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Autoimmune diseases, gastrointestinal disorders and the microbiome in schizophrenia: More than a gut feeling

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Abstract

Autoimmunity, gastrointestinal (GI) disorders and schizophrenia have been associated with one another for a long time. This paper reviews these connections and provides a context by which multiple risk factors for schizophrenia may be related. Epidemiological studies strongly link schizophrenia with autoimmune disorders including enteropathic celiac disease. Exposure to wheat gluten and bovine milk casein also contribute to non-celiac food sensitivities in susceptible individuals. Co-morbid GI inflammation accompanies humoral immunity to food antigens, occurs early during the course of schizophrenia and appears to be independent from antipsychotic-generated motility effects. This inflammation impacts endothelial barrier permeability and can precipitate translocation of gut bacteria into systemic circulation. Infection by the neurotropic gut pathogen, *Toxoplasma gondii*, will elicit an inflammatory GI environment. Such processes trigger innate immunity, including activation of complement C1q, which also functions at synapses in the brain. The emerging field of microbiome research lies at the center of these interactions with evidence that the abundance and diversity of resident gut microbiota contribute to digestion, inflammation, gut permeability and behavior. Dietary modifications of core bacterial compositions may explain inefficient gluten digestion and how immigrant status in certain situations is a risk factor for schizophrenia. Gut microbiome research in schizophrenia is in its infancy, but data in related fields suggest disease-associated altered phylogenetic compositions. In summary, this review surveys associative and experimental data linking autoimmunity, GI activity and schizophrenia, and proposes that understanding of disrupted biological pathways outside of the brain can lend valuable information regarding pathogeneses of complex, polygenic brain disorders.

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Contributors

Drs. Severance, Yolken and Eaton all wrote and approved the final manuscript.

Conflict of Interest

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

Autoimmunity; Psychosis; Microbiota; Immune system; Psychiatry; Intestinal

1. Introduction

Schizophrenia is a complex brain disorder with lifetime prevalence rates estimated to range from 1.6–12.1/1000 persons, with some variability according to age and sex (Eaton et al., 2011; Pedersen et al., 2014). The disorder is characterized by behavioral abnormalities and is diagnosed by a set of criteria defined in the Diagnostic and Statistic Manual of Mental Disorders, 5th edition (DSM-5) (APA, 2013). Among the criteria used to diagnose schizophrenia are the presence of psychotic symptoms, such as delusions and hallucinations, as well as cognitive disorganization, apathy and withdrawal (APA, 2013). The causes of schizophrenia have not been fully defined, but prevailing evidence supports an interaction of genetic and environmental variables as central to its etiology (Demjaha et al., 2012; Modinos et al., 2013; Tsuang, 2000).

The relationship between autoimmune diseases and schizophrenia has been studied for more than half a century. In the past decade, the focus of this autoimmune research has been narrowed to a certain extent to gastrointestinal (GI) disorders, while at the same time has broadened somewhat to include dysfunctions of the immune system. As the largest immune organ in the body, the GI tract is a plausible junction to reconcile hypotheses regarding how the autoimmune response and GI-related products can become neuropathogenic. This paper traces some of these developments and, following the logic of translational research, links the epidemiologic observations to molecular studies of the gut-brain axis and the gut's main bio-processor, its resident microbiota. An overview of the interactions described in this review is depicted in Figure 1.

2. Autoimmunity and schizophrenia

2.1 Origins

The earliest interest connecting autoimmunity and schizophrenia stems from a repeated finding of a low prevalence of rheumatoid arthritis in individuals with schizophrenia, beginning with studies in the 1950's and including analyses up to the present (Eaton et al., 1992; Oken and Schulzer, 1999; Pilkington, 1955; Sellgren et al., 2014; Trevathan and Tatum, 1953; Vinogradov et al., 1991). The finding was replicated more than a dozen times, and various explanations were offered, such as that neuroleptic medications had a protective effect; or that persons with schizophrenia were less likely to report pain; or that life as an inpatient was less physically active and thereby less prone to raising risk for rheumatoid arthritis. Each of these hypotheses was evaluated in studies with research designs that effectively discounted those explanations (Mellsop et al., 1974; Mohamed et al., 1982; Pilkington, 1955; Trevathan and Tatum, 1953). There have been several studies of genes, immune-related factors, and common infections which might explain the inverse association (de la Fontaine et al., 2006; Genevay et al., 2002; Hopkins et al., 1988; Taylor, 1978; Torrey and Yolken, 2001; Wright et al., 1998), including a compelling meta-analysis showing that

the antagonist to the receptor of the inflammatory cytokine IL-1 was more prevalent in individuals with schizophrenia, thus protecting them from rheumatoid arthritis (Potvin et al., 2008).

2.2 Autoimmunity link to the GI tract

Autoimmune disorders can be triggered by dietary components and antigens derived from the GI tract. One such autoimmune condition characterized by altered GI structure and functioning is celiac disease, a disorder that arises from the interaction of gene and environmental factors. Upon the ingestion of wheat gluten by people who are genetically susceptible, an immune reaction is launched that damages the epithelial lining of the small intestine (Green et al., 2005; Guandalini and Assiri, 2014). During digestion, the gluten protein in wheat is broken down into toxic peptides that are modified through deamidation and/or transamidation by tissue Transglutaminase (tTG), so that the modulated peptide might stimulate the immune system more effectively and thus be more easily cleared. Through the process of molecular mimicry, tTG becomes the target of a T-cell-mediated immune attack, and resulting inflammation causes extensive histopathological changes in the small intestine (Alaedini and Green, 2008; Di Sabatino et al., 2012; van Heel and West, 2006). Clinically-defined celiac disease will be the focus of this portion of this discussion, and this condition differs in diagnosis from non-celiac disease gluten sensitivity, which will be discussed later.

