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Is there a role for immune-to-brain communication in schizophrenia?

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Abstract

Schizophrenia is characterised by hallucinations, delusions, depression-like so-called negative symptoms, cognitive dysfunction, impaired neurodevelopment and neurodegeneration. Epidemiological and genetic studies strongly indicate a role of inflammation and immunity in the pathogenesis of symptoms of schizophrenia. Evidence accrued over the last two decades has demonstrated that there are a number of pathways through which systemic inflammation can exert profound influence on the brain leading to changes in mood, cognition and behaviour. The peripheral immune system-to-brain communication pathways have been studied extensively in the context of depression where inflammatory cytokines are thought to play a key role. In this review, we highlight novel evidence suggesting an important role of peripheral immune-to-brain communication pathways in schizophrenia. We discuss recent population-based longitudinal studies that report an association between elevated levels of circulating inflammatory cytokines and subsequent risk of psychosis. We discuss emerging evidence indicating potentially important role of blood–brain barrier endothelial cells in peripheral immune-to-brain communication, which may be also relevant for schizophrenia. Drawing on clinical and preclinical studies, we discuss whether immune-mediated mechanisms could help to explain some of the clinical and pathophysiological features of schizophrenia. We discuss implication of these findings for approaches to diagnosis, treatment and research in future. Finally, pointing towards links with early-life adversity, we consider whether persistent low-grade activation of the innate immune response, as a result of impaired foetal or childhood development, could be a common mechanism underlying the high comorbidity between certain neuropsychiatric and physical illnesses, such as schizophrenia, depression, heart disease and type-two diabetes.

Keywords

Schizophrenia; Psychotic disorder; Inflammation; Immunity; Immune system; Cytokine; IL-6; CRP; Blood–brain barrier; Endothelial cell; Treatment; Common-cause hypothesis

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Introduction

Based on the psychopharmacological signature of anti-psychotic drugs, mechanisms involving monoamines and acetylcholine have underpinned pathophysiologic explanations and approaches to drug therapy for schizophrenia for over half a century (Klawans et al. 1972; Meltzer 1989). However, dopamine abnormalities are not universally present in schizophrenia and there is heterogeneity in its clinical presentation, course and treatment response (Demjaha et al. 2012; Howes et al. 2012; Howes and Kapur 2014; Roberts et al. 2009), which indicates additional mechanisms. A potential role of inflammation in the pathogenesis of psychosis was described nearly a century ago (Menninger 1926). Recent studies have demonstrated that interactions between the immune system and the brain can lead to changes in mood, cognition and behaviour (Dantzer et al. 2008), which may be relevant for some of the symptoms of schizophrenia (Monji et al. 2009; Schwarz et al. 2001; Smith 1992; Smith and Maes 1995).

Contrary to the traditional view that the brain is an immunologically privileged site shielded behind the blood–brain barrier (BBB), evidence accrued over the last two decades now points towards a number of pathways through which systemic inflammation can exert a profound influence on the brain. The peripheral immune system-to-brain communication pathways have been studied extensively in the context of depression. This review considers the relevance of peripheral immune system-to-brain communication pathways, involving cytokines and endothelial cells in the BBB, in the pathogenesis of schizophrenia and related psychosis. Drawing on recent clinical and preclinical research, we discuss whether immune-mediated mechanisms could contribute to clinical and pathophysiological features of schizophrenia, such as positive and negative symptoms, cognitive dysfunction, impaired neurodevelopment and neurodegeneration. We discuss implication of these findings for diagnosis and treatment of schizophrenia as well as future research. Finally, pointing towards links with early-life adversity, we consider whether persistent low-grade activation of the innate immune response, as a result of impaired foetal or childhood development, might contribute to the high comorbidity between certain neuropsychiatric and physical illnesses, such as schizophrenia, depression, heart disease and type-two diabetes.

We begin with an overview of the epidemiological and genetic studies linking inflammation and immunity with schizophrenia.

