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The gut microbiota and the emergence of autoimmunity: relevance to major psychiatric disorders

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Abstract

Background—Autoimmune phenotypes are prevalent in major psychiatric disorders.

Disequilibria of cellular processes occurring in the gastrointestinal (GI) tract likely contribute to immune dysfunction in psychiatric disorders. As the venue of a complex community of resident microbes, the gut in a homeostatic state equates with a functional digestive system, cellular barrier stability and properly regulated recognition of self and non-self antigens. When gut processes become disrupted as a result of environmental or genetic factors, autoimmunity may ensue.

Methods—Here, we review the issues pertinent to autoimmunity and the microbiome in psychiatric disorders and show that many of the reported immune risk factors for the development of these brain disorders are in fact related and consistent with dysfunctions occurring in the gut. We review the few human microbiome studies that have been done in people with psychiatric disorders and supplement this information with mechanistic data gleaned from experimental rodent studies.

Results—These investigations demonstrate changes in behavior and brain biochemistry directly attributable to alterations in the gut microbiome. We present a model by which autoantigens are produced by extrinsically-derived food and microbial factors bound to intrinsic components of the gut including receptors present in the enteric nervous system.

Conclusion—This new focus on examining activities outside of the CNS for relevance to the etiology and pathophysiology of psychiatric disorders may require new modalities or a re-evaluation of pharmaceutical targets found in peripheral systems.

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Conflict of Interest

Dag Tveiten is the managing director and shareholder in Lab1. Robert Yolken is a member of the Stanley Medical Research Institute Board of Directors and Scientific Advisory Board. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies. None of the other authors report any potential conflicts of interest.

Keywords

Microbiota; schizophrenia; autism; psychosis; NMDA receptor; bacteria; virus; gluten; celiac disease; gut-brain axis

1. Introduction

Psychiatric disorders such as schizophrenia and bipolar disorder have complex etiologies that are likely the product of environmental interactions with multiple gene susceptibility loci [1–6]. Dysfunction of immune system pathways reconciles both genetic and environmental hypotheses of psychiatric disease pathogenesis [7–18]. Under this umbrella of aberrant immunity is the finding of numerous autoimmune phenotypes, even though these disorders are not considered to be “classic” autoimmune diseases [19–23]. Examination of the mechanisms driving autoimmunity may shed some light onto how immune dysregulation might be a relevant etiological agent or comorbid pathology of complex brain disorders. Data generated to date suggest that among the many sources of immune dysfunction in psychiatric disorders is the disequilibrium of cellular processes occurring in the GI tract [10, 24–27]. Thus, the failure to fully understand autoimmunity in psychiatry may be due to the currently under-considered role of intestinal microbes and the gut-brain axis. Gut disturbances in human psychiatric disorders have a long and expansive history that predates the use of many psychotropic medications including first generation antipsychotics introduced in the 1950s [28]. As the largest organ of the immune system, the GI tract serves as an interface between the environment and the host and thus may represent an important source of autoimmune pathologies that have both an environmental and genetic basis.

Technical advances in genome sequencing and the establishment of large human microbiome consortias have accelerated progress in our understanding of how microbial dysbioses are associated with a diversity of diseases including cancer, obesity, liver dysfunction and inflammatory bowel diseases [29]. For brain disorders, altered microflora compositions in the disease state are evident in analyses of human biospecimens, as described in a later section. Whether or not these dysbioses represent artifacts of treatment and lifestyle factors or a true physiological reflection of disease pathogenesis is not currently known. Further insight thus comes from complementary experimental in vivo models, which demonstrate changes in behavior and brain biochemistry directly attributable to alterations in the gut microbiome, both at the community microbial level and for specific bacterial taxa. In this review, we examine autoimmune and microbiome interactions within a context of gut-brain axes relevant to psychiatric disorders. We will focus on evidence from human studies of schizophrenia, but for certain key points, we also include results from studies of autism, bipolar disorder, major depressive disorder and experimental animal models. We review the associations with psychiatric disorders of specific autoimmune diseases, evidence for autoimmune antibodies against brain targets, and GI-based risk factors for psychiatric disorders. We will propose a model premising that under the right set of environmental circumstances, all of these components may collectively promote an autoimmune-propagating state with the potential to impact pathways of the central nervous system. Our model reveals that therapeutic agents based on GI, neuronal and immunological pathways