The GI system connection with autoimmune issues in schizophrenia came about with clinical observations of co-associations of celiac disease and schizophrenia, starting with Bender in 1953 (Bender, 1953), and later in 1961, when two residents in psychiatry reported a higher number than expected of people with celiac disease among their psychiatric patients (Graff and Handford, 1961). This finding interested F. Curtis Dohan who spent the remainder of his career focusing on a link between wheat consumption and schizophrenia (Dohan, 1973, 1980; Dohan, 1970). His first epidemiologic study of wartime admissions for schizophrenia showed that populations in countries whose consumption of wheat had decreased during the war saw a decrease in hospital admissions for schizophrenia, whereas those populations in countries with an increase in consumption of wheat during the war had an increase in hospital admissions for schizophrenia (Dohan, 1966a, b). Dohan analyzed other epidemiologic data consistent with the hypothesis that eating wheat was linked to higher rates of schizophrenia, as evident by areas of the south Pacific region where consumption of wheat was low having lower rates of schizophrenia than areas where wheat consumption was high (Dohan et al., 1984). He also conducted several controlled trials removing gluten from the diet (Dohan and Grasberger, 1973; Dohan et al., 1969), the results of which supported the hypothesis that celiac disease was related to schizophrenia. Clinical trials conducted by others were sometimes supportive of the idea (Rice et al., 1978; Singh and Kay, 1976; Vlissides et al., 1986), and sometimes failed to replicate it (Potkin et al., 1981; Storms et al., 1982). One explanation for the diverse results is the effect of random sampling in a population of persons with a heterogeneously complex disease such as schizophrenia, of whom only a small proportion might actually have celiac disease (King, 1985). Thus, some studies might have had enough persons with schizophrenia to detect an effect, but other samples would have few or none with celiac disease, with no possibility of a

positive effect of removal of gluten from the diet. There are several case studies of gluten withdrawal showing dramatic improvement or even elimination of symptoms (De Santis et al., 1997; Jackson et al., 2012; Jansson et al., 1984; Kraft and Westman, 2009).

2.3 Shared HLA predisposition in celiac disease and schizophrenia

The association between celiac disease and schizophrenia was hypothesized by Dohan, and others, to be the result of a gene by environment interaction (Dohan, 1988; Wei and Hemmings, 2005). A surge in interest in the 6p21 region as a susceptibility locus for schizophrenia was generated following publication of three genome-wide association studies (Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009). This chromosomal region houses the major histocompatibility complex (MHC) locus and its resident human leukocyte antigen (HLA) genes which comprise an immune gene network designed to respond to a variety of antigens, with some gene products that function in the brain during synapse development (Boulanger, 2009; Corvin and Morris, 2014). Individuals with celiac disease almost exclusively have the HLA-DQ2 heterodimer or DQ8 haplotype (van Heel and West, 2006). A linkage study of schizophrenia in western Ireland highlighted the short arm of chromosome 6, telomeric from the HLA region (Straub et al., 1995). This region, which includes the dysbindin locus, has attracted attention of several replications (Benson et al., 2004; Camargo et al., 2007; Fanous et al., 2005; Guo et al., 2009; Papaleo and Weinberger, 2011; Riley et al., 2009; Schwab et al., 1995; Schwab et al., 1998; Schwab et al., 2003; Shi et al., 2009; Van Den Bogaert et al., 2003). An independent study of celiac disease in western Ireland pointed to the same general area of chromosome 6 (Zhong et al., 1996), but there has yet to be further conclusive evidence about the dysbindin locus and celiac disease. Another gene with a history of association to celiac disease is the MY09B locus in the short arm of chromosome 19, and this has been associated with schizophrenia in a study by Jungerius (Jungerius et al., 2007).

2.4 Epidemiology links schizophrenia with celiac disease

The most convincing epidemiologic data connecting celiac disease and schizophrenia came from studies using health registers. In 1980, data from the Oxford Health Register revealed a cross sectional association of schizophrenia with celiac disease (relative odds of about 3) (Baldwin, 1980). In a prospective study based in the national register system of Denmark (Eaton et al., 2004), the diagnosis of celiac disease in the individual or the family raised the risk for later diagnosis of schizophrenia by 2.7. In contrast, the risk for Crohn’s disease or irritable bowel syndrome, two other autoimmune diseases with similar symptom presentations as celiac disease, was not significantly different from 1.0. Of note, however, a Finnish birth cohort study had previously found that inflammatory diseases of the bowel including ulcerative colitis and Crohn’s disease were significantly overrepresented in schizophrenia compared to non-psychiatric controls, 3.4% vs 0.3% (Makikyro et al., 1998). The association between non-celiac disease wheat sensitivity, intestinal inflammation and schizophrenia will be discussed further in subsequent sections.

2.5 Current focus on autoimmunity and schizophrenia

The linkage of two distinct autoimmune diseases to schizophrenia (albeit in opposite directions) contributed to interest in the role of autoimmune diseases in general to

schizophrenia. The epidemiologic literature soon yielded results broader than the initial focus on rheumatoid arthritis and celiac disease, including several small family studies (Gilvarry et al., 1996; Wright et al., 1996). A further study in Denmark showed a 45% increased relative risk for schizophrenia (adjusted for other major risk factors such as urbanicity of birth, family history of schizophrenia, and wealth) for persons who had one or more of 30 autoimmune diseases in their own history or in their first degree relatives, prior to diagnosis of schizophrenia (Eaton et al., 2006). This same positive association turned up in a cross-sectional analysis in Taiwan (Chen et al., 2012), and in a later prospective study from Denmark, with the additional detail that the results were not similar for bipolar disorder (Eaton et al., 2010). Another study in Denmark showed that a history of serious infection was predictive of onset of schizophrenia, and that the history of infection interacted with a history of autoimmune diseases in raising risk (Benros et al., 2011). An analysis of this Danish register which reversed the temporal direction indicated that people with schizophrenia were at a significantly increased risk for the development of autoimmune diseases, with that risk further elevated in those with a history of an infection requiring hospitalization or a family member with schizophrenia (Benros et al., 2014).

