseases require latent *Toxoplasma* infection to cause psychotic symptoms or whether strong neuroinflammation caused by any pathogen is able to produce psychosis by itself.

It is important to note that any microbial infection alone is not enough to explain schizophrenia, as many people carry these diseases without having any psychotic symptoms. It seems that to cause psychotic symptoms or schizophrenia, the infection should enter the brain and cause neuroinflammation. In many diseases, this seems to happen only for a subset of infected people because usually the immune system is able to eliminate the pathogen. In addition, in many microbial infections, the timing of the infection during an individual's lifespan seems to play an important role in the development of schizophrenia. Epidemiological studies have shown that prenatal microbial infection increases the risk of developing schizophrenia (Babulas et al., 2006; Brown and Derkits, 2010; Cheslack-Postava and Brown, 2021; with the exception of HSV-1 and CMV: see Khandaker et al., 2013). Naturally, prenatal or perinatal infection may lead to abnormalities in brain development which may explain many negative symptoms of schizophrenia. Nevertheless, it is also possible that prenatal or perinatal infection in the central nervous system leads to latent infection that is later activated by stress. Prenatal maternal influenza infection, for instance, increases schizophrenia risk (Cheslack-Postava and Brown, 2021). Studies also show that elevated levels of markers of inflammation in pregnant mothers are associated with increased risk of offspring schizophrenia (Cheslack-Postava and Brown, 2021). It is possible that maternal immune activation and prenatal or perinatal viral infection prime microglia cells, making individuals more vulnerable to severe neuroinflammation after stress later in life. This potential mechanism requires further research.

The fact that schizophrenia is not a single disorder and may be caused by different microbial infections explains why it has been traditionally divided into different subtypes based on different symptoms. Such subtypes include paranoid schizophrenia, catatonic schizophrenia, hebephrenic schizophrenia, undifferentiated schizophrenia, and residual schizophrenia (cf. McGlashan and Fenton, 1991). The most recent classification systems (DSM-5 and ICD-11) have abandoned these subtypes and catatonia is now classified separately (American Psychiatric Association, 2013).

It is possible that different microbial species produce symptoms of different subtypes of schizophrenia. This would explain why there is a lot of geographical variation in the prevalence of different schizophrenia subtypes (Jablensky et al., 1992), as parasite prevalence varies significantly between countries (e.g., Fincher et al., 2008; Fincher and Thornhill, 2012; Luoto, 2019; Rostami et al., 2019). For example, catatonic schizophrenia occurs in 10% of patients with schizophrenia in developing countries but in only 1% in more developed countries (Jablensky et al., 1992). On the other hand, hebephrenic schizophrenia, which begins early in individual development, occurs in 13% of developed countries, compared with only 4% in developing countries (Jablensky et al., 1992). Since many different pathogens may cause schizophrenia, it is not surprising that the same antipsychotic drug does not work in all patients, and one third of patients have treatment-resistant schizophrenia (Mizuno et al., 2020). Recent studies suggest that there are distinct neuroanatomical subgroups of schizophrenia (Chand et al., 2020; Green et al., 2020; Honnorat et al., 2019; Lizano et al., 2021). Unfortunately, the patients in these studies were not tested for microbial infections. It is possible that different pathogens and/or timing of infection (e.g., prenatal infection; see Cheslack-Postava and Brown, 2021) cause the reported neuroanatomically heterogeneous schizophrenia subtypes. We encourage researchers to test whether different pathogens produce different symptoms and neuroanatomical schizophrenia subgroups.

3. Schizophrenia as a disease of modern lifestyle

There is substantial geographic variation in the prevalence of schizophrenia. Schizophrenia becomes linearly more common farther away from the equator and towards colder climates (Kinney et al., 2009). However, there is a latitudinal gradient in the age at onset of schizophrenia, with onset being earlier in areas close to the equator, following a strong increased age–latitudinal gradient moving farther from the equator (Shaner et al., 2007). Darker-skinned populations show higher rates of the disorder after controlling for the effect of latitude (Kinney et al., 2009).

The course of schizophrenia also varies geographically (Kulhara et al., 2009; Myers, 2011). For example, results of a 2-year follow-up conducted by WHO on patients in different countries in the 1970s indicated that patients diagnosed with schizophrenia on the basis of standardized assessments and clearly specified criteria demonstrated marked variations in course and outcome between countries over a 2-year period. Patients with schizophrenia treated in the medical centers of developing countries had, on average, considerably better outcomes than schizophrenic patients in the centers of more developed countries (Craig et al., 1997). These findings have also been called into question, with new evidence from cohorts in developing countries suggesting gloomier schizophrenia outcomes than originally believed (Cohen et al., 2008; Patel et al., 2006). As such, the jury is still out on whether these cross-national patterns are reliable, with more research needed especially in developing countries (Esan et al., 2012; Jablensky and Sartorius, 2008). It should also be noted that developing countries are not static entities but have undergone substantial changes during the decades since the WHO analyses were conducted in the 1970s, leading to possible longitudinal within-country variation in ecological factors influencing schizophrenia prevalence and recovery.

It appears that schizophrenia is very rare or completely absent in people with hunter-gatherer lifestyles (Dohan et al., 1984; Hollan and Wellenkamp, 1994, 1996; Keyes, 1986; Schieffelin, 1986; Seligman, 1929). For example, in Papua New Guinea, Seligman (1929) did not find any person with psychosis “in the villages among natives living their own normal life” but reported six cases of psychosis among natives who were living in close contact with European settlers. An epidemiological study in Papua New Guinea in the 1980s found only 121 cases of schizophrenia in a population of 1 859,000 people (Torrey et al., 1974). The prevalence varied between districts from 2 out of 156,000 to 16 out

of 55,000. The percentage of population enrolled in primary school correlated positively with the prevalence of schizophrenia (Torrey et al., 1974). Dohan et al. (1984) examined over 65,000 adults in non-westernized societies of Papua New Guinea (1950–1967), Malaita, Solomon Islands (1980–1981), and Yap (1947–1948), finding only two individuals with schizophrenia (Dohan et al., 1984).

The highest lifetime prevalence reported among modern countries we were able to find was from northeastern Finland where the lifetime prevalence of schizophrenia was 2.21%, while the prevalence in whole Finland was 1.21% (Hovatta et al., 1997). Another markedly high lifetime prevalence (1.46%) was reported in Canada from 5,996,925 participants (Vanasse et al., 2012). In comparison, a study surveying Hutterites living in an isolated religious rural community in Canada in 1950–1953 found that the prevalence of schizophrenia was only 0.09% (Torrey, 1995). Among American Old Order Amish with a lifestyle characteristic of the 18th century (Egeland and Hostetter, 1983) only four out of 8,186 individuals had schizophrenia, with five-year prevalence being 0.049%, which is substantially lower than in people with contemporary western lifestyles in North America. The notable association between schizophrenia and contemporary western lifestyles calls for a more detailed mechanistic analysis.