may be promising primary or adjunctive targets and should be evaluated in clinical studies for individualized and synergistic effects in the context of psychiatric disorders and brain symptom amelioration.

2. Overview of mechanisms that generate autoimmunity

Autoimmunity, or the loss of self-tolerance, occurs when the immune system no longer can distinguish between self and non-self antigens, and it proceeds to attack cells and tissues of its own organs [30]. Mechanisms to explain how autoimmune disorders might arise generally converge on the idea that there is dysfunction associated with the recognition molecules found on the surface of T and B lymphocytes [31]. During innate immune activation, for example, pattern recognition receptors are responsible for detection of pathogen based signals (Pathogen Associated Molecular Patterns) and recognized antigens include bacterial, viral and fungal components. The detection by pattern recognition receptors of host cell signals (Damage Associated Molecular Patterns) is triggered by cellular debris and is indicative of tissue injury following necrosis and apoptosis [30, 32]. Notably for schizophrenia, studies of susceptibility loci consistently point to the human leukocyte antigen (HLA) region that is responsible for presenting pathogen-related fragments to the cell surface for cell destruction by the immune system [16–18, 33, 34]. In the gut, intestinal epithelial cells have innate immune pattern recognition receptors, toll-like receptors, Nod-like receptors and helicases, all of which enable an active response to invaders [35]. It is easy to visualize the unfolding of an autoimmune process if resident bacteria integral to normal gut function are perceived as foreign and the body's cellular immunity launches an inflammatory attack to dismiss trespassers [32]. Like psychiatric disorders, autoimmune disorders may be rooted in the host's genetic architecture as well as extrinsic environmental influences. With the presence of numerous types of autoimmune diseases, it is likely that varied mechanisms contribute to different disease etiologies [30, 36].

Predominant mechanistic themes that arise in conjunction with autoimmunity and psychiatry lead to hypotheses involving altered antigenicity of host proteins, molecular mimicry, and the generation of autoantibodies that are cross-reactive against brain proteins. Sometimes a self-antigen can become altered by the inappropriate attachment of a hapten or conversion of an arginine to a citrulline, processes that can be particularly prevalent during inflammation. One end result is the creation of a novel epitope that the immune system does not recognize as self [30, 37, 38]. Post-translational modifications can create nonself-antigens from self-antigens, or self-antigens can also be hidden and once unmasked become immune system targets [30]. Another mechanism that generates autoimmunity is molecular mimicry, which is the structural similarity of self antigens to extrinsic or non-self, often microbial, antigens [39]. Resident microbiota are also capable of inducing an autoimmune state, but do so through excess generation of Th17 cells and suppression of Tregs [39]. Another hypothesized mechanism is the hygiene hypothesis where an infection-free infancy predisposes an individual to autoimmunity [38]. There is also indication that the process of autoimmunity is dynamic where gut bacteria alterations cyclically enhance or attenuate susceptibilities to the autoimmune state [38]. While genetic susceptibilities may predispose certain individuals to these autoimmune processes, all of the proposed mechanistic

hypotheses also are modifiable by environmental factors including microbial dysbioses, pathogen infection, hormonal imbalances, stress and exposure to xenobiotics [30].