Another emerging area of interest in the context of pathogenic autoantibody production and schizophrenia are the human endogenous retroviruses (HERVs), which are fossil infectious retroviruses that have integrated into the human genome. HERVs have been associated with schizophrenia and other psychiatric diseases in a number of studies (Dickerson et al., 2012; Huang et al., 2011; Karlsson et al., 2001; Lillehoj et al., 2000), and it is thought that HERV expression may induce an autoimmune state through molecular mimicry especially when coupled with viral or other infections (Brodziak et al., 2012; Leboyer et al., 2013; Ogasawara et al., 2010; Perron et al., 2012). A recent report of HERV-related immunoreactivity in plasmacytoid dendritic cells of the duodenum from patients with myalgic encephalomyelitis further links the gut to neuroinflammatory autoimmune processes by means of this retroelement mechanism (De Meirleir et al., 2013).

3. Extra-autoimmune GI connection to schizophrenia

3.1 The dietary exorphin hypothesis

As thus far described, numerous studies indicate that schizophrenia may have a strong autoimmune component. However, the broader nature of the risk structure, beyond celiac disease to other autoimmune diseases and infections, suggested a wider range of possible etiologic pathways. An alternative or additional explanation for the wheat and schizophrenia connection is suggested by Dohan who called these peptides “exorphins” because he felt they resembled the brain-reactive chemicals endorphins, suggestive of a capacity to bind to opioid receptors found throughout the body, but particularly in the brain (Dohan, 1988). Early studies document increased levels of neuroactive food antigen peptides in the bloodstream, CSF and urine in individuals with schizophrenia (Cade et al., 1990; Drysdale et al., 1982; Lindstrom et al., 1986; Reichelt et al., 1981; Reichelt et al., 1996; Reichelt and Stensrud, 1998). The presence of these exorphins has also been found in some analyses of urine samples from children with autism, and in one study, peptide levels correlated with symptom severity scores (Reichelt et al., 2012; Sokolov et al., 2014). A third study failed to

replicate these findings (Hunter et al., 2003), but overall these studies have low sample sizes, and this area of research would benefit from larger, well-designed, case-control analyses. The pathological potential of these exorphins might also occur in a non- or extra-autoimmune capacity that is not due to the classically-defined celiac disease. For example, these exorphins may be related to the more general condition known as gluten enteropathy (Kabbani et al., 2014) or alternatively, to the potency potential of the peptide ligands at opioid receptors (Fukudome and Yoshikawa, 1992; Zioudrou et al., 1979). Furthermore, the neuroactive peptides hypothesis is not exclusive to gluten, and Dohan and Reichelt theorized that the digestion of the principal component of bovine milk, casein, also resulted in the production of these exorphins (Reichelt et al., 1996).

For the exorphin hypothesis to operate, a means of penetrating the GI epithelial and endothelial barriers would be necessary. The production of IgG antibodies against these proteins thus might suggest barrier penetrance, but additional simultaneous measures are needed for proof of concept. Direct activation of the GI immune mucosa could also result in secretory IgA antibody production, provided the peptides can penetrate the mucosal layer and interact with the gut's lymphoid tissue. Peyer's patches are located in the lamina propria layer of the mucosa in the ileum and are where T-, M- and B-cells are activated in the presence of an antigen (Mantis et al., 2011). The presence of these peptides in multiple clinical and experimental biospecimen types support that these exorphins have the ability to extend their range beyond gut walls.

3.2 Diet-generated humoral immune activation

Activation of an IgG antibody response against a number of morphologically related food exorphins suggests the presence of an IgG sensitivity or intolerance that is different from the biomarker profiles used to diagnose celiac disease. For wheat, this non-celiac IgG sensitivity is accompanied by a diversity of GI and extra-intestinal symptoms that appear immediately following the ingestion of gluten and disappear upon removal of gluten from the diet. GI inflammation, barrier permeability changes and intestinal dysbioses are all thought to contribute to the pathogenesis of this non-celiac disease gluten intolerance (Catassi et al., 2013; Kabbani et al., 2014; Sapone et al., 2011). As early as 1979, Ashkenazi showed that there was a general immune reaction to wheat in persons with psychosis (Ashkenazi et al., 1979), and in 1998, Reichelt described, with a small sample, that antibodies to the gliadins (the soluble components of gluten) were more common in persons with schizophrenia than in the general population (Reichelt and Landmark, 1995). This gliadin-antibody link was replicated in the CATIE sample (Cascella et al., 2011), and later in three further replications in Taiwan (Jin et al., 2010), Tunisia (Sidhom et al., 2012), and Germany (Okusaga et al., 2013) with a similar association, reported in slightly different form in Baltimore as well (Dickerson et al., 2010). A meta-analysis of gluten sensitivity studies suggests that the nature of this immune response to wheat by individuals with schizophrenia differs from the classic celiac disease immune response (Lachance and McKenzie, 2014). Persons with schizophrenia tend to have three or four times the proportion with antibodies to tTG as the general population (i.e., about 5% versus 1.5 percent), and three or four times the proportion with anti-gliadin antibodies (i.e., about 20% versus about 5%). This pattern expands the

immunologic picture beyond the adaptive immune system, implicated in the tTG antibodies, to the innate immune system, implicated by the anti-gliadin antibodies.