We suggest that one reason why the prevalence of psychosis among people with hunter-gatherer and traditional lifestyles is so much lower than in people with contemporary western lifestyles is due to chronic stress and low-grade systemic inflammation caused by western lifestyle. Low schizophrenia prevalence among hunter-gatherers and people with traditional lifestyles does not mean that they would never experience stress. Short-term stress is beneficial and improves performance and immunoprotection at critical moments (Dhabhar, 2014). When the threat that causes stress is over, stress hormones return to normal levels. Stress becomes a problem if it continues and becomes chronic (e.g., Dhabhar, 2014). It appears that hunter-gatherer and more traditional lifestyles protect against chronic psychological stress (Brenner, 2015; Fedurek et al., 2020). Chronic stress is known to cause persistent low-grade inflammation (Miller et al., 2019) and studies have revealed that hunter-gatherers do not suffer from low-grade systemic inflammation: although the high rate of infections in hunter-gatherers raises inflammatory biomarkers at any one time (Bernstein and Dominy, 2013; Kaplan et al., 2017; Vasunilashorn et al., 2010), various lines of evidence, including lower rates of western lifestyle diseases in hunter-gatherer and ancestral populations (Hamman, Barancik, and Lilienfeld, 1981; Hsueh et al., 2000; Kaplan et al., 2017; Stein et al., 2016), indicate that biomarkers of inflammation are not consistently elevated in hunter-gatherer populations, suggesting low prevalence of low-grade systemic inflammation (McDade et al., 2012; though to be fully generalizable, the findings should be systematically replicated in various hunter-gatherer populations and populations with traditional lifestyles). The lack of low-grade systemic inflammation in hunter-gatherer populations provides more support for the mismatch hypothesis of schizophrenia, as do findings on how western diet increases low-grade systemic inflammation in the body (Berger, 2021; Christ et al., 2019). Low-grade systemic inflammation is also known to increase stress sensitivity (Maydych, 2019) and neuroinflammation (Troubat et al., 2021), which may increase the risk of psychosis (Fond et al., 2019; Trepanier et al., 2016) and other mental disorders such as depression and bipolar disorder (Rantala et al., 2018, 2021).

A meta-analysis reported that the incidence of schizophrenia increased almost linearly in developed countries with an increase in urbanicity (Vassos et al., 2012) (see also Luo et al., 2021; Coid et al., 2020). In contrast, a study on nationally representative general population probability samples comprising 215,682 people across 42 countries reported that urbanicity was not associated with elevated odds for psychosis in developing countries (DeVylder et al., 2018). These conflicting results could have arisen because urban–rural patterns of socioeconomic disparities and other factors that influence the risk of developing schizophrenia vary between developing and developed

nations. Nevertheless, in China, the lifetime prevalence of schizophrenia has more than doubled in urban areas between 1990 (0.39%) and 2010 (0.83%), while in rural areas the corresponding increase has been less significant (0.37% in 1990, 0.43% in 2000, and 0.50% in 2010) (Chan et al., 2015). Exposure to natural environments in neighborhoods or around residential areas is associated with lower schizophrenia rates (Engemann et al., 2019, 2020; Kristine et al., 2018), while ambient air pollution is positively correlated with schizophrenia admissions and outpatient visits to hospitals (Attademo et al., 2017; Bai et al., 2020; Duan et al., 2018; Liang et al., 2019). The more years a child spends in an urban area, the greater the risk of developing schizophrenia, implying that the urban risk factor is also dose-dependent (March et al., 2008). This urban risk factor may explain more than 30% of all schizophrenia incidences (Van Os, 2004). A recent longitudinal study following 579, 039 people born in Denmark between 1972 and 1981 found that urbanicity increased schizophrenia risk even after controlling for a number of individual-level and specific contextual factors (Pedersen et al., 2022).

In light of the parasite x genotype x stress model, a probable explanation for why living in cities increases the risk of schizophrenia is increased chronic stress caused by urban living (see Lederbogen et al., 2011). City living is associated with increased amygdala activity and affects the perigenual anterior cingulate cortex, a key region for regulation of amygdala activity, negative affect, and stress (Lederbogen et al., 2011). Functional magnetic resonance imaging research has shown that city living and urban upbringing are associated with altered neural processing of acute social stress (Lederbogen et al., 2011). There is also substantial evidence indicating that visiting green spaces and being exposed to natural environments reduce psychological stress (Ewert and Chang, 2018).

Living in cities can increase contact with *Toxoplasma gondii* through domestic cats because cats have a more limited choice of defecation sites in urban areas (Torrey and Yolken, 2014). Likewise, it is possible that the high prevalence of schizophrenia among people with contemporary western lifestyles compared to hunter-gatherers might be caused by the higher prevalence of domestic cats and diseases associated with them. It is also possible that contemporary western lifestyles and living in cities negatively influence gut health and gut microbiota (Fig. 1). Further evidence for this hypothesis comes from findings showing that people with hunter-gatherer lifestyles have more diverse microbiota than people with contemporary western lifestyles (Sanchez-Quinto et al., 2020; Segata, 2015; Singh et al., 2019; Yatsunencko et al., 2012).

4. Microbiota and schizophrenia

Gut microbiota is known to modulate brain function and behavior, with many mental disorders now being associated with disturbed gut microbiota (reviewed in Golofast and Vales, 2020; Jarbrink-Sehgal and Andreasson, 2020). Gut microbiota can communicate with the brain via the vagus nerve, enteric nervous system, immune system, enteroendocrine signaling, and by producing microbial metabolites, such as short-chain fatty acids (reviewed in Kelly et al., 2021). This microbiota–gut–brain axis signaling influences brain development, immune homeostasis, blood–brain barrier development, neurogenesis, myelination, dendrite formation, and neurotransmission (Kelly et al., 2021; Yuan et al., 2019).

Recent advances in this field have shown that patients with schizophrenia have deviant microbiota compared with healthy controls, albeit taxonomic results have been somewhat inconsistent (Li et al., 2020; Nguyen et al., 2019; Schwarz et al., 2018; Shen et al., 2018; Thirion et al., 2022; Xu et al., 2020; Zheng et al., 2019; Zhu et al., 2020b). A meta-analytic review of 15 schizophrenia studies noted limited differences in the number or distribution (α -diversity) of gut bacteria between schizophrenia cases and controls, while most studies reported dissimilarities between schizophrenia cases and controls in overall gut bacteria community composition (β -diversity) (McGuinness et al., 2022). Studies

in which gut microbe samples of schizophrenic subjects have been transferred into germ-free mice have found schizophrenia-like abnormal behavior and changes in neurochemistry and dysregulation of immune system in the mice (Zheng et al., 2019; Zhu et al., 2020a, 2020b). Overall, these studies suggest that patients with schizophrenia have deviant microbiota, particularly β -diversity, which can alter neurochemistry and neurologic function in ways that may be relevant to schizophrenia psychopathology, including increases in neurotoxin and inflammatory mediators (Yuan et al., 2019). Unfortunately, all studies implicating gut dysbiosis in schizophrenia patients have, to our knowledge, been cross-sectional. Thus, evidence about the causal relationship between schizophrenia and gut dysbiosis is lacking in humans. Large-scale prospective studies would be needed to show such a causal relationship.