3. Autoimmune disorders and autoantibody associations in psychiatric disorders

Epidemiological evidence offers several linkages between autoimmunity and human psychiatric disorders. In this section, we will concentrate on studies of schizophrenia and psychosis, as exemplified by several high-profile analyses of large registry databases that revealed a strong association between autoimmune disorders and these psychiatric disorders [20, 40]. Of note, however, there are also data for mood disorders, which associate with a variety of autoimmune diseases including autoimmune thyroiditis, inflammatory bowel diseases, and autoimmune hepatitis [41–43]. One of the first indications that schizophrenia might have an autoimmune component was the discovery of an inverse correlation in incidence between rheumatoid arthritis and schizophrenia, a finding that has been replicated several times [44–46]. Other autoimmune diseases that co-occur with psychosis included multiple sclerosis, systemic lupus erythematosus, autoimmune thyrotoxicosis, autoimmune hepatitis and psoriasis [45, 47]. Interestingly, a history of infection has been shown to further elevate the relative risk for schizophrenia above the 45% increase achieved with just a history of autoimmune disease [40]. This is not surprising given that infection is a process that leads to and perpetuates autoimmunity [48]. People with schizophrenia have increased levels of antibodies against microbial pathogens and in particular, viruses. Numerous studies have documented that exposure to infectious disease pathogens during the pre- and post-natal period is significantly associated with the future development of or current status of schizophrenia [9, 49–57]. Interestingly, exposure to viral infections is also associated with decreased cognitive function and progressive gray matter loss [58–60].

A goal of this review was to convey how risk factors for schizophrenia and other psychiatric disorders can be connected within the context of gut-based processes. One of the strongest associations of infectious disease pathology with schizophrenia is that of *Toxoplasma gondii*, a neurotropic parasite that enters the host through the GI tract [49, 61–63]. Immune sensitivity to wheat is another topic that has been studied in various forms from associations of the autoimmune GI disorder, celiac disease, to a separate condition termed non-celiac disease gluten intolerance [64–71]. In celiac disease, ingested wheat gluten is broken down by tissue transglutaminase and subsequently in genetically predisposed individuals, an autoimmune attack is launched against the epithelial lining of the small intestine [72–74]. This mechanism represents an example of how an extrinsic, gut-derived peptide (gluten) that when bound to the host's cellular machinery (the transglutaminase enzyme) creates a novel non-self epitope against which the host's immune system reacts. A CNS-related pathology may ensue when binding of gluten antibodies to brain proteins occurs [75–77].

The search for autoantibodies reactive against brain proteins is an ongoing quest that has been enthusiastically pursued and simultaneously disputed for a long time [12, 15, 22, 78–86] [87–90]. The glutamate NMDA receptor serves as a currently well-discussed antigenic target in this context [8, 12, 91–96]. Other sources of autoantibody activity relevant to

psychiatric disorders include Neuregulin-2, HERVs, cholinergic muscarinic receptors, nicotinic acetylcholine receptors, dopamine D2 receptors, mu-opioid receptors, serotonin receptors, AMPA receptors, GABA receptors, GAD, potassium channel receptors, cardiolipin, DNA, histones, mitochondria [12, 93–95]. While neurotransmitter receptors are logical entities to examine for hypofunction via autoantibody suppression, the antibody response against extrinsic antigens is equally relevant, as exemplified by the earlier discussed wheat gluten. The diversity of antigens that may precipitate the production of autoantibodies extends to microbes and the discussion of another relevant disorder, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS). In PANDAS, certain behaviors such as obsessive compulsive disorder and tic disorders are attributable to brain-active autoantibodies generated in response to a streptococcal infection [97, 98].