There is also precedence for the formation of a non-celiac disease autoimmune response against other gluten-associated cellular entities (Vojdani et al., 2004a; Vojdani et al., 2004b; Vojdani et al., 2003). In children with autism, a strong association between anti-gliadin and anti-peptidase antibodies suggested that during processing, gliadin might bind to aminopeptidases to induce autoantibodies, perhaps in people with predisposing HLA molecules (Vojdani et al., 2004a). Similarly, anti-gliadin antibodies were associated with autoantibodies to the immune molecules, CD26 and CD69, indicating that these peptides bind to these immune receptors and an autoimmune reaction is generated (Vojdani et al., 2003). Ultimately, the concern with respect to autoimmune pathogenicity in brain diseases is whether there is cross-reactivity of anti-gliadin antibodies with brain proteins, and several studies provide support for this hypothesis (Alaedini et al., 2007; Briani et al., 2008; Hadjivassiliou et al., 2002).

An increased seroprevalence of antibodies to another type of food-derived exorphin, bovine milk casein, has also been reported in schizophrenia compared to controls (Niebuhr et al., 2011; Severance et al., 2010). Studies on a prospective cohort indicated that increases in antibodies to casein can be detected as early as two years prior to the onset of psychiatric symptoms or the initiation of therapy, suggesting the possibility that the pathology may precede the onset of diagnosis (Niebuhr et al., 2011). Bovine milk casein itself has not been associated with the same celiac disease-related pathology as gluten, yet levels of antibodies directed against these food antigens were often extremely well-correlated in both control and schizophrenia groups (Severance et al., 2012a). Furthermore, anti-food antigen antibodies were significantly correlated with a surrogate marker of intestinal inflammation and microbial translocation, anti-*Saccharomyces cerevisiae* antibodies (ASCA), in the schizophrenia but not control groups (Severance et al., 2012a). These findings suggest a role of inflammation in enabling gut-located antigens to activate the immune system or penetrate the GI endothelial barrier. Although ASCA is predominately a marker that can help discriminate GI-related inflammatory diseases, this marker is also elevated in patients with a variety of other autoimmune conditions such as systemic lupus erythematosus, Graves' disease, cryoglobulinemia and vasculitis (Ben-Ami Shor et al., 2012).

3.3 GI inflammation and schizophrenia

3.3.1 Early evidence of co-morbid GI inflammation—GI co-morbidities in mental illness have been described for as long as such maladies have been documented, with purgatives and emetics offered as predominant treatment strategies in the older literature (Prichard, 1837). Among recent and historical accounts are reports of extensive inflammatory changes throughout the GI tract of patients with psychiatric symptoms (Alander et al., 2005; Buscaino, 1953; Hemmings, 2004; Reiter, 1926; Schneck, 1946). In one autopsy study of 82 patients with schizophrenia, as many as 50% had gastritis, 88% enteritis and 92% colitis (Buscaino, 1953; Hemmings, 2004). In hindsight, this extensive inflammation could have reflected any number of states including the aforementioned and described celiac disease, but the prevalence seems too high to be accounted for by a single

enteropathic disease. Studies of inflammatory indices in schizophrenia support the possibility that there exists a non-celiac disease GI pathology inherent to schizophrenia. Gluten sensitivity, for example, in the absence of celiac disease may also produce intestinal pathologies (Catassi et al., 2013; Kabbani et al., 2014; Sapone et al., 2011). Furthermore, as mentioned previously, there are other reports of increased rates of inflammatory bowel disease, including ulcerative colitis and Crohn's disease, and of irritable bowel syndrome in schizophrenia (Gupta et al., 1997; Makikyro et al., 1998).

3.3.2 The effects of antipsychotics on GI inflammation—It is difficult to distinguish GI conditions generated by lifestyle factors or antipsychotic effects from GI symptoms that are part of the disease pathology of schizophrenia. Both first and second generation antipsychotics are suspected to have strong intestinal motility consequences resulting in numerous GI conditions such as constipation and bowel obstruction (Dean, 2010; Dome et al., 2007; McNamara et al., 2011; Watanabe et al., 2010). Of note, however, a number of reports that document GI-related inflammation preceded the development of antipsychotics that were first discovered in the 1950s (Preskorn, 2010). As mentioned earlier, measures of serological ASCA are used diagnostically for inflammatory bowel diseases including ulcerative colitis and Crohn's disease (Ashorn et al., 2009; Desplat-Jego et al., 2007; Kotze et al., 2010; Mallant-Hent et al., 2006; Oshitani et al., 2000). In a recent study of gut inflammation in schizophrenia, the highest levels of ASCA were found in individuals who were in the early stages of disease and/or who were medication-naïve (Severance et al., 2012a). Thus while antipsychotic agents may affect the type or degree of inflammation (Beumer et al., 2012a; Drexhage et al., 2010; Drexhage et al., 2011; Leonard et al., 2012; Miller et al., 2012; Steiner et al., 2012), some part of disease-associated inflammation is likely present before the start of pharmacological treatment.