Gastrointestinal problems such as irritable bowel syndrome, inflammatory bowel disease, and celiac disease are prevalent comorbidities in schizophrenia, occurring much more commonly among patients with schizophrenia than in healthy controls (Ahmed and Rasool, 2016; Nguyen et al., 2018). Dysbiosis could exacerbate inflammation in the disorder through increased intestinal permeability. Indeed, studies suggest that patients with schizophrenia or first-episode psychosis have increased gut permeability, microbial translocation, and markers of intestinal inflammation (Severance et al., 2012, 2014, 2016b). It seems possible that there is a link between *Toxoplasma* infection and gastrointestinal problems, because *Toxoplasma* often infects through the gastrointestinal tract, while penetration of *Toxoplasma* through the intestinal wall can increase gut permeability, microbial translocation, and cause inflammation (Severance et al., 2016a; Watanabe et al., 2018). In addition, it seems possible that *Toxoplasma* infection may alter intestinal microbiota. For example, chronic *Toxoplasma* infection alters the composition of the intestinal microbiota in mice as long as for five months following infection (von Klitzing et al., 2017). Furthermore, both chronic and acute stressors can affect gut microbiota (Madison and Kiecolt-Glaser, 2019).

It is possible that the effect of maternal immune activation (Aguilar-Valles et al., 2020) on the risk of developing schizophrenia is at least partly caused by changes in gut microbiota. For example, activation of maternal immune system in mice led to changes in gut microbiota, which was interpreted to be similar as observed in patients with schizophrenia (Juckel et al., 2021).

There are many ways in which gut dysbiosis could contribute to the development of schizophrenia. First, intestinal microbiota influences the integrity of the blood–brain barrier (BBB) (Braniste et al., 2014), and microbiota alterations can be associated with BBB impairment (Geng et al., 2020). Gut dysbiosis could therefore make it easier for microbes to enter the brain and cause neuroinflammation. Second, intestinal microbiota influences the function of the HPA axis, which can increase stress sensitivity (Misiak et al., 2020). Third, gut dysbiosis may contribute to enhanced release of cytokines and synthesis of small bioactive molecules that contribute to neuroinflammation (Cerovic et al., 2019; Nguyen et al., 2021). Fourth, the effect could manifest via the vagus nerve, which would influence neuroinflammation through the cholinergic anti-inflammatory pathway (for a review, see Bonaz et al., 2017). It therefore seems that in addition to overall chronic stress and microbial infection in the brain, gut dysbiosis plays an important role in the etiology of schizophrenia; furthermore, all these effects can interact (Fig. 1). In addition, antipsychotics influence the composition of gut bacteria and, reciprocally, microbiota may affect the pharmacokinetics of antipsychotic medication (for a review, see Seeman, 2021), which may explain why it has been so difficult to solve the puzzle of schizophrenia and to find a cure for it.

5. Previous evolutionary hypotheses for schizophrenia

The original idea that microbial agents may cause psychotic disorders was proposed by Emil Kraepelin in his book *Psychiatrie* already in

1896 (Noll, 2004), and the evidence supporting the hypothesis has been accumulating after that. Even so, over the years, evolutionarily oriented researchers have suggested many hypotheses (visualized in Fig. 2) to explain why natural selection has not eliminated the genetic variants associated with schizophrenia. Next, we review these previous hypotheses, and discuss them critically in Section 6.

5.1. Balanced polymorphism hypothesis

Researchers have hypothesized that some latent factor—perhaps an unknown advantageous phenotypic quality—maintains the genotype associated with schizophrenia in contemporary human populations. For example, Huxley et al. (1964) proposed that schizophrenia could be associated with genetic polymorphisms accompanied with advantageous and disadvantageous phenotypic characteristics that allow the continued presence of the genes in human populations. This hypothesis is known as “balanced genetic polymorphism.” The net result would be no positive or negative selection pressure for the genotype (Huxley et al., 1964; Nesic et al., 2019). Huxley et al. (1964) also suggested that higher resistance to shock, infection, allergies, and stress compensates for the reduced fecundity in people with schizophrenia, which could explain the evolutionary paradox underlying schizophrenia.

Relatedly, Kellett (1973) hypothesized that characteristics associated with schizophrenia may have assisted in negotiating hierarchical tensions. For example, some schizophrenia traits, such as inventiveness and the ability to tolerate low levels of stimulation while remaining alert, could have been advantageous to territorial animals. However, Kellett (1973) did not explain the existence of psychotic symptoms in schizophrenia.

5.2. The mismatch hypothesis

The idea that some traits related to schizophrenia were useful in the past and could now be deleterious because of major changes in human lifestyles and environments is known as “the mismatch hypothesis” (Abed and Abbas, 2011a; Di Rienzo and Hudson, 2005; Gluckman and Hanson, 2006). The mismatch hypothesis states that genes and gene forms that predispose to schizophrenia may persist over time because fluctuating environmental conditions impose variable selective pressures (Feinberg and Irizarry, 2010) or because the genetic variants underlying schizophrenia are under neutral selection (Tooby and Cosmides, 1990). This hypothesis is merely theoretical and has not been formally substantiated with empirical evidence. The mismatch hypothesis of schizophrenia has been formulated in various ways in the existing evolutionary literature. These include (1) as a part of the outgroup intolerance hypothesis (Abed and Abbas, 2011a) (described in the next section) as well as (2) symptoms of schizophrenia comprising extreme manifestations of normal psychological variation—manifestations that may have provided such adaptive purposes as increased alertness to dangers in the human environment of evolutionary adaptedness (Cook et al., 2020). The parasite x genotype x stress interaction model presented in Section 3 expands on the mismatch hypothesis, showing how contemporary western lifestyles may cause a mismatched environment, increasing the prevalence of schizophrenia because of a range of evolutionarily novel environmental factors.