4. Basic functions of the gut microbiome

The GI system coordinates a complex interaction of cellular and molecular mechanisms to facilitate digestion and nutrient absorption and to protect the body from dangerous antigens, toxins and infectious agents [99]. Normal gut operations are managed by a diverse community of over a trillion resident microbial agents, mostly bacteria, but also viruses, fungi and archaea, which live in close proximity to epithelial surfaces. In the healthy state, these species are at equilibrium with host cell activities [37, 100]. A healthy microbiome can become disrupted by numerous factors such as diet, antibiotics, toxins, infectious agents and host genetics [37]. The gut microbiome has multiple functions including the regulation of metabolism, maintenance of the integrity of the gut-blood barrier, and development of the host's immune response [99, 101–103]. In gut-brain models relevant to psychiatric diseases, we are particularly interested in the mechanisms commensal gut microbes use to modulate epithelial barrier permeability and to establish and regulate immunity. Gut microbes coordinate the downregulation of epithelial inflammatory responses, expression of anti-microbial proteins, defense of epithelial surfaces by mucus production and repair of damaged intestinal tissue [101]. These microbes generally act in concert as a community, but some specific bacterial taxa have been shown to play a role in barrier maintenance [104–109]. Bacterial species from the two phyla, Bacteroidetes and Firmicutes, generally dominate the healthy gut microbiome, but compositions can be altered by the initial colonization by the maternal microbiome, geography, age and other disruptive environmental factors previously listed [100]. Regarding immune system regulation, the microbiome is integrally connected to the development of the immune response and tolerance to auto-antigens [37, 103, 110]. In a review of the evidence for this role, it has been demonstrated that gnotobiotic mice developed abnormal gut-associated lymphoid tissue, Peyer's patches, and lower Tregs and were less able to suppress Th17 [37].

5. GI processes in psychiatric disorders

Dysfunctions attributable to an imbalanced gut microbiome include impaired digestion, dysmotility, inflammation, and compromised integrity of the gut-blood barrier [37, 100]. In this section, we review these gut-based processes as they relate to findings from studies of schizophrenia. GI conditions are long-standing comorbidities of mental illnesses, and this

association predates current diagnostic classification systems and the development of antipsychotics [28]. Interestingly, a subset of individuals with autoimmune gut diseases such as Crohn's Disease, ulcerative colitis, Irritable Bowel Syndrome and Celiac Disease report psychiatric symptoms [111–115]. We have identified multiple risk factors for the development of schizophrenia, which are components of pathways that are operant in the gut [10]. In our studies, people with schizophrenia have increased immune activation against a diversity of antigens ranging from food proteins (wheat gluten and milk casein) to pathogens (the parasite *T. gondii* and certain viruses). Chronic inflammation of the digestive system, a state that can be propagated by the continual exposure to antigens, may compromise the integrity of the gut-blood barrier. Inflammation of the gut was most dramatically documented in a series of post-mortem examinations from 1953 where up to 90% of people with schizophrenia had evidence of gastritis, enteritis or colitis [116, 117]. Since this study was performed before the widespread availability of antipsychotic medications, it demonstrated that intestinal inflammation in individuals with schizophrenia can not be attributed totally to medications. More recently, we examined a marker for GI inflammation used to help diagnose Crohn's Disease, anti-*Sacharomyces cerevisiae* antibodies, and found elevated levels of this biomarker in both schizophrenia and bipolar disorder compared to controls [10, 27]. As mentioned, an important sequela of this inflammatory state, which might be compounded by repeated sensitivities and exposures to antigenic entities, is that the epithelial and endothelial barriers become compromised. In this scenario, digested food peptides, bacterial peptides or bacterially-derived toxic products are hypothesized to permeate the barrier, generate more inflammation and contribute to autoimmunity. We found that markers of the process of bacterial translocation were altered in schizophrenia and correlated with the antibody response to food antigens, thus suggesting the co-translocation of food-derived and microbial-derived antigenic peptides [118]. Furthermore, food-based peptides may directly impact gut permeability through modulation of tight junction proteins or indirectly through, for example, the production of cytokines [119–124]. In children with autism, peptides derived from gluten and casein were found to release inflammatory hormones in the gut [125]. Cross involvement of inflammatory hormones, sustained and intermittent inflammation and gut wall permeability might explain the often fluctuating symptoms in many individuals with psychiatric disorders. Thus inflammation derived from the GI tract is initialized and sustained in various forms and can be included among other documented peripheral and CNS states of inflammation associated with psychiatric disorders [8, 9, 63, 126–136].