3.3.3 GI permeability—Inherent to the rationale of a GI role in psychiatric disorders is the idea of disease-associated GI permeability that impacts barriers both in the gut and in the central nervous system (CNS). Inflammation and stress are potent perpetrators of endothelial barrier permeability (Collins and Bercik, 2009; Lambert, 2009; Soderholm and Perdue, 2001). GI-derived antigenic peptides presumably enter the general circulation because of compromised GI epithelial and/or endothelial barriers, but they also may selectively breach intra-epithelial tight junction proteins. Tight junctions (zonula occludens) are present between the epithelial cells that line the lumen of the GI tract; similar tight junctions comprise the blood brain barrier (Deli, 2009; Jong and Huang, 2005). The cerebrospinal fluid (CSF)- brain and CSF-blood barrier at the choroid plexus and arachnoid membrane also represent a junction by which faulty architecture might allow passage of bioactive or infectious peptides (Laterra et al., 1999). There is evidence that gluten peptides directly induce zonulin release from intestinal epithelial cells thereby modulating barrier permeability (Clemente et al., 2003; Fasano, 2012; Lammers et al., 2008; Thomas et al., 2006). In addition to gluten, exposure to bacteria is another powerful trigger of zonulin release in the gut (Fasano, 2012). Zonulin, a precursor for haptoglobin-2, is able to reversibly regulate intestinal permeability and is thus thought to represent a point of pathway convergence in the gut for allergic, inflammatory and autoimmune diseases (Tripathi et al., 2009). Haptoglobin is an acute phase protein that has been implicated both genetically and

physiologically in studies of schizophrenia (Maes et al., 2001; Wan et al., 2007; Yang et al., 2006).

The integrity of epithelial and endothelial barriers could also be compromised by an infection of the gut by a virus or parasite. Exposure to the parasite *Toxoplasma gondii*, a gut pathogen, is a well-known risk factor for the development of schizophrenia (Mortensen et al., 2007; Torrey et al., 2007; Xiao et al., 2009; Yolken et al., 2009). This parasite also provides a tool for modeling inflammatory bowel disorders in rodents (Bereswill et al., 2010; Craven et al., 2012; Erridge et al., 2010; Hand et al., 2012; Munoz et al., 2009; Schreiner and Liesenfeld, 2009). If the inflammatory state in schizophrenia were the result of a generalized, polyspecific activated immune state, it would be expected that antibody levels to food antigens would correlate with those of infectious disease antigens. An analysis of this type of relationship, however, showed that antibodies to food-based antigens, while significantly and expectedly inter-correlated, were correlated with only one of the studied infectious agents, *T. gondii* (Severance et al., 2012a). This association was especially evident in individuals with schizophrenia who had a recent onset of disease. These findings were supported by a mouse model of peroral *T. gondii* infection where infected animals had elevated antibody levels to dietary gluten compared to those that were uninfected (Severance et al., 2012c). Links between measures of *T. gondii* exposure and celiac disease have also been reported, although it was not possible to determine if infection or the enteropathic state came first (Lidar et al., 2009; Rostami Nejad et al., 2011). Additional studies have documented that *T. gondii* infection impacts the resident microbiota communities and brings about a state of inflammation conducive to the process of bacterial translocation, a surrogate measure of GI permeability (Craven et al., 2012; Grainger et al., 2013; Hand et al., 2012; Heimesaat et al., 2006).

When the GI tract is compromised, resident gut microbiota can translocate into systemic circulation and create a state of low-level inflammation, as the immune system is activated to clear invading antigenic microbes from circulation (Brenchley et al., 2006; Lambert, 2009; Sandler and Douek, 2012). This process of bacterial translocation and its occurrence in major depressive disorder is a current topic of extensive research and appears to be a demonstrable source of inflammation associated with this disease (Maes et al., 2008; Maes et al., 2012a; Maes et al., 2012b). In a study of bacterial translocation in schizophrenia, two surrogate biomarkers, soluble CD14 (sCD14) and lipopolysaccharide (LPS) binding protein (LBP), were found to be inter-correlated in both case and control groups, as expected based on their similar physiological roles in alerting the immune system to the bloodstream presence of a bacterial endotoxin (Severance et al., 2013). The two markers were also both significantly correlated with a general marker of inflammation, C-reactive protein, and gluten IgG in individuals with schizophrenia, suggesting a common pathway of associated inflammation. Marker levels, however, were only significantly elevated in schizophrenia compared to controls for sCD14 (multivariate OR=3.09). LBP, but not sCD14, was found to correlate with BMI scores in schizophrenia. Obesity and its accompanying metabolic state are increasingly implicated in gut permeability, bacterial translocation and resulting inflammatory processes, all as mediated by gut microbiota (Shen et al., 2013; Turnbaugh et al., 2009). The discordant patterns of sCD14 and LBP implicate additional pathogenic mechanisms related to bacterial translocation and dysregulated monocyte activation inherent

to schizophrenia. Other investigators have reported abnormal monocyte or macrophage activation in schizophrenia and other psychoses, and it is thought that this might reflect a state of innate immune hyper-reactivity (Beumer et al., 2012a; Beumer et al., 2012b; Drexhage et al., 2010; Drexhage et al., 2011; Miller et al., 2012; Muller et al., 2012).

3.3.4 GI activation of innate immunity and relevance to the brain—There is increasing evidence that the activation of the innate immune pathways by gut processes may impact the brain. Immune proteins, such as complement C1q and MHC I, have been identified as critically important to neuronal development in the brain with effects on synapses by mechanisms that are not part of historically described immune pathways (Boulanger, 2009; Goddard et al., 2007; Lackner et al., 2008; Perry and O'Connor, 2008; Rupprecht et al., 2007; Stevens et al., 2007; Yuzaki, 2010). C1q and MHC I may selectively tag cells or excessive synapses in the CNS for clearance by microglia (Boulanger, 2009; Chu et al., 2010; Fourgeaud and Boulanger, 2007; Huh et al., 2000; Ma et al., 2013; Stevens et al., 2007).