Epidemiological and genetic studies link inflammation and schizophrenia

The idea that inflammation may lead to psychosis is as old as the history of the schizophrenia syndrome. Kraepelin postulated *dementia praecox* (conceptual predecessor of current schizophrenia) was caused by ‘autointoxication’ from a focal somatic infection (Noll 2004). The idea that infection might cause schizophrenia gained support from very early on because it fitted well with clinical observations. Psychotic symptoms, mood disturbance and cognitive dysfunction are often observed during and shortly after a known infectious illness. This clinical wisdom was matched with research breakthroughs that included the discovery of *Treponema pallidum* in 1905 as the cause of syphilis and associated psychosis (Yolken and Torrey 2008). Following the 1918 influenza epidemic, Menninger described a series of

200 cases of post-influenzal psychosis; a third of whom were reported to resemble *dementia praecox* (Menninger 1926).

Epidemiological data of considerable breadth and depth now support a role of infection and immunity in schizophrenia. Schizophrenia is associated with increased prevalence of various infections including neurotropic viruses from the *Herpes viridae* family (Bartova et al. 1987; Delisi et al. 1986; Torrey et al. 2006) and the intracellular parasite, *Toxoplasma gondii* (Torrey et al. 2007). Infection during foetal and childhood development is also associated with the risk of psychotic illness in adult life (reviewed by Khandaker et al. 2012, 2013). In 1988, Mednick and colleagues reported increased risk of schizophrenia in adult offspring of women pregnant during the 1957 influenza pandemic (Mednick et al. 1988). Consistent with the then-novel neurodevelopmental hypothesis of schizophrenia (Murray and Lewis 1987; Weinberger 1987), which posits abnormal neurodevelopment as a cause of the illness, the findings spurred on a great deal of interest into early-life infection. However, many subsequent epidemic studies failed to replicate this finding, which could be due to misclassification of exposure (reviewed by Selten et al. 2010). These studies defined maternal exposure to influenza as being pregnant at the time of an epidemic rather than direct measurement of exposure at the individual level.

More recently, studies have used clinical examination or serological assays to determine prenatal maternal infection at the individual level. A systematic review of these studies indicates prenatal maternal infection with any of a number of pathogens is associated with the risk of schizophrenia-related psychosis in adult offspring (Khandaker et al. 2013). These include Herpes simplex virus type-2 (HSV-2), *T. gondii*, cytomegalovirus, influenza virus as well as nonspecific bacterial, upper respiratory and genital/reproductive infections (Babulas et al. 2006; Blomstrom et al. 2012; Brown et al. 2004a, 2005; Buka et al. 2001a; Mortensen et al. 2007, 2010; Sorensen et al. 2009). Increased maternal serum levels of C-reactive protein (CRP), tumour necrosis factor alpha (TNF- α) and interleukin (IL)-8 during pregnancy are also associated with schizophrenia in offspring (Brown et al. 2004b; Buka et al. 2001b; Canetta et al. 2014). Similarly, childhood infections have been associated with risk of psychosis. Exposure to Epstein-Barr virus in early childhood is associated with subclinical psychotic symptoms in adolescence (Khandaker et al. 2014b). Childhood CNS infections are associated with nearly twofold increased risks of subclinical psychotic symptoms in adolescence (Khandaker et al. 2015) and schizophrenia in adult life (Khandaker et al. 2012).

Further support for a role of the immune system in schizophrenia comes from studies pointing to links with atopy and autoimmunity. Childhood atopic disorders (presence of both asthma and eczema compared with no atopic disorders) are associated with an odds ratio of 1.44 (95 % confidence interval (CI), 1.06–1.94) for psychotic symptoms in adolescence (Khandaker et al. 2014c). Atopic disorders particularly asthma are associated with a similar increase in the risk of future hospitalisation with schizophrenia (relative risk, 1.59; 95 % CI, 1.31–1.90) (Pedersen et al. 2012). The prevalence of auto-immune conditions is increased in people with schizophrenia and their unaffected first-degree relatives (Eaton et al. 2006). Schizophrenia is associated with serum antibodies against dietary antigens, such as gliadin and casein (Lachance and McKenzie 2014). Recently, auto-antibodies against neuronal cell