5.3. The social brain hypothesis

The social brain hypothesis (Barton and Dunbar, 1997; Brothers,

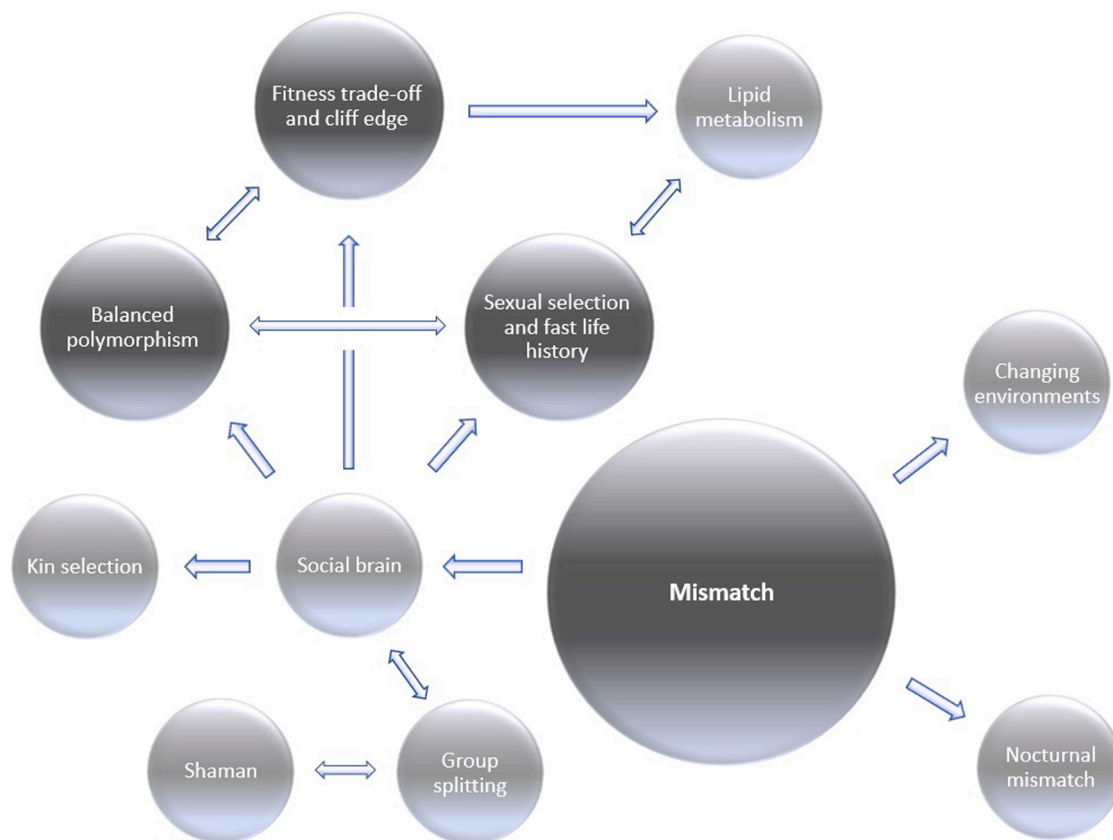


Fig. 2. Hypotheses on the evolution of schizophrenia. The relative size of each hypothesis in the figure reflects the amount of existing evidence in support of that hypothesis: the larger the circle, the more evidence for that hypothesis. Arrows between the hypotheses indicate potential causal relationships between the hypotheses, with the direction of the arrows indicating the direction of potential causality. This reflects the view that the hypotheses may be interrelated in various ways.

1989, 1990; Byrne and Whiten, 1988) proposes that social cognition in humans and other primates is linked to specialized brain systems that evolved for the accurate evaluation of the dispositions and intentions of other individuals (Barton and Dunbar, 1997; Brothers, 1990) which are closely related to within-group cooperation and intergroup competition processes (Alexander, 1989).

Based on the social brain hypothesis, Burns (2007) proposed that the emergence of the social brain, with its complex circuits, produced a vulnerability to atypical connectivity. Thus, schizophrenia would be the result of abnormal connectivity in the fronto-temporal and fronto-parietal circuits, which evolved in our species as a neuroanatomical substrate for the social brain. Abed and Abbas (2011a, b) formulated the outgroup intolerance hypothesis according to which schizophrenia might be the result of the exposure to novel social conditions of modern urban societies. As these conditions are very different from those prevailing in the ancestral human environment(s), the chronic stress associated with the exposure to these novel social conditions would exert a detrimental effect on the development and normal functioning of the social brain system, leading to the development of non-affective psychosis in vulnerable individuals (Abed and Abbas, 2011b). According to Abed and Abbas's (2011a,b) hypothesis, schizophrenia and non-affective psychosis arose as novel phenomena in the post-Neolithic period as a result of living in larger and more complex human groups, which increased the interactions with out-group members. In support of this hypothesis, evidence shows that schizophrenia incidence is higher in immigrants and highly urbanized societies (Pedersen and Mortensen, 2006). The outgroup intolerance hypothesis explains not only the higher risk of schizophrenia in immigrants and urban settings but also in ethnic minorities in neighborhoods with low same-group ethnic density (Abed and Abbas, 2014; Radua et al., 2018).

In general, this hypothesis suggests that whereas the genetic and biological roots of schizophrenia are ancient, their deleterious effects on the development of the human brain system are now evident mainly because of the mismatch between the ancestral human environment and the current urbanized social life (Abed and Abbas, 2011a). As such, this hypothesis can be seen as an extension of the mismatch hypothesis.

5.4. Psychosis as an evolutionary adaptation to changing environments

Another line of thinking has proposed that psychosis could be a natural defense mechanism for individuals or groups to survive in specific social circumstances, like surviving after leaving home and starting a life of one's own (Scheepers et al., 2018). According to Scheepers et al. (2018), this natural response to a new environment is no longer functional if it becomes too extreme. This extreme response and its dysregulation would constitute what we know as schizophrenia.

To adapt to a new environment, individuals need cognitive flexibility, easy mental shifting, good social skills, and trustful relationships (Boyer and Bergstrom, 2011). However, these factors are disturbed during psychosis (Sitskoom et al., 2004), and behavior could become pathological when individuals are exposed to chronic stress or early traumatic experiences (Scheepers et al., 2018).

5.5. The nocturnal hypothesis of schizophrenia

Feierman (1982, 1994) proposed "the nocturnal hypothesis of schizophrenia," which suggests that within an evolutionary context, the behavioral and psychological dysfunctions associated with schizophrenia would result from being forced to live a diurnal life with a partially nocturnal brain. From this point of view, schizophrenia would be the phenotypic result of the interaction between genetic and non-genetic factors, where the genetic determinant is the biological predisposition to be night-active whereas the non-genetic determinant is natural daylight (Feierman, 1982).

5.6. Kin selection: benefit experienced by family members of affected individuals

The persistence of schizophrenia could be seen as an adaptation that benefits the relatives of affected individuals by enhancing their physiological and psychological states (Brune, 2004). For example, it has been suggested that genes related to deleterious phenotypes in homozygous carriers could survive if the heterozygote genotype gives some advantage such as superior social skills, creativity, or academic success (Jeste et al., 2000; Karlsson, 1970; Kuttner et al., 1967; Mucci et al., 2018). Evidence supporting this view has reported superior academic success among relatives of schizophrenics (Karlsson, 1970; Miller et al., 2018). However, there is also evidence that shows that both schizophrenic individuals and their relatives perform worse than healthy individuals on several cognitive tasks such as executive functioning, verbal memory, and attention (Sitskoom et al., 2004; Snitz et al., 2006). Thus, there is very little evidence demonstrating that relatives of individuals with schizophrenia indeed have superior social adaptation.

5.7. The group-splitting hypothesis

The group-splitting hypothesis of schizophrenia (Stevens and Price, 2000) posits that proliferating tribal communities must eventually split to maintain optimum numbers. According to this hypothesis, schizotypal traits in certain prominent individuals may be advantageous to ensure survival of the offshoot group. These prominent individuals could use paranoia, delusions, religious themes, and neologisms to fraction disaffected groups and to seed new cultures. Stevens and Price (2000) proposed that this type of leadership might be seen as altruistic behavior and be thereby maintained in populations via group selection. However, assessing whether group selection mechanisms contribute to the persistence of risk alleles for schizophrenia is difficult, if not impossible (van Dongen and Boomsma, 2013), and group selection in general is not a generally accepted mechanism of biological evolution.