Permeability of endothelial barriers can be achieved via numerous environmental factors, or a person may have genetic mutations that compromise the cytoarchitecture of these barriers [137–139]. Specific genes that have previously been identified for susceptibility in schizophrenia and psychosis include, for example, the tight junction protein claudin-5, actin, haptoglobin and nitric oxide synthetase [140–149]. Structures found at the gut-blood and brain-blood barriers are sufficiently similar to propose that processes that disrupt the GI locale might similarly perturb the CNS locale [150, 151]. The cerebrospinal fluid (CSF)-brain and -blood interfaces are somewhat different with important areas of access to the brain found at the choroid plexus and arachnoid membrane [152]. A compromised CNS barrier has been hypothesized in schizophrenia with investigations of CSF dynamics

revealing a low-grade, systemic inflammation [138, 139, 153–155]. Our studies couple this loss of barrier integrity with the finding that food antigen antibodies are well correlated in serum and CSF of people with schizophrenia but not in controls, a further indication that a regulatory entity in the CSF is compromised in the disease state [155]. Corresponding measures of standard plasma and CSF protein provided evidence for anatomical defects or restricted CSF flow in people with schizophrenia. A decreased CSF flow rate may have numerous physiological causes [156, 157], including choroid plexus calcification, arachnoid cysts and decreased brain volume [152, 156–165].

An elevated humoral immune response directed at food antigens and subsequently altered IgG dynamics in the CSF suggest in part that peptide portions of these food proteins may enter into systemic circulation via a permeable endothelial barrier. Indeed hyperpeptiduria has been documented in people with schizophrenia, depression and autism, and opioids compose a prevalent component of the peptide load [166–171]. The bioactive peptide products of gluten and casein are opioid receptor ligands that also stimulate dopaminergic activity in experimental models [166, 167]. Increased binding of opioids to resident receptors was found in clinical specimens including CSF in schizophrenia and postpartum depression [172, 173]. It is believed that these bioactive and potentially antigenic peptides may be derived from an inefficient breakdown during digestion by peptidases and proteinases, enzyme dysfunctions that may be genetically encoded [174, 175]. The binding of exorphins derived from food antigens to enteric opioid receptors or lymphocyte receptors and associations of these peptides with gut enzymes during protein breakdown provide additional autoimmune candidates [176].

6. The gut microbiome and psychiatric disorders

Examination of the gut-brain axis in psychiatric disorders is a promising new research frontier in a field where pharmacological discoveries have been disappointingly static for many decades now. A role for the gut microbiome in psychiatry and brain processes is the subject of numerous recent reviews [10, 28, 39, 177–181]. Human studies of the gut-brain interface document predominantly associative findings, while mechanistic connections are explored in experimental animal models. In Table 1, we list some of the published studies of clinical data that provide evidence of an altered gut microbiome composition in disorders such as schizophrenia, major depressive disorder and autism. Of interest are two metagenomic sequencing studies from our laboratory, which examine microbiota compositions of the oropharynx in people with schizophrenia compared to controls [182, 183]. In both studies, differential abundances associated with lactic acid bacteria were detected. In one study, the lactobacilli and bifidobacteria, genera that are involved with inflammation modulation, were more abundant in schizophrenia [182]. In the other study, people with schizophrenia had altered levels of *Lactobacillus phiadh*, a bacterial phage that infects the bacteria *Lactobacillus gasseri*. This bacteria is a resident of the oral and GI mucosae and is involved in functions related to epithelial cell maintenance and immune system modulation [183].