surface targets, such as *N*-methyl-D-aspartate receptor (NMDAR) and components of the voltage-gated potassium channel complex, have been reported in some cases of psychosis (Parthasarathi et al. 2006; Steiner et al. 2013; Zandi et al. 2011). NMDAR antibodies have been typically associated with the eponymous encephalitis, which is often associated with psychotic symptoms (Dalmau et al. 2011). However, it has been reported that some NMDAR antibody positive cases of psychosis do not have classic features of encephalitis (Lennox et al. 2014). Elimination of antibodies by immunotherapy has been reported to improve psychotic symptoms in some cases of first episode psychosis (Zandi et al. 2014; Zandi et al. 2011). Together these findings indicate NMDAR auto-antibodies might play a causal role in some cases of psychosis. An association between NMDAR antibody and schizophrenia is biologically plausible; NMDAR blockade with ketamine produces psychotic symptoms in healthy volunteers (Pomarol-Clotet et al. 2006).

Since a variety of infections, atopic disorders and auto-immune conditions are associated with schizophrenia, it is possible that they share a common underlying pathway most likely involving the inflammatory immune response. Epidemiological studies lend support to this idea. One study found that patients with schizophrenia who are hospitalised due to an acute psychotic relapse are nearly 30 times more likely to have a urinary tract infection compared with stable outpatients with schizophrenia or healthy controls (Miller et al. 2013). Risk of schizophrenia increases in a linear fashion with the number of severe infections in individuals with a previous history of auto-immune disease (Benros et al. 2011).

Genome-wide association studies (GWAS) provide strong evidence for a role of the immune system in schizophrenia. A recent GWAS that identified 108 genetic loci associated with schizophrenia suggests the illness can be broadly seen as a condition involving two systems: the CNS and the immune system (Schizophrenia Working Group of the Psychiatric Genomics, C 2014). In addition to genes expressed in the brain, the study found genes involved in adaptive immunity (CD19 and CD20 B-lymphocytes) and the major histocompatibility complex (MHC) region on chromosome six. The MHC region contains many immune-related genes including those involved in antigen presentation and inflammatory mediators. These findings are consistent with two previous GWAS also implicating this region in schizophrenia (Shi et al. 2009; Stefansson et al. 2009).

Schizophrenia is associated with alteration in components of peripheral immune-to-brain communication

Inflammatory cytokines

A role for cytokines in schizophrenia was proposed nearly two decades ago (Smith 1992; Smith and Maes 1995), with many subsequent studies reporting alteration of the cytokine milieu in schizophrenia with the propensity for the production of proinflammatory cytokines (Ganguli et al. 1994; Maes et al. 1994, Maes et al. 1995). Meta-analyses of a large number cross-sectional studies now confirm that anti-psychotic naïve first episode psychosis and acute psychotic relapse are associated with increased serum levels of proinflammatory cytokines, such as IL-1 β , IL-6, TNF- α and decreased serum levels of the anti-inflammatory cytokine, IL-10, which are normalised after remission of symptoms with anti-psychotic

treatment (Miller et al. 2011; Potvin et al. 2008; Upthegrove et al. 2014). Serum IL-6 levels are associated with the severity and duration of illness (de Witte et al. 2014; Maes et al. 1994). Although there are very few studies, IL-6 levels are reported to be elevated in the serum of people at increased clinical risk for psychosis (Stojanovic et al. 2014). IL-1 β and IL-6 levels have been reported to be elevated in the cerebrospinal fluid (CSF) of schizophrenia patients (Garver et al. 2003; Hayes et al. 2014; Soderlund et al. 2009). An important limitation of these cross-sectional studies, however, is they cannot determine whether cytokine alteration is a cause or consequence of illness.

Recently, a prospective study from the Avon Longitudinal Study of Parents and Children (ALSPAC), a general population birth cohort, has reported twofold increased risk of psychotic disorder at age 18 years for higher serum levels of IL-6 at age 9 years (Khandaker et al. 2014a) (Fig. 1). The study also reports a robust, dose-response relationship between higher IL-6 levels in childhood and subsequent risk of subclinical psychotic symptoms in young adulthood, which persists after taking into account a number of potential confounders including sex, body mass and psychological and behavioural problems preceding the measurement of IL-6. In this study, serum CRP levels were not associated with future psychiatric outcomes, although another recent study reported increased risk of late onset schizophrenia for higher serum CRP levels at baseline (Wium-Andersen et al. 2014). While psychological stress may contribute to a proinflammatory state (Black 2003), these longitudinal studies indicate that the inflammation-psychosis association is not merely an artefact of concurrent stress. Thus, these findings point towards a potentially causal role of inflammation in the pathogenesis of psychosis. However, further longitudinal studies are required to replicate these findings in other populations. Studies are also needed on the associations between psychological stress, cortisol and cytokine concentrations in different stages of schizophrenia.