5.8. The shaman hypothesis

The shaman hypothesis provides a completely different perspective on schizophrenia. It proposes that schizophrenia might have enhanced the ability of shamans to conduct religious rituals. According to this hypothesis, religious rituals are likely to be both genetically rooted and relevant to the survival of human beings, seeing that such rituals are universally found in all cultures. The shaman hypothesis posits that psychosis would be advantageous to shamans spearheading religious rituals (Polimeni and Reiss, 2002). The substantial prevalence of religious delusions in schizophrenia supports this position (Brewerton, 1994; Maslowski et al., 1998). Nevertheless, the main shortcoming of this hypothesis, as Nichols (2009) stated, is that shamans' visions need to be produced and terminated on demand and to be culturally relevant. Shamans themselves need to be able to maintain their position with acceptable social behavior when not performing rituals—yet none of these characteristics are in line with schizophrenia.

5.9. Schizophrenia, sexual selection, and life history evolution

Nettle (2001) hypothesized that psychosis-proneness or *schizotypy* may confer mating advantages to individuals who do not develop a psychiatric condition. This hypothesis suggests that the mating advantages of schizotypy may be mediated by increased verbal and artistic creativity. These traits are likely to be especially adaptive in short-term mating contexts (Nettle, 2001). To test the hypothesis, Nettle and Clegg (2006) investigated the relationship between schizotypal personality traits, creative activity, and mating success in British poets, visual artists, and other adults, finding that two components of schizotypy—unusual experiences and impulsive non-conformity—were positively correlated with mating success (Nettle and Clegg, 2006).

A related hypothesis has suggested that schizophrenia represents the negative, maladaptive extreme of a sexually selected fitness indicator, that is, a trait (or a suite of correlated traits) that reveals an individual's underlying genetic quality and condition to potential mates (Shaner et al., 2004). In an individual with high genetic quality (e.g., a low deleterious mutation load) and high condition (a favorable prenatal and postnatal environment yielding a robust organism), schizotypy would produce a highly attractive phenotype, while in poor environmental conditions these neurodevelopmental processes should result in an aberrant brain prone to unsuccessful courtship behavior that repels potential mates, which, according to the authors, is what we know as schizophrenia (Shaner et al., 2004).

Based on the sexual selection hypothesis of schizophrenia (Nettle, 2001), Del Giudice and colleagues have developed a model that integrates life history theory to explain the expression of schizotypal traits (Del Giudice, 2010, 2017; Del Giudice et al., 2014). In short, life history theory refers to the trade-offs that organisms face from allocating limited resources of time and energy in two primary biological processes: reproduction and survival-enhancing activities (Del Giudice and Ellis, 2016; Figueredo et al., 2006). In stable and predictable environments, organisms tend to allocate more energy in growth and developmental processes, delaying reproductive activities (i.e., slow life history strategy), whereas in harsh and unpredictable environments, organisms tend to allocate more energy in reproductive activities than in growth and developmental processes (i.e., fast life history strategy) (Ellis et al., 2009; Woodley of Menie et al., 2021; see also Luoto et al., 2019a; Luoto et al., 2019b, for a critical discussion and caveats).

Prior research in humans has shown that life history strategies may vary on a slow-to-fast continuum, where fast life history strategies are associated with high mating effort such as precocious sexuality, sexual openness, low interest in long-term relationships, high impulsivity, risk-taking, and low agreeableness and conscientiousness, whereas slow life history strategies are related to high somatic and parenting effort such as investment in bodily growth, acquisition of resources, delayed sexuality, fewer sex partners, self-control, and high agreeableness and conscientiousness (Belsky et al., 1991; Del Giudice, 2017; Luoto et al., 2019a). More recently, however, this unidimensional model of life history strategies in humans has been called into question, suggesting instead a multidimensional model of human life history (e.g., Richardson et al., 2021). Overall, life history strategies have wide-ranging implications for physiology, personality, behavior, health (Luoto et al., 2019a; Wells et al., 2017; Woodley of Menie et al., 2021), and possibly the development of mental disorders (Del Giudice, 2014; Del Giudice and Haltigan, 2021; Kavanagh and Kahl, 2018).

Existing evidence suggests that schizotypy is associated with high mating effort and reduced parenting effort, thereby demonstrating the hallmarks of fast life history strategies (Del Giudice, 2017; Kaplan and Gangestad, 2005). Therefore, according to the sexual selection hypothesis of schizophrenia, schizotypy may be understood as a high-risk strategy oriented toward short-term mating (Nettle, 2001). The problem arises when schizotypy (as a fast life history strategy trait) becomes pathological, reducing reproductive success as a result of the interaction among developmental perturbances, genetic mutations, parasitic infections, nutritional deficits, and/or stressful situations in vulnerable individuals (Brüne et al., 2010; Del Giudice et al., 2014).

These hypotheses are undermined by the fact that individuals with schizophrenia show very low reproductive success relative to controls (about 0.3–0.8 on average) and that, contrary to predictions arising from an evolutionary biological sexual selection hypothesis, the reduction in fertility is more severe in male patients (Bassett et al., 1996; Haukka et al., 2003; MacCabe et al., 2009; Svensson et al., 2007). Thus, it is commonly thought that fertility in non-affected individuals is not high enough to offset the reproductive costs of schizophrenia, as would also be predicted based on the balanced polymorphism hypothesis. Del Giudice (2010) mathematically showed that reduced fertility in the families of schizophrenic patients might coexist with selective neutrality

of schizotypy-increasing alleles, or even with positive selection on schizotypy in the general population. There is some evidence linking the genetic predisposition for schizophrenia with earlier age at first birth in women, though the effect appears to be pleiotropic rather than causative (Ni et al., 2019). Lawn et al. (2019) investigated correlational and causal effects of genetic liability for schizophrenia on number of children, age at first birth, and number of sexual partners in non-affected individuals using data from the Psychiatric Genomics Consortium and UK Biobank. They did not find any effect of genetic liability for schizophrenia on number of children or age at first birth in non-affected individuals. However, they reported a small positive effect of genetic liability for schizophrenia on number of sexual partners (0.165 increase in the number of sexual partners in non-affected individuals) (Lawn et al., 2019). The effect appears too weak to compensate for the fitness costs of schizophrenia in affected individuals. It is therefore not likely that alleles that increase the risk of schizophrenia would be maintained simply because of their beneficial effect on reproductive success of non-affected individuals.

It is nevertheless possible that the fitness costs and benefits associated with schizophrenia risk alleles have been different in our evolutionary history; schizophrenia, after all, appears to be a disease of modern lifestyle (see Section 3), and widespread contraception use in modern populations may eliminate some of the reproductive advantages (e.g., lower age at first reproduction, shorter inter-birth interval, higher total number of offspring) that would otherwise accrue from fast life history strategies. Thus, the costs of carrying alleles that increase the risk of schizophrenia might have been weaker or absent among our ancestors with hunter-gatherer lifestyles, while the benefits of having such alleles may have been more pronounced. This would be a fruitful avenue for further research in populations with hunter-gatherer or pre-industrial lifestyles.