Complement activity can be genetically and functionally linked to schizophrenia. Genetic studies of the complement pathway in schizophrenia reveal disease-associations of the C1QB gene, complement control-related genes, and complement surface receptor gene CD46 (Havik et al., 2011; Zakharyan et al., 2011). In multiple reports, elevated levels of complement-containing circulating immune complexes were found in individuals with schizophrenia compared to controls (Arakelyan et al., 2011; Boyajyan et al., 2008; Mailian et al., 2005; Mayilyan et al., 2008; Severance et al., 2012b; Vetlugina et al., 1984). This complement activity can be triggered by exposure to gluten and casein. In many individuals with schizophrenia, C1q forms immune complexes with these food antigens at increased rates compared to controls (Severance et al., 2012b). Interestingly, gut C1q was linked to psychopathology in a study of intestinal biopsies where IgG deposition and C1q infiltration of the duodenum was present in autism, a disorder as etiologically complex as schizophrenia, but not in celiac disease, cerebral palsy, mental retardation and normal controls (Torrente et al., 2004; Torrente et al., 2002). In rodent models, serological C1q elevations accompanied increased gluten IgG levels in animals infected with *T. gondii* compared to those that were not infected (Severance et al., 2012c). In a separate rodent study, *T. gondii* infection induced inflammatory cascades including heightened brain C1q expression (Hermes et al., 2008). It has also been found that in mice, microglial activation and brain C1q synthesis precedes experimentally-induced blood brain barrier dysfunction (Lynch et al., 2004). Thus, peripheral activation of C1q by antigenic peptides of gut origin may have the propensity to activate inflammatory pathways in the brain, given the correct set of factors are in place, including food sensitivity, pathogen exposure, gut and systemic inflammation, and barrier permeability defects.

The role of innate immune activation in schizophrenia can be additionally presented in the context of the prenatal exposure hypotheses; yet for the purposes of this section, the proposition that immune molecules might function peripherally as well as centrally is the focus rather than the timing of the immune activation. MHC I and C1q are perhaps the best known of these types of multi-venue functioning molecules; however, as described above, sCD14 may also contribute to brain processes in this context. Plasma and CSF levels of

sCD14 were associated with cognitive function in patients with HIV dementia presumably as a result of CNS invasion by peripheral blood-derived monocytes and precipitated by microbial translocation (Ancuta et al., 2008; Fischer-Smith et al., 2001; Ryan et al., 2001). Cytokines, pentraxin, and the toll-like receptors (TLRs) may all be active in neurogenesis and other brain functions, with the TLRs especially implicated in blood brain barrier integrity and neurodegenerative disorders (Frodl and Amico, 2014; Garate et al., 2013; Nagyoszi et al., 2010; Pribiag and Stellwagen, 2014; Trotta et al., 2014). Research described in previous sections supports an association of gluten immunoreactivity with sCD14 (Severance et al., 2013), and opioid ligands may be potent modulators of TLR in the gut (Meng et al., 2013). By the same rationale, bacteria residing in the gut mucosa might produce peptides or themselves might directly interact with the intestinal lumina and resident recognition receptors including TLRs and NOD2 (Hong and Rhee, 2014).

4. The microbiome and implications for schizophrenia

The human GI tract is a reservoir of a large diversity of bacteria, and we are only just beginning to understand the multiplicity of functions that these microbial agents confer to the human body in terms of nutrition, metabolism, and immune system development (Douglas-Escobar et al., 2013; Hornig, 2013). An estimated 10^{14} cells make up the human microbiome, and the five bacterial phyla include *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria* and *Fusobacteria* (Caminero et al., 2014; Cryan and Dinan, 2012). These phyla are found throughout the gut in varying degrees with the colon characterized predominantly by *Firmicutes, Bacteroidetes* and *Actinobacteria* (Caminero et al., 2014; Hong and Rhee, 2014)). A current working hypothesis is that dysbioses of GI microbial communities contribute to inflammation in the GI tract; thus, changes in bacterial communities in patients with inflammatory bowel disorders compared to controls are expected, with the requisite qualifications that differences in biospecimen type (fecal vs biopsy, luminal vs mucosal), intestinal location sampled, diet, antibiotic use, probiotic use, age of patient and other factors will impact the results (Daulatzai, 2014; Gevers et al., 2014; Hong and Rhee, 2014; Kostic et al., 2014). In patients with irritable bowel syndrome, most recent studies support disease-associated *Firmicutes* abundances and decreased *Bacteroides*, although there is a variability in relative species dynamics among the studies reviewed (Hong and Rhee, 2014). As such, enteropathologies in schizophrenia, as evident by autoimmune conditions, food sensitivities, and inflammation might be the result of altered gut microbial compositions.

4.1 The gut microbiome and the brain

Mental health research currently is hampered by a dearth of human data regarding resident biota and consequent effects on the CNS. Thus, the mechanisms by which microorganisms located at anatomical sites apart from the brain might impact neuronal connections are not known, but are surmised to involve metabolic, endocrine (cortisol), immunological or neuronal (vagus, enteric) routes (Clarke et al., 2013; Collins et al., 2012; Cryan and Dinan, 2012; Diaz Heijtz et al., 2011; Gareau et al., 2011). An analogous association between gut microbiota and behavior in people with schizophrenia may be gleaned from studies of autism spectrum disorders, where there are numerous reports of autism-related altered

communities of the intestinal microbiome (Adams et al., 2011; Finegold et al., 2010; Finegold et al., 2012; Kang et al., 2013; Parracho et al., 2005; Williams et al., 2011; Williams et al., 2012). Further information regarding how the microbiome might impact the brain can be extrapolated from rodent studies, where research thus far shows that manipulations of gut microbiota result in behavioral, biochemical and molecular changes (Collins et al., 2012; Foster and McVey Neufeld, 2013; Hsiao et al., 2013; Stilling et al., 2014). Diaz-Heijtz, for example, documented that these behavioral effects were accompanied by modulations of the synaptic markers, synaptophysin and PSD95, in the striatum (Diaz Heijtz et al., 2011). In these animal studies, the use of gnotobiotic (germ-free) animals, vagectomy, probiotics and/or antibiotics each has been used to effectively recover animal phenotypes.