It is well established that circulating peripheral cytokines can communicate with the brain using a number of pathways, including neural and humoral pathways, ultimately leading to activation of microglia (resident immune cells of brain) (Fig. 2). The mechanisms of cytokine-mediated immune-to-brain communication have been reviewed extensively (see, Dantzer 2004; Dantzer et al. 2008; Miller et al. 2009). In short, in the neural pathway, peripherally produced pathogen-associated molecular patterns (PAMPs) and cytokines activate primary afferent nerves, such as the vagus nerve. The signal then reaches the primary and secondary projections of the neural pathway reaching first the nucleus tractus solitarius and subsequently various hypothalamic brain nucleus (Dantzer et al. 2000). The humoral pathway involves circumventricular organs (CVOs) that lack an intact BBB. CVOs provide direct access for PAMPs which induce the local production of proinflammatory cytokines by macrophage-like cells. The cytokines are then thought to reach the brain by volume diffusion (Vitkovic et al. 2000). Finally, there is a cellular pathway through which proinflammatory cytokines, notably TNF- α , are able to stimulate microglia to produce monocyte chemoattractant protein-1 (MCP-1), which in turn, is responsible for the recruitment of monocytes into the brain (D'Mello et al. 2009). Once within the CNS, the cytokine signal activates microglia leading to the secretion of proinflammatory cytokines, chemokines and proteases within the brain. These messengers breakdown tryptophan along the kynurenine pathway, increase oxidative stress, and activate the hypothalamic-pituitary-

adrenal axis (Dantzer 2004; Dantzer et al. 2008; Miller et al. 2009). These effects could contribute to the negative, cognitive and positive symptoms of schizophrenia, as well as to impaired mood, cognition and perception that are important parts of many psychiatric disorders (see below).

Blood–brain barrier endothelial cells

Schizophrenia is associated with an increase in serum markers of endothelial cell and platelet activation. Studies comparing unmedicated, acutely unwell cases of schizophrenia defined by DSM-IV or ICD-10 criteria with healthy controls have reported increased soluble P (sP)-selectin, sL-selectin, D-dimer levels in serum as well as increased number of integrin $\alpha_{IIb}\beta_{IIIa}$ receptors on platelets in schizophrenia (Iwata et al. 2007; Masopust et al. 2011; Walsh et al. 2002). These findings could not be explained by concurrent inflammation or physical illness (Masopust et al. 2011). One study focusing on different selectin molecules found that serum sL-selectin was increased in schizophrenia even after controlling for lymphocyte count (Iwata et al. 2007). P-selectin and L-selectin are members of the selectin family of adhesion molecules. Integrins are also adhesion molecules while D-dimer is a marker of thrombogenesis. Increased levels of sP-selectin reflect activation of endothelial cells and platelets (Woollard 2005). Emerging evidence suggests that activation of endothelial cells in the cerebral vasculature following systemic inflammation is associated with transmigration of inflammatory cells into the brain tissue (D'Mello and Swain 2014). Selectins and integrins play important roles in the transmigration of circulating monocytes.