The availability of gnotobiotic rodents has greatly accelerated progress toward understanding the mechanisms guiding the gut-brain axis. Various manipulations of gut

microbiota in germ-free and/or pathogen-specific animals have consistently resulted in biochemical and molecular changes in brain physiology and altered behaviors [104, 184–187]. In these studies, recovery of pre-manipulation phenotypes was achieved with further manipulations or corrections of bacterial compositions, vagotomy, and administration of probiotics and/or antibiotics. Furthermore, a direct relationship was demonstrated between gut microbiota activity and blood-brain barrier permeability [188]. Germ-free animals had increased blood-brain barrier permeability compared to animals with normal gut flora. Following transplantation of germ-free animals with a normal microbiota, blood-brain barrier integrity was recovered. Another important finding was the strict regulation of microglia by gut microbiota [189]. In this study, elimination and recolonization of host microbiota had dramatic effects on microglial homeostasis and structure, and a critical role of short chain fatty acids and bacterial fermentation products were discovered to drive these changes [189].

7. Relevance of peripheral pathology to the brain

Animal studies of the gut-brain axis demonstrated an effect of gut microbiota on brain physiology, and there are a number of hypothesized mechanisms by which this process would ensue. Several discoveries in the last decade indicate the importance of molecules and proteins of the immune system to the developing brain, a significant consideration if psychiatric disorders such as schizophrenia and autism are fundamentally disorders of neurodevelopment. Critical neurodevelopmental processes include initial proliferation of glia and neurons, consequent migration, apoptosis, synapse genesis, myelination, and synapse pruning with the overall endpoint to establish functional neuronal circuits [11].

In the developing immune system, complement C1q and the major histocompatibility complex 1 (MHC1) were some of the first immune molecules identified to function in synapse development and pruning in the brain [190–194]. Very recently, complement C4 was found to be genetically and biologically linked to synaptic overpruning in schizophrenia [195]. The complement pathway-related C1QB gene, complement control-related genes, and complement surface receptor gene CD46 have also all been candidate loci associated with schizophrenia [196, 197]. Several studies reported that complement-containing circulating immune complexes were elevated in individuals with schizophrenia compared to controls and we found that a primary antigenic component of these immune complexes was casein and gluten [198–203]. We then showed that levels of maternal C1q IgG increased the odds for psychosis in offspring [204]. These studies supported the presence of autoantibodies directed against the C1q molecule. Thus, if autoantibodies to C1q are present in the mother, there is the possibility of maternal autoantibody interaction with fetal C1q during critical periods of brain development. Disruption of normal C1q-mediated synapse formation and pruning will presumably alter synaptic connections in the developing brain either through an over- or under-pruning process.

In the adult with psychiatric disease, the question arises as to how peripheral immune mediators such as autoantibodies and C1q might cause immune changes in the brain. We provided data in support of a gut generated inflammatory state that impacts epithelial and endothelial barriers including the CSF-blood and CSF-brain barriers [205]. Blood-borne

factors that might penetrate epithelial and endothelial barriers in this context include hormones, metabolites, cytokines, neurotransmitters, opioid peptides, immune factors, and short chain fatty acids [206]. Of very recent interest is the discovery of a novel route for immune molecule passage from the CNS via functional meningeal lymphatic vessels. These vessels line the dural sinuses and carry fluid and immune cells from the CSF and connect to cervical lymph nodes [207]. This intriguing new route may be applicable to peptides, antibodies and immune factors travelling between the brain and the periphery.

Another area that likely contributes to the gut-autoimmune-psychiatric disease interactome is the enteric nervous system and its repertoire of neurotransmitter receptors that are likewise present in the CNS. The vagus nerve is the most direct connection between the gut and brain and among the many receptor types common to the enteric and central nervous system are those relevant to studies of psychiatric disorders including cholinergic, dopaminergic, glutamate and opioid receptors. Interestingly, the NMDA receptor, a currently well-studied target in psychiatric disorders, is found throughout the enteric nervous system and among its activities is a role in the mediation of visceral pain associated with colitis [208]. We have shown that *T. gondii* infection produces anti-NMDA autoantibodies in mice [209]. In our conceptual model diagrammed in Figure 1, gut-derived peptides from food and microbial antigens are all probable ligands for related enteric receptors. Thus, when an extrinsic ligand is bound to a cellular entity in the presence of infection, inflammation or genetic predisposition, autoantibodies could be generated against the receptor-ligand unit. Therefore, inflammation may create an autoimmune-prone environment locally in the GI tract against the same neuronal and possibly glial entities that are present in the brain. Collectively, a gut system in dysbiosis would contribute in a variety of ways to the production of an immune response against altered and novel epitopes, which may, in turn, activate similar immune machinery in the brain.