5.10. Schizophrenia as a fitness trade-off, and the “cliff edge” fitness model

A related hypothesis suggested by Farley (1976) posits that schizophrenia could be interpreted as a manifest fitness trade-off at the extreme end of normal behavior. This hypothesis assumes that many symptoms associated with schizophrenia, such as disordered thinking and delusions, could be viewed as outliers of a normal continuum of social behavior, and that they occur as a result of natural variation in normal brain evolution and development (Randall, 1983, 1998) (see also: Cook et al., 2020). In this context, it has been proposed that the origin and evolution of language and schizophrenia might be closely related: the predisposition toward schizophrenia could reflect extreme phenotypic variation associated with the capacity for language (Crow, 1993, 1995, 2000; Murphy and Bentez-Burraco, 2016). According to Crow (2000), positive selection for those gene variants that enhanced cerebral flexibility would allow the emergence of intelligence and language. However, variation in psychological functioning would constitute a disadvantageous byproduct of cerebral plasticity and complexity, resulting in the expression of mental disorders like schizophrenia at the phenotypic extremes. In other words, the risk of developing schizophrenia could be seen as the price that humans pay for having complex social skills, language, and creativity (Burns, 2004; Pearson and Folley, 2008). In a closely related perspective, “the cliff edge” fitness model proposes that certain adaptive traits may overshoot their optimum, which would result in aberrant and maladaptive consequences such as those in schizophrenia (Abed and John-Smith, 2020).

Genetic evidence supporting the fitness trade-off hypothesis and the cliff edge model has shown that parts of the genome known as Human Accelerated Regions (HAR), which are conserved among vertebrates but have undergone higher rates of nucleotide substitutions in human evolutionary lineage (Levchenko et al., 2018), function as enhancers of genes involved in the development of the brain (Capra et al., 2013). Thus, it is possible that certain HAR might have been subject to positive

selection, which would result in increased cognition and intelligence but also in higher vulnerability to mental disorders (Levchenko et al., 2018). Likewise, other studies have shown that variants in brain-related genes conferred significantly higher susceptibility to schizophrenia than variants in other genes (Srinivasan et al., 2016), although these schizophrenia risk alleles are not located among HAR (Srinivasan et al., 2017). However, this evidence provides, at best, only circumstantial evidence for the fitness trade-off hypothesis and the cliff edge model.

5.11. The lipid metabolism hypothesis

Closely related to the fitness trade-off hypothesis, Horrobin (1998, 1999) proposed “the lipid metabolism hypothesis,” which suggests that *Homo sapiens*’s greater availability (relative to the great apes) of arachidonic acid and docosahexaenoic acid (essential fatty acids), in combination with phospholipase mutations and changes in lipid metabolism, could have resulted in enhanced neuronal microconnectivity in the course of human evolution. The increased microconnectivity would allow superior intelligence, creativity, and possibly the emergence of complex cumulative culture; however, abnormalities in lipid metabolism may predispose to several psychiatric disorders such as schizophrenia, dyslexia, and major depression (Horrobin, 2001). Based on Horrobin’s ideas, the effect of high concentrations of Omega-3 fatty acids on schizophrenic patients has been tested but the results have been inconsistent (Abed and John-Smith, 2020). The evidence for this hypothesis is therefore still inconclusive.

6. Critical evaluation of previous evolutionary hypotheses for schizophrenia

Many of these previous evolutionary hypotheses lack proper empirical validation (Fig. 2). Above and beyond the critical discussion presented in this article, scientific approaches to schizophrenia would benefit from critical appraisals and rigorous research devising crucial experiments that pitch each hypothesis against one other (cf. Platt, 1964). Even though some of the previous evolutionary hypotheses presented above might explain some of the characteristic manifestations of psychosis or delusions and their relations to the genetics of schizophrenia, all of them—with the exception of the mismatch hypothesis—fail to provide a convincing explanation for the negative symptoms of schizophrenia such as blunting of affect, violent behavior, aggression, apathy, anhedonia, loss of motivation, or cognitive deficit. The hypotheses—with the exception of the mismatch hypothesis—also fail to explain impairments in executive functions typically observed in schizophrenic patients. In addition, the hypotheses have not been able to explain why schizophrenia is commonly comorbid with many other mental disorders (Buckley et al., 2009; Tsai and Rosenheck, 2013). Major depressive disorder, for instance, constitutes a common psychiatric comorbidity in patients with schizophrenia. A recent meta-analysis found that 32.6% of patients with schizophrenia would meet the diagnostic criteria of major depressive disorder (Etchecopar-Etchart et al., 2021) and symptoms of major depressive disorder are common prodromal symptoms of psychosis (Hafner and an der Heiden, 2011). In addition, a 12-month follow-up study found that 80% of patients with first-episode psychosis would also fulfill the diagnostic criteria of major depressive disorder (Upthegrove et al., 2010). Psychosis may also occur in patients with major depressive disorder, bipolar disorder, and schizoaffective disorder (Dubovsky et al., 2021), highlighting that these disorders are not completely separate entities. The comorbidity of these disorders is most elegantly explained by the parasite hypothesis of schizophrenia presented in Section 2, as well as their shared genetic basis (Anttila et al., 2018; Hindley, 2021; Legge et al., 2021). These disorders are characterized by sickness behavior, which is caused either by the activation of the immune system via low-grade systemic inflammation (Rantala et al., 2018, 2021) or direct manipulation of host behavior by parasites (Borráz-León et al., 2021).

Schizophrenia is not a discrete disorder and separating it from other disorders is often difficult. This makes all previous evolutionary hypotheses (except the mismatch hypothesis) somewhat problematic. The classification of these disorders is often difficult because of overlapping symptoms, which may result in a patient receiving different diagnoses from different psychiatrists. Hallucinations and delusions occur also in patients with bipolar disorder and Alzheimer’s disease. About half of Alzheimer’s patients have psychosis (Murray et al., 2014) and a study on 1,342 patients with bipolar disorder type I found that 73.8% had a lifetime prevalence of psychotic symptoms (van Bergen et al., 2019). A plausible scientific framework would also explain occurrences of psychosis, delusions, and hallucinations in other disorders, not just in schizophrenia. The parasite hypothesis is able to explain why psychosis may occur in other disorders: differences in the parasite species that individuals are infected with, differences in timing of infection, genetic vulnerability, and microbiota may explain whether a person will have symptoms of schizophrenia or, say, bipolar disorder, or depression with psychotic features (see Section 2.3).

Schizophrenia has traditionally been classified into different subtypes that differ in symptomatology. The prevalence of these subtypes varies geographically and temporally (Jablensky et al., 1992). Schizophrenia is not a single disorder. Instead, it seems that schizophrenia is only an umbrella term for a group of separate disorders with some overlapping symptoms. None of the previous evolutionary explanations for schizophrenia have explained the heterogeneous subtypes of schizophrenia and their persistence in modern human populations—although the mismatch hypothesis and the balanced polymorphism hypothesis could conceivably account for these findings. The parasite hypothesis, in contrast, provides an explanation for the heterogeneity by suggesting that it results from different parasite/pathogen species causing schizophrenia and/or individual differences in responses to microbial infections (see Section 2).