Systemic inflammation is associated with activation of cerebral endothelial cells as well as increase in circulating monocytes. In mice with liver inflammation, there is an increase in the number of circulating monocytes, a large proportion of which are activated (Kerfoot et al. 2006). These mice also show increased expression of adhesion molecules in cerebral endothelial cells, which together with integrin, mediate the adhesion of monocytes to these cells. Intravital microscopy has confirmed that an increased number of monocytes are in contact with cerebral vasculature of mice with liver inflammation, which ultimately leads to infiltration of brain parenchyma by the inflammatory CCR2 expressing monocytes (D'Mello et al. 2009; Kerfoot et al. 2006). Activation of cerebral endothelial cells has been shown to be important for cognitive and behavioural changes associated with systemic inflammation. Blocking cerebral transmigration of CCR2 monocytes with systemic injection of anti-P-selectin alleviates the behavioural signs of sickness that develop in mice with liver inflammation (D'Mello et al. 2009). Similarly, inhibition of cerebral monocyte recruitment prevents anxiety-like behaviours in mice subjected to repeated social defeat (Wohleb et al. 2013). It has been suggested that IL-6 play a critical role in mediating sickness behaviour in mice with liver inflammation. In this model, sickness behaviour is associated with cerebral endothelial cell activation as well as higher levels of IL-6 in the liver and peripheral circulation, all of which are significantly reduced in IL-6 deficient mice (Nguyen et al. 2012). Together, these findings suggest that alterations in the integrity of the BBB and/or the blood-CSF barrier (Muller et al. 1999; Schwarz et al. 1998), in the form of increased transmigration of inflammatory cells into the brain due to activation of endothelial cells in cerebral vasculature, play a crucial role in the peripheral immune-to-brain communication.

Further support for a role of endothelial cells comes from genetic studies. Similar to schizophrenia, bipolar disorder is associated with increased serum levels of P-selectin and proinflammatory cytokines (Bai et al. 2014). There is a great deal of overlap in the aetiology (including genetic) of schizophrenia and bipolar disorder (Green et al. 2010; Lichtenstein et al. 2009; O'Donovan et al. 2008; Van Snellenberg and de Candia 2009). Recently, a study has reported genome-wide significant association for a single nucleotide polymorphism linked to the NDST3 gene with risks of bipolar disorder and schizophrenia (Lencz et al. 2013). The NDST3 is a brain-expressed gene that encodes an enzyme critical to heparan sulphate metabolism. The authors discuss possible role of heparan sulphate in axonal and neurite outgrowth to explain the findings. However, a large number of studies have identified important roles of heparan sulphate in inflammatory response, in particular, leukocyte transmigration through the blood-vessel wall. Heparan sulphate is involved in the initial adhesion of leukocytes to the inflamed endothelium, subsequent chemokine-mediated transmigration through the vessel wall and the establishment of both acute and chronic inflammatory reactions; reviewed (Parish 2006). Therefore, it can be postulated that the NDST3 gene contributes to CNS inflammation by facilitating transmigration of leukocytes across the BBB leading to neuropsychiatric symptoms relevant for schizophrenia and bipolar disorder.

Could immune-to-brain communication contribute to clinical features of schizophrenia?

Clinically, the schizophrenia syndrome is characterised by positive symptoms (e.g. paranoia, thought disorder, hallucinations, delusions), negative symptoms (e.g. social withdrawal, apathy) and cognitive dysfunction (e.g. poor executive function and memory). Impaired neurodevelopment and accelerated neurodegeneration are also important features of schizophrenia. A key result of peripheral immune-to-brain communication is activation of microglia, which release proinflammatory cytokines, chemokines and proteases within brain tissue. There is evidence for microglia activation in schizophrenia. Neuroimaging positron emission tomography studies suggest both recent onset schizophrenia and acute exacerbations of schizophrenia are associated with activation of microglia in the entire grey matter and the hippocampus (Doorduyn et al. 2009; van Berckel et al. 2008). Post-mortem studies have also reported evidence of microglia activation in schizophrenia (Radewicz et al. 2000; Steiner et al. 2008; Steiner et al. 2006).