Preliminary studies in humans indicate that the pharyngeal and intestinal microbiome are altered in individuals with schizophrenia as compared to controls. These studies investigating the biological and pathogenic consequences of this altered microbiome are ongoing (Yolken and Dickerson, 2014).

4.2 Dietary considerations, immigrant status and the microbiome

The microbiome and its diversity are greatly affected by diet (David et al., 2014; Hong and Rhee, 2014; Kau et al., 2011). Dietary options are impacted by a multitude of cultural and lifestyle factors and may in turn play a role in contributing to certain risk factors for schizophrenia such as immigrant status. With some variability, being an immigrant from sub-Saharan African or Caribbean nations to the United Kingdom is a well-replicated risk factor for the development of schizophrenia (Cantor-Graae and Selten, 2005; Morgan et al., 2010; Selten et al., 2007; Sharpley et al., 2001). Some have attributed this risk to social explanations involving stress, discrimination, and exclusion (Eaton and Harrison, 2000, 2001; Selten and Cantor-Graae, 2005); others to vitamin D levels (McGrath, 1999); and yet others to cephalopelvic disproportion in the fetus (Warner, 1995); but see (Hutchinson et al., 1997). The high prevalence among Afro-Caribbeans is likely not due to genetic differences, because the prevalence in the countries of origin is not elevated when compared to rates in the UK's general population (Bhugra et al., 1996; Hickling, 1991).

It could be that dietary influences related to wheat may contribute as one hit in the two-hit hypothesis scenarios in schizophrenia. Consumption and preparation of grains in Africa are usually different than in Europe and the U.S, both of which are heavy consumers of wheat- and corn-based products. In Africa, the primary type of grain produced is maize (corn) followed by millet, rice and sorghum foods, with wheat production at a very distant 5th (Haard et al., 1999). African grains are prepared via fermentation to produce an acid porridge that lacks the difficult-to-digest outer hull component (Gaffa et al., 2002; Steinkraus, 1996; Tou et al., 2006; Vieira-Dalode et al., 2007). Thus, when an immigrant raised on a grain fermentation-based diet first encounters western wheat-based foods, the individual is being exposed to a brand new, potentially antigenic, protein structure. The consequences of a suddenly altered diet on the microbiome, in turn, are likely to be significant.

In a study of the gut microbiome in children from urban centers in Europe compared to rural Africa, African children had significant abundances of *Bacteroidetes*, minimal *Firmicutes* and a number of unique species from the genuses *Prevotella* and *Xylanobacter*. These latter two species contain a set of genes needed for cellulose and xylan hydrolysis not typically required by people with an urban diet (De Filippo et al., 2010). The ability to digest certain foods is thus likely dictated by the resident microbiota repertoire, and the differential processing of food proteins by inefficient, dysfunctional or absent intestinal peptidases may be the result of altered resident gut microbiota. The diet-gut microbiome functional connection is further evident in an experimental comparison of a short-term animal-based diet with one predominantly composed of plant products fed to U.S. volunteers. The animal-based diet was associated with increased abundances of bile-tolerant microbes and decreases in those necessary to metabolize plant polysaccharides (David et al., 2014). The gut microbiome of rodent consumers of a Western diet has been found to reflect a generally low diversity of bacteria, accompanied by a higher circulating LPS and blood brain barrier permeability (Bested et al., 2013; Cani et al., 2007; Davidson et al., 2012; Freeman and Granholm, 2012).

4.3 Digestion of caseins and glutens by bacteria

Inefficiencies or disruption of the digestion powerhouses of the gut commensal bacteria might impact how certain food peptides become antigenic. Casein and gluten-derived peptides might be incompletely or aberrantly digested in schizophrenia, thus forming antigens associated with the foods that are novel. These novel antigens might prime the immune system differently upon first exposure to the subject food. Indeed, individuals with psychiatric disorders recognize epitopes within the food-derived antigenic proteins, which are not recognized by control individuals (Samaroo et al., 2010; Severance et al., 2010). Gluten is notoriously difficult to completely digest by resident digestive proteases (Caminero et al., 2014). In experimental analyses of human gut bacteria isolated from fecal samples, it was predominantly the *Firmicutes* and *Actinobacteria* that were deemed effective in metabolizing gluten and especially the *Bifidobacterium* and *Lactobacillus* genera (Caminero et al., 2014). Of interest, the bioactive peptides that are believed to trigger the inflammatory response in celiac disease were susceptible to digestion by several bacterial species including *Lactobacillus mucosae, L. rhamnosus* and *Clostridium botulinum/sporogenes* (Caminero et al., 2014). Another study identified in the oral microbiome, a series of bacteria with gluten-degrading enzymes including species of *Rothia, Actinomyces, Streptococcus, Neisseria* and *Capnocytophaga* (Fernandez-Feo et al., 2013). Given this preliminary evidence that the gut bacterial profile likely impacts an indivdual's ability to digest gluten, it is not surprising that a gluten-free diet might aid in limiting the abundance and diversity of the *Bifidobacteria* (De Palma et al., 2009; Nistal et al., 2012). Interestingly, autistic patients on casein-free and gluten-free diets compared to those who received unrestricted diets generally show less immune-associated infiltration and intestinal permeability (Ashwood et al., 2003; Ashwood et al., 2004; de Magistris et al., 2010).