With the exception of the mismatch hypothesis, all previous evolutionary hypotheses also fail to provide a rationale for why and how neuroinflammation plays a role in schizophrenia (see Section 2.1.) and why there are inflammatory marker subtypes in schizophrenia (e.g., Lizano et al., 2021). The parasite hypothesis, in combination with the mismatch hypothesis, explains why neuroinflammation occurs in schizophrenia and why there are different inflammatory marker subtypes. The parasite x genotype x stress model also explains why schizophrenia is more common in cities than in rural areas (see Section 3). Since chronic stress—which is often a triggering factor in psychosis—is rare among people with hunter-gatherer lifestyle(s) (Brenner et al., 2015), the parasite x genotype x stress model, coupled with the mismatch hypothesis, explains why schizophrenia is rare among them (cf. Abed and Abbas, 2011b). Except for the mismatch hypothesis, previous evolutionary hypotheses for schizophrenia have not been able to explain why schizophrenia is more common in people with modern western lifestyles and why exposure to natural environments in neighborhoods or around residential areas is associated with lower schizophrenia rates (Engemann et al., 2019, 2020; Kristine et al., 2018).

None of the previous evolutionary hypotheses have been able to explain why adverse life events play an important role in the onset of schizophrenia and psychosis. For example, exposure to childhood trauma is associated with a 2- to 3-fold increase in risk of psychotic outcomes (Croft et al., 2019; Rokita et al., 2021; Trotta et al., 2015). Likewise, cumulative stress pathophysiology is often a triggering factor in psychosis (Nugent et al., 2015), and cortical stress regulation is disrupted in patients with schizophrenia (Schifani et al., 2018). There are also differences in gut microbiota between healthy people and those with schizophrenia (Section 4). These observations do not fit well with previous evolutionary hypotheses for schizophrenia, with the exception of the mismatch hypothesis. Thus, most existing evolutionary hypotheses do not explain empirical findings about schizophrenia and have acquired limited empirical support of their own. The parasite x genotype x stress model, in contrast, suggests that stress negatively impacts immune

function and thereby facilitates parasitic/pathogenic effects on the brain (see Section 2).

Many of the previous evolutionary explanations for schizophrenia are examples of evolutionary storytelling: they provide adaptive explanations for a phenomenon which is neither adaptive nor an adaptation, but rather a pathological side effect of microbial infection and chronic stress. Although the parasite x genotype x stress model can explain the occurrence of schizophrenia at one level of analysis, the sexual selection hypothesis (Nettle, 2001), the reformulated social brain hypothesis (Abed and Abbas, 2011b), and the life history hypothesis of schizophrenia (Del Giudice, 2010, 2017; Del Giudice et al., 2014) may partly explain why genetic variants that interact with pathogen infection and chronic stress (Fig. 1) may exist in the human gene pool in the first place. Furthermore, the mismatch hypothesis is an integral component of the parasite x genotype x stress model; environmental mismatch, after all, leads to the chronic stress that makes individuals with contemporary western lifestyles more susceptible to schizophrenia than people with traditional lifestyles (Fig. 1). Despite the abundant evidence supporting the parasite x genotype x stress model coupled with the environmental mismatch hypothesis of schizophrenia, it is also possible that future research will discover other hypotheses at proximate and ultimate levels of analysis, which will more accurately carve the biopsychosocial and heterogeneous nature of schizophrenia at its joints.

7. Treatment options

7.1. Current treatments

Antipsychotic drugs, most notably clozapine (Fond et al., 2019), are currently the cornerstone of schizophrenia treatment (Stepnicki et al., 2018). The function of these drugs is thought to be based on dopamine antagonism (Brisch et al., 2014; Sonnenschein et al., 2020), but some of these drugs (haloperidol, dapsone, and valproic acid) also inhibit cell invasion and replication of *T. gondii* tachyzoites (Webster et al., 2006). These drugs are efficient only for 50–60% of schizophrenia patients (Fond et al., 2019; Stepnicki et al., 2018), which is consistent with the pathogen hypothesis of schizophrenia, acknowledging as it does that schizophrenia may be caused by pathogens other than just *T. gondii*. Although antipsychotic drugs may help relieve symptoms in many patients, they cause severe neurological and metabolic side effects and may lead to sexual dysfunction or agranulocytosis (in the case of clozapine) (Stepnicki et al., 2018).

7.2. Treatments based on the parasite x genotype x stress model

If the parasite x genotype x stress model (Fig. 1.) becomes clinically validated, the treatment of schizophrenia should focus on detecting and treating the underlying microbial infections rather than just alleviating symptoms with drugs. In light of the parasite x genotype x stress model, researchers should also subtype schizophrenia patients according to the underlying microbial infection, such as *C. spittaci* infection with psychotic features. This would make psychiatric diagnosis more scientific and, for the first time in psychiatry, blood tests could be used to verify and/or support diagnoses. Future research should verify whether symptoms of schizophrenia differ with microbial infections and timing of infection.

Common to patients with schizophrenia is that they have poor eating habits and insufficient physical activity (Kalinowska et al., 2021). The severity of schizophrenia symptoms is correlated with the degree of unhealthy eating habits and physical inactivity (Kalinowska et al., 2021). As chronic stress often acts as a trigger for the psychotic cycle in people with schizophrenia and also in other psychotic disorders (Nugent et al., 2015; Schifani et al., 2018), it is necessary to improve stress tolerance in the treatment and prevention of psychotic disorders. This could be done by many lifestyle treatments that are known to reduce stress and improve stress tolerance. These lifestyle treatments include

adopting a healthy diet (Calder, 2017; Kaulmann and Bohn, 2014; Stachowicz and Lebedzinska, 2016), avoiding alcohol (Wang et al., 2010), engaging in regular exercise (Kvam et al., 2016; Nabkasorn et al., 2006), engaging in mindfulness (Morton et al., 2020), yoga (Pascoe et al., 2017), and increasing contact with nature (Antonelli et al., 2019).

A recent meta-analysis of eighteen studies found that exercise interventions (any type of physical exercise including yoga and tai chi, lasting 3–52 weeks) provided a moderate ($g = -0.596$) improvement in scores on the positive and negative syndrome scale (PANSS) in schizophrenia (a commonly used medical scale for measuring symptom severity of patients with schizophrenia) (Fernandez-Abascal et al., 2021). Likewise, a meta-analysis of twenty-one studies examining post-intervention changes in positive and negative symptoms (separately) found that exercise interventions reduced both positive symptoms ($g = -0.426$) and negative symptoms ($g = -0.539$) (Fernandez-Abascal et al., 2021). Although more studies are needed in order to identify optimal ways to provide exercise interventions, it is clear that they should be an integral part of schizophrenia treatment because they do not only effectively reduce schizophrenia symptoms but also improve patients' general health (Fernandez-Abascal et al., 2021). It is important to note that exercise is known to reduce low-grade systemic inflammation (Thompson et al., 2020), improve stress tolerance, and influence gut microbiota (Munukka et al., 2019), providing indirect support for the hypothesis that schizophrenia is a disease of modern lifestyle and is exacerbated by these factors (Section 3 and Fig. 1).