Psychotic symptoms and cognitive dysfunction

IL-6 and other proinflammatory cytokines activate indoleamine 2,3 dioxygenase (IDO), an enzyme that breaks down tryptophan along the kynurenine pathway, leading to increased levels of kynurenic acid and quinolinic acid, both involved in glutamatergic neurotransmission (Fig. 3). Quinolinic acid is a NMDAR agonist and is neurotoxic (see below), while kynurenic acid is the only naturally occurring NMDAR antagonist in the human CNS (Schwarcz and Pellicciari 2002; Stone 1993). NMDAR antagonism and glutamatergic hypofunction have long been proposed to underlie psychotic symptoms and cognitive dysfunction in schizophrenia (Carlsson and Carlsson 1990; Pomarol-Clotet et al. 2006). Indeed, studies have reported elevated levels of kynurenine and kynurenic acid in the

CSF and brain tissue of schizophrenia patients compared with healthy controls (Erhardt et al. 2001; Linderholm et al. 2012; Nilsson et al. 2005; Schwarcz et al. 2001). Injection of ketamine (an NMDAR antagonist) in healthy volunteers has been reported to cause positive symptoms such as paranoid ideation, thought disorder as well as phenomena resembling negative symptoms (Pomarol-Clotet et al. 2006). Kynurenic acid, which is primarily produced in astrocytes, can impair cognitive function by reducing the release of glutamate and dopamine; reviewed (Haroon et al. 2012; Schwarcz and Pellicciari 2002). It has been shown that intra-striatal administration of kynurenic acid leads to marked reduction in extracellular dopamine concentration in rodents (Wu et al. 2007). In addition, mice with a genetic deletion that leads to reduced brain concentrations of kynurenic acid show better cognitive performance compared with wild-type animals (Potter et al. 2010).

Kynurenic acid might also contribute to cognitive symptoms of schizophrenia through its effect on the $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$ nAChRs) (Hilmas et al. 2001). Inhibition of presynaptic $\alpha 7$ nAChRs by kynurenic acid could be causally related to hypoglutamatergic and hypocholinergic tones, and consequent cognitive dysfunction in schizophrenia (Hilmas et al. 2001; Pellicciari et al. 1994). This idea is supported by two small treatment trials that reported some improvement in cognitive function in schizophrenia patients who received DMXB-A, an $\alpha 7$ nAChR agonist (Freedman et al. 2008; Olincy et al. 2006). Cyclooxygenase (COX)-1 inhibition increases levels of kynurenic acid while COX-2 inhibition decreases them (Schwieler et al. 2005). Thus, manipulation of the COX enzymes might be used as a tool for changing the kynurenic acid levels in the brain in order to elucidate its role in psychosis. Celecoxib (a selective COX-2 inhibitor) has been reported to improve cognitive function in early stages of schizophrenia (Akhondzadeh et al. 2007; Muller et al. 2002, 2005, 2010), although its overall effectiveness as an adjunct to anti-psychotic therapy in schizophrenia have been questioned in a recent meta-analysis (Sommer et al. 2014).

Several lines of investigation indicate proinflammatory cytokines play a key role in sickness behaviour and depression; reviewed (Dantzer 2004; Dantzer et al. 2008; Miller et al. 2009). Nonspecific peripheral immune activation caused by injection of lipopolysaccharide (LPS) in healthy volunteers increases serum IL-6 levels as well as inducing low mood, anxiety and reduced cognitive performance (Reichenberg et al. 2001). Rodent studies have demonstrated physiological roles of cytokines in memory and learning, including long-term potentiation, synaptic plasticity and neurogenesis (reviewed by Yirmiya and Goshen 2011). Mild systemic inflammation has been reported to produce impairments in spatial memory in humans via its action on glucose metabolism in the medial temporal lobe (Harrison et al. 2014). Severe systemic inflammation is associated with long-term cognitive decline in the elderly (Iwashyna et al. 2010; Khandaker and Jones 2011). Together, these findings suggest that cytokine-mediated inflammatory processes could contribute to positive, negative and cognitive symptoms of schizophrenia.