5. Conclusions and future directions

Our understanding of the gut and microbial effects on the brain in individuals with schizophrenia would be greatly advanced with carefully designed, case-control, longitudinal studies that incorporate biomarkers of physiological processes and behavioral indices. Biomarkers might include measurement of those molecules depicted in Figure 1 in conjunction with microbiome sampling from multiple biological sites and behavioral measures such as symptom and cognitive scores from Positive and Negative Syndrome Scale (PANSS) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Kay et al., 1987; Randolph et al., 1998). Informative markers that associate with schizophrenia could be developed into screening tools to help define physiologically-based inclusion criteria for use in clinical trials. Toward this end, those individuals with schizophrenia who would most benefit from specific GI- and immune-based treatments could be identified. In autism, for example, a variety of outcomes of gluten-free and casein-free diets on symptoms have been reported, yet success of these diets were only apparent in those trials that specifically targeted individuals with GI pathologies who might respond to treatment (Elder, 2008; Hyman et al., 2010; Marcason, 2009; Reichelt and Knivsberg, 2009; Sponheim, 1991; Whiteley et al., 2010).

Other treatment modalities in need of careful clinical evaluation for safety and efficacy in schizophrenia include anti-inflammatory agents, dietary interventions, digestive enzyme-based aids, prebiotics, and probiotic supplementation. Additional compounds in development to treat celiac disease and gluten sensitivity might also be candidates for clinical trials in individuals with schizophrenia (Freeman, 2013). For example, recent reports in experimental *in vitro* and mouse models of celiac disease suggest that intestinal treatment with elafin, an endogenous serine protease inhibitor, normalized inflammation and intestinal barrier function (Galipeau et al., 2014). Another compound, sevelamer, that is used to treat symptoms of chronic kidney disease may be applicable to GI pathologies, as evident by a recent finding that this drug can bind bacterial proteins, prevent these proteins from translocating from the gut into circulation, and effectively reversing the “leaky gut” syndrome (Kristoff et al., 2014).

The dysfunction of gut and immune processes in schizophrenia hints at dysregulated pathways that might serve as promising targets for gene susceptibility studies. Genes in pathways that impact endothelial barriers, peptidases, antigen recognition or detection and monocyte activation are all possible candidates. Schizophrenia susceptibility loci identified by techniques such as GWAS should be re-evaluated for activity in these related biological pathways. Another intriguing hypothesis relates to the role of epigenetic machinery on host-microbe, gut-brain interactions as extensively reviewed by Stilling et al (Stilling et al., 2014).

In this paper, we have proposed a number of means by which the immune system, the GI tract, the microbiome and the brain might be connected in schizophrenia. While some of these links are hypothetical, they are consistent with data derived from numerous epidemiological, biological and experimental studies and consistent with a focus away from the traditional view that schizophrenia is a disease originating solely from the brain.

Although some of the concepts presented here have been around for a long time, progress in this field is only beginning to accelerate.

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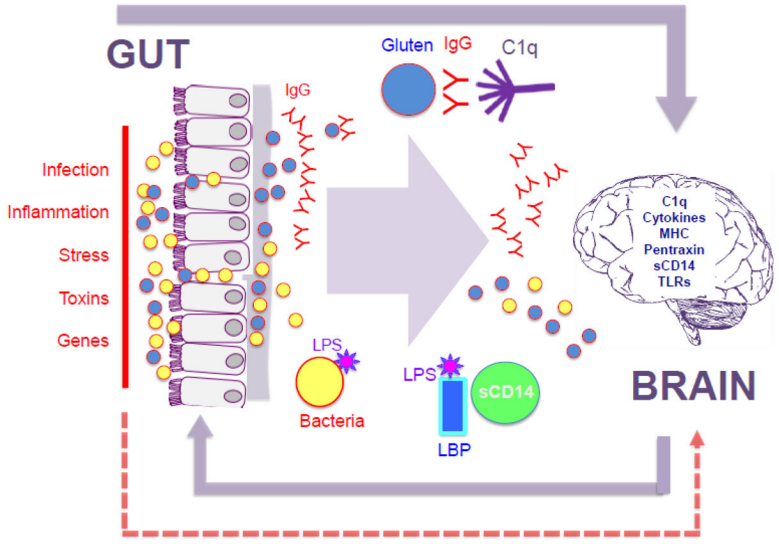

Figure 1. Overview of autoimmunity, GI and brain connections in schizophrenia

Aspects of the gut to brain axis described in this review are depicted. Multiple environmental and genetic factors can contribute to inflammation in the GI tract and a compromised GI epithelial and endothelial barrier (left side of diagram, text in red). The same series of factors may also cause permeability of the blood brain barrier (dashed red arrow). Loss of barrier integrity can lead to translocation of food-derived peptides (blue circle) and resident gut microbiota (yellow circle). In individuals with celiac disease, an autoimmune response following ingestion of wheat gluten (blue circle) causes the formation of antibodies (red Y structure) that attack the self-protein tTg (not shown). In individuals who do not have a biomarker profile of classically-defined celiac disease, an IgG sensitivity to wheat gluten and to bovine milk casein can occur, and the humoral immune response (also red Y structure) leads to activation of innate immunity. C1q forms immune complexes with invading antigens including gluten, casein and bacterial peptides and corresponding antibodies. Soluble CD14 (sCD14) is activated in the presence of serological lipopolysaccharide (LPS) and its binding protein, LBP. C1q and sCD14 are also both active in the brain, as are other innate immune molecules such as the major histocompatibility complex (MHC), cytokines, pentraxin and toll-like receptors (TLRs). Alternatively, gut-derived food and bacterial peptides, and corresponding antibodies, might exert direct effects on the brain. The gut-brain axis is bi-directional, but this review focuses on GI factors impacting the brain in schizophrenia. Details are described in the main text.