There are dietary guidelines and programs to help schizophrenia patients manage weight and physical illness, but there are no nutritional guidelines for the treatment of psychiatric symptoms (Aucoin et al., 2020). A recent meta-analysis found that 19 of 25 dietary intervention studies on schizophrenia reported significant improvement in one or more mental health domain, including quality of life, psychiatric symptoms, increased function, decreased mental healthcare utilization, and/or improved cognition (Aucoin et al., 2020). However, more studies should be conducted before any nutritional guidelines on psychiatric symptoms can be made. It is also possible that schizophrenia patients' diets should be tailored individually because of individual differences in gut microbiota and food hypersensitivities.

Since patients with schizophrenia tend to have an abnormal gut microbiota (e.g., Kelly et al., 2021; McGuinness et al., 2022; Thirion et al., 2022), and since disturbances in microbiota influence stress sensitivity and neuroinflammation (see Section 4), treatment of schizophrenia should include different therapies that target gut dysbiosis more directly than just via dietary intervention. In the future, these interventions could include such options as probiotics, prebiotics, antibiotics to kill harmful microbes, or fecal microbiota transplantation from a healthy donor (Bioque et al., 2021). These treatments should be tailored individually depending on the microbiota of the patient. Nonetheless, studies in this field are still too scarce for any guidelines to be developed. For instance, to our knowledge, there are no studies testing whether fecal transplantation from a healthy person would have an effect on schizophrenia symptoms (cf. Cuomo et al., 2018; Zhu et al., 2020a). We encourage more research on this and related questions (Table 1).

8. Conclusions

Current evidence indicates that schizophrenia is not an evolutionary adaption nor a byproduct of other adaptations like most previous evolutionary hypotheses of schizophrenia have suggested. Instead, as schizophrenia is very rare among people with non-westernized lifestyles and much more common in people with contemporary western lifestyles, the environmental mismatch hypothesis (Sections 3 and 5.2) provides the most plausible evolutionary explanation for schizophrenia.

At a mechanistic level, chronic stress often seems to be the triggering factor of psychosis, with neuroinflammation, microbial infection(s), and gut dysbiosis mediating this relationship. There is substantial evidence

Table 1

Open questions.

- 1) Genotype analyses on Europeans have shown that individuals with schizophrenia carry an increased burden of deleterious mutations (Loohuis et al., 2015). Is this also true in non-European populations, including those with ancestral lifestyles?
- 2) Are the costs of carrying the alleles that increase the risk of schizophrenia lower or absent among populations with hunter-gatherer lifestyles than in contemporary populations? Are the benefits of having such alleles more pronounced in hunter-gatherer populations than in contemporary western societies?
- 3) Are genotypes that predispose to schizophrenia under stronger negative selection pressures in populations with contemporary western lifestyles than in populations with traditional pre-agricultural lifestyles?
- 4) Do different pathogens produce different symptoms and neuroanatomical schizophrenia subgroups?
- 5) Does the timing of microbial infection in ontogeny affect the specific presentation of schizophrenia symptoms later in life?
- 6) What are the neuropsychiatric implications of alterations in the microbiota-gut-brain axis signaling for schizophrenia, particularly at early developmental stages or during adolescence?
- 7) Can microbiota-based interventions reduce the development of psychosis in at-risk individuals?
- 8) Are there specific genotype x diet x microbiota x stress interactions in psychosis?
- 9) Can there be one-size-fits all dietary interventions for schizophrenia or to what extent should they be personalized, taking into account factors such as an individual's inflammatory status and microbiota?

for the hypothesis that neuroinflammation has an important role in psychosis. Nevertheless, immunological studies on patients with psychosis have produced heterogeneous results with regard to immune markers, as discussed in Section 2.1. Potential reasons for this heterogeneity include the additional role that microbial infections play in schizophrenia, which is further complicated by the diversity of pathogens that are able to trigger psychosis by causing neuroinflammation. Chronic stress appears to be rare among people who have not adopted contemporary western lifestyles (Brenner et al., 2015; Fedurek et al., 2020; further confirmatory research in various hunter-gatherer populations and populations with ancestral lifestyles is required to be able to conclusively generalize this finding) but very common among people who have. Furthermore, current evidence indicates that hunter-gatherer populations do not suffer from low-grade systemic inflammation (e.g., McDade et al., 2012; a finding that should also be replicated in various hunter-gatherer populations to be fully generalizable), making them less susceptible to neuroinflammation while also increasing their stress tolerance.

This proximate-level mechanistic explanation, which connects chronic stress, gut dysbiosis, neuroinflammation, and microbial infections with schizophrenia (Fig. 1), is consistent with the ultimate-level mismatch hypothesis, which posits that contemporary western lifestyles cause a cascade of risk factors, leading to higher rates of schizophrenia in contemporary environments than in ancestral ones. In combination, the proximate-ultimate synthesis presented here provides the most plausible explanation for the relatively high prevalence of schizophrenia spectrum disorders among people with contemporary western lifestyles.

The fact that parasites and chronic stress play an important role in the etiology of schizophrenia may explain why natural selection has not erased alleles that make people vulnerable to schizophrenia despite the reduced reproductive success that it causes and the high heritability that schizophrenia has in contemporary western people. Many people who carry these risk alleles may never develop schizophrenia because they might not be exposed to the pathogens that cause schizophrenia, or they have not experienced chronic stress to the extent that would trigger psychosis. With schizophrenia mainly being caused by the interaction between contemporary western lifestyles, genetics, and parasites, it is possible that not enough time has passed for current negative selection pressures to erase alleles that make individuals vulnerable to schizophrenia.

Over the past decades, researchers have used billions of dollars in order to uncover the genes and neuroanatomical substrates underlying schizophrenia. However, for the most part, these research efforts have

not been beneficial for patients (Insel, 2022). We hope that the parasite x genotype x stress model presented in this article will help shift the focus from genetics towards environmental factors, including parasites, chronic stress, inflammation, and lifestyle factors, which are naturally easier to address than genetic factors. We encourage researchers to study the role of parasites behind schizophrenia more rigorously and to find a cure for latent *T. gondii* infections. We also encourage more systematic studies on the prevalence, presentation, and fitness-related outcomes of schizophrenia and other mental disorders among hunter-gatherer populations, including systematic studies on the prevalence of chronic stress and low-grade systemic inflammation in such populations.

In contrast to some previous evolutionary hypotheses, the parasite x genotype x stress model presented in this article in combination with the mismatch hypothesis constitutes an empirically testable and falsifiable hypothesis. The model also explains why lifestyle interventions can alleviate schizophrenia symptoms (Section 7.2). Ultimately, we hope that the parasite x genotype x stress model coupled with the evolutionary mismatch hypothesis will help advance further empirical work and to provide major improvements in the treatment of schizophrenia.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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