Neurodegeneration

There is little doubt that schizophrenia is associated with a neurodegenerative process beyond that seen in healthy people, as evidenced by progressive cognitive decline, loss of

cortical grey matter and neuronal atrophy in some cases (Harrison 1999; Veijola et al. 2014). Inflammation can contribute to neurodegeneration. Microglia activation is increasingly being recognised as an important component in the pathogenesis of degenerative brain conditions, such as Alzheimer's disease (Perry et al. 2010). Quinolinic acid, produced primarily in microglia and infiltrating macrophages, is associated with lipid peroxidation and oxidative stress (Rios and Santamaria 1991). Activated microglia produces glutamate which may also interfere with neuronal survival by inducing excitotoxicity in the brain (Dantzer and Walker 2014). Activated microglia and macrophages take in extracellular glutamine that is metabolised to glutamate via the enzyme glutaminase (Takeuchi et al. 2006). Glutamate is then released into the extracellular space via a transporter, known as system x_c^- , that transports cysteine into the cell in exchange for glutamate (Eugenin et al. 2001; Kigerl et al. 2012). During inflammation, activation of system x_c^- functions as an endogenous anti-oxidant response because influx of cysteine helps to preserve the redox status of the cell (Conrad and Sato 2012), consequently increasing extracellular glutamate. On the other hand, inflammation downregulates excitatory amino acid transporter (EAAT) 1 in astrocytes which, together with increased extracellular glutamate, can lead to excitotoxicity (Takaki et al. 2012). It has been shown that LPS-induced immunoactivation activates system x_c^- in mice (Kigerl et al. 2012). Inflammation-associated activation of IDO has been shown to increase oxidative stress by enhancing the production of two kynurenine metabolites, 3-hydroxykynurenine and 3-hydroxyanthranilic acid, both of which are potent generators of radical oxygen species. (Eastman and Guilarte 1989; Smith et al. 2009). Thus, it can be proposed that inflammation contributes to neurodegeneration by converting oxidative stress to excitotoxic stress in the context of IDO activation (Dantzer and Walker 2014).

Neurodevelopment

Microglia plays an important role in neurodevelopment. Postnatal brain development is severely perturbed in mice that are genetically deficient of microglia and all other macrophages, which strongly support a role for microglia in brain development and function (Erblich et al. 2011). Interference with brain development from early-life infection/inflammation is consistent with a neurodevelopmental view of schizophrenia (Murray and Lewis 1987; Weinberger 1987). Exposure to kynurenic acid during periods of brain development, ranging from prenatal life to adolescence, has been reported to be associated with deficits in learning and memory in adult rats (Akagbosu et al. 2012; Pocivavsek et al. 2014). Animal studies have demonstrated that proinflammatory cytokines may mediate adverse neurodevelopmental effects of early-life infection. Simulated viral or bacterial infection or direct injection with IL-6 in pregnant mice has been reported to produce intermediate phenotypes related to schizophrenia in the adult offspring (reviewed by Meyer and Feldon 2010). Some of these phenotypes, such as deficits in sensory gating and abnormal latent inhibition, are reversible by treatment with clozapine (Smith et al. 2007). It has been proposed that microglia are likely to retain an immune memory of the neuropathology, which, in turn, is associated with heightened responsiveness to new systemic inflammation (Perry et al. 2010). Thus, it can be speculated that early developmental insults such as childhood CNS or severe systemic infection have a priming effect on microglia (Schroder et al. 2006), which might increase microglial activation and

psychosis risk following subsequent infections. Longitudinal studies are required to test this hypothesis.

Could inflammation be a common link between neuropsychiatric and physical illnesses?

Low-grade systemic inflammation might be a common mechanism underlying the high comorbidity between certain neuropsychiatric and physical illnesses of adult life. Risk of heart disease, impaired glucose tolerance and type-two diabetes is higher in schizophrenia, which persists after taking into account effects of anti-psychotic medication and life-style factors (Bushe and Holt 2004; Curkendall et al. 2004). Patients with major depression are twice as likely to develop heart disease after controlling for effects of smoking and hypertension (Anda et al. 1993; Barefoot and Schroll 1996). Large-scale population-based longitudinal studies have reported associations of higher serum IL-6 with future risks of heart disease (Danesh et al. 2008), type-two diabetes (Pradhan et al. 2001), depression and psychosis (Khandaker et al. 2014a). The findings could be linked with early-life factors influencing inflammatory regulation, such as impaired foetal development or childhood maltreatment. This idea is consistent with the common-cause or developmental programming hypothesis. Developmental programming refers to permanent alteration in physiological system(s) following exposure to adversity during a specific 'developmental window'. The physiological alterations, in combination with genetic and/or other environmental factors, can increase risks of several diseases in adulthood (Barker 1993). Empirical evidence from longitudinal studies supports the developmental programming hypothesis. Low birth weight (a marker of suboptimal foetal development) is associated with increased circulating CRP levels (Tzoulaki et al. 2008) as well as risks of heart disease (Barker 1993), diabetes (Barker 1993), depression and schizophrenia (Abel et al. 2010). Furthermore, evidence from the Dunedin birth cohort suggests higher levels of CRP mediate the association between childhood maltreatment and risk of depression in adulthood (Danese et al. 2008).