8. Implications for pharmaceutical design

This new focus to examine factors outside of the CNS for relevance to the etiology and pathophysiology of psychiatric disorders requires a re-examination of pharmaceutical targets. Assigning pathogenic mechanisms to an extraordinarily heterogeneous group of diseases such as the psychiatric disorders is difficult. Thus when designing treatment strategies, it is extremely important to be able to identify the subsets of people who have, for example, immune, neurotransmitter or gut phenotypes, so that tailored treatments can be evaluated. Understanding the specific targets of autoimmunity in psychiatric disorders is a step towards this type of individualized therapy. For example, some people may better benefit from an NMDA receptor directed treatment whereas others might require complement inhibition. The correction of gut dysbioses and normalization of gut function might be accomplished with anti-inflammatory agents, dietary interventions, digestive enzyme-based aids, prebiotics, probiotics, specific species enrichment, or immunomodulatory nutrients. Compounds in development to treat celiac disease and gluten sensitivity might also be candidates for clinical trials in individuals with schizophrenia [210]. For example, treatment of mice with an endogenous serine protease inhibitor, elafin, normalized inflammation and intestinal barrier function [211]. Another compound, sevelamer, currently used to treat symptoms of chronic kidney disease, was found to bind

bacterial proteins and prevent these proteins from translocating from the gut into circulation [212]. In individuals with inflammatory bowel disease, some success has been achieved with anti-tumor necrosis factor- α which helps to reduce mucosal inflammation [213]. Reduction in intestinal permeability may also be achieved with certain fatty acids (propionate, butyrate, omega-3), vitamin D- and zinc-based treatments [214]. Thus, treating the gut to reduce permeability may in turn aid the resolution of autoimmunity and might improve psychiatric symptoms in some individuals. Future therapeutic strategies might involve monoclonal antibodies or other immunosuppressive treatments directed at specific targets. The rapid advance in the use of monoclonal antibodies for the treatment of autoimmune disorders provides hope that such therapies can also have a major impact on schizophrenia and other brain disorders as well. Therefore, a better understanding of gut processes and autoimmunity in psychiatric disorders may lead to novel methods for preventing and treating these devastating disorders.

9. Conclusions

In this review, many associative findings linking the gut microbiome, autoimmunity and the central nervous system in psychiatric disorders were presented. These findings are reconciled in a proposed model where we envision the gut as a source of long-term or transient malleable antigenic structures including neuronal receptors, proteins and cells of the enteric glial and enteric nervous systems. When the immune system becomes inappropriately primed against certain of these enteric targets, additional well-timed events may occur to result in an autoimmune attack directed against the central nervous system. The newness of this field allows for numerous hypotheses-building opportunities, while at the same time uncovers a diverse array of pharmacological targets not traditionally evaluated for treatment of psychiatric disorders by the pharmaceutical industry.

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List of Abbreviations

AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
GABA	G-aminobutyric acid
GAD	Glutamic acid decarboxylase
GI	Gastrointestinal
HERV	Human endogenous retrovirus
NMDA	<i>N</i> -methyl- <i>D</i> -aspartate

PANDAS Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections

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Figure 1.

Proposal of a gut-autoimmune-brain interactome model for psychiatric disorders

In this model, we hypothesize that a compromised epithelial and endothelial cytoarchitecture at the blood-gut and blood-brain barriers leads to the translocation of microbial and food-based products. The genesis of barrier permeabilization could be initiated by any number of environmental or genetic factors, including dysbiosis of the microbiome, which creates an inflammatory state that promotes an autoimmune-prone environment. The presence of perceived foreign substances in systemic circulation activates the adaptive and innate immune responses. Antibodies against extrinsic- and auto-antigens are produced, including antibodies directed against neurotransmitter receptors and other proteins of the enteric nervous system. Blood-brain or CSF-brain barrier permeability would allow the inappropriate passage of circulating gut-derived peptides, classic immune factors, antibodies or anti-neuronal autoantibodies. The entrance to the brain of perceived antigens would similarly launch the resident glial immune machinery, including pathways such as complement that might result in inappropriate synaptic pruning.

Table 1

Human gut microbiome studies of complex brain disorders

Reference	Brain disorder	Biospecimen	Disease-associated microbial alteration	Functional consequences/conclusions	Method
Castro-Nallar et al 2015	Schizophrenia	Oropharyngeal microbiota	Increased Ascomycota, lactic acid bacteria	Increased metabolite transport pathways; decreased energy metabolism	Metagenomic sequencing
De Angelis et al 2013	Autism	Fecal microbiota	Altered Firmicutes, Bacteroidetes, Fusobacteria, Verrucomicrobia. Elevated Bacteroidetes, Clostridia, Sutterellaceae	Diagnostic, prevention, treatment implications	16S rRNA pyrosequencing
Finegold et al 2010	Autism	Fecal microbiota	High Bacteroidetes, Low Firmicutes	Diagnostic, prevention, treatment implications	Pyrosequencing
Gondalia et al 2012	Autism	Fecal microbiota	No significant differences	Not generally significant	Pyrosequencing
Jiang et al 2015	Major Depressive Disorder	Fecal microbiota	Increased Bacteroidetes, Proteobacteria, Actinobacteria; Reduced Firmicutes	Increased prevalence of harmful bacteria & reduction of beneficial genera	Pyrosequencing
Kang et al 2012	Autism	Fecal microbiota	Decreased prevotella, <i>Coprococcus</i> spp.	Low abundance of carbohydrate-degrading & fermenters; Less diversity associated with symptom severity	16S rRNA pyrosequencing
Naseribafrouei et al 2014	Severe Depression	Fecal microbiota	Increased Bacteroidetes; Decreased Lachnospiraceae	Altered taxa may be associated with stress & production of GABA homologue valeric acid	16S rRNA sequencing
Parracho et al 2005	Autism	Fecal microbiota	Increased <i>Clostridium histolyticum</i>	<i>Clostridium</i> spp are toxin producers & have systemic metabolic effects	Fluorescent in situ hybridization
Son et al 2015	Autism	Fecal microbiota	Generally few significant differences, but several low abundance taxa	Not generally significant	16S rRNA sequencing
Tomova et al 2015	Autism	Fecal microbiota	Decreased Bacteroidetes/Firmicutes ratio; Elevated <i>Lactobacillus</i> ; Desulfovibrio associated with autism severity	Microbiome alterations normalized with probiotics	Real-time quantitative PCR
Williams et al 2011	Autism	GI microbiota (ileal/cecal biopsy)	Decreased Bacteroidetes; Increased Firmicutes to Bacteroidetes; Increased Betaproteobacteria	Impaired carbohydrate digestion and transport	16S rRNA pyrosequencing
Williams et al 2012	Autism	GI microbiota (ileal/cecal biopsy)	Increased family Alcaligenaceae due to increased sutterella	Sutterella associated with GI dysfunction in autism	Sutterella 16S rRNAPCR
Yolken et al 2015	Schizophrenia	Oropharyngeal microbiota	Increased <i>Lactobacillus</i> phage phiadh	Phage abundance correlated with immunological disorder prevalence	Metagenomic sequencing