Recently, early-life adversity (measured by low birth weight and maternal depression during pregnancy) has been shown to be associated with higher serum levels of IL-6 in childhood in the ALSPAC birth cohort (Rabhi et al. 2014). It is understood, in mammals foetal developmental programming occurs via two common mechanisms: exposure to excess glucocorticoids (or stress) (Edwards 1993) or malnutrition (Barker et al. 1993). During pregnancy, foetus is protected from higher levels of maternal glucocorticoids by a foeto-placental enzyme, 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) (Brown 1993). Studies on human and other primates have shown that infection/proinflammatory cytokines reduce placental 11 β -HSD2 activity (Johnstone et al. 2005), thus exposing the foetus to excessive levels of maternal glucocorticoids. People exposed to excess levels of glucocorticoids during pregnancy are more likely to develop hypertension, hyperglycaemia, hyperinsulinemia, hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, and alerted affective behaviour as adults (Barker et al. 1993; Seckl and Holmes 2007). Similarly, activation of the HPA axis is associated with increased blood pressure, insulin resistance, glucose intolerance and hyperlipidaemia (Reynolds et al. 2001). Together, these studies

might indicate that permanent low-grade activation of the innate immune response as a result of developmental programming is a common mechanism for adult schizophrenia, depression, heart disease and type-two diabetes.

Schizophrenia is associated with increased blood glucose and lipids, which also are established risk factors for heart disease and diabetes. While these metabolic alterations could be attributed to anti-psychotic associated weight gain in some cases, evidence suggests that patients with schizophrenia have impaired glucose tolerance even before they begin treatment (Bushe and Holt 2004). Recently, a large meta-analysis has shown that genetic factors influencing serum IL-6 levels also increase the risk of coronary heart disease, but these genes are unrelated to the classic risk factors for the illness, such as smoking, lipid concentrations or adiposity (Collaboration et al. 2012). The findings indicate inflammation contributes to heart disease independently of other risk factors. Longitudinal studies are needed to tease apart to what extent the comorbidity between schizophrenia, depression, heart disease and diabetes is due to shared metabolic or inflammatory risk factors.

Therapeutic implications of an immune/inflammation link to schizophrenia

A clearer understanding of the immunological and inflammatory aspects of schizophrenia might lead to novel approaches to diagnosis and treatment. Inflammatory cytokines, activation of BBB endothelial cells and brain microglia may contribute to different features of schizophrenia, depression and possibly other psychiatric disorders. Therefore, shifting the focus of research from syndrome to symptom (or constellation of symptoms) may help to elucidate the role of inflammation more fully. The use of the research domain criteria (RDoC) could lead to a better understanding of the mechanisms of psychopathology because the effects of inflammation are likely to cut-across traditional diagnostic categories. This framework would allow examining how inflammation influences developmental trajectories of neuropsychiatric symptoms or cognition over the life course. At the clinical level, phenotyping of patients based on their immunological characteristics may be helpful for choosing the right treatment or monitoring treatment response. It has been reported that a subset of schizophrenia cases are characterised by immunological abnormalities (Schwarz et al. 2014). In depression, the lack of clinical benefit from conventional anti-depressants is thought to be related to activation of the inflammatory system (Carvalho et al. 2013). Therefore, some patients with schizophrenia may benefit from an additional immunologic treatment. Indeed, randomised controlled trials (RCTs) of anti-inflammatory agents as adjunct to standard therapy have shown promising results in schizophrenia. Celecoxib has been reported to improve cognitive function in early stages of schizophrenia (Muller et al. 2002, 2005). Stratification of patients according to their immune phenotype has been proved useful in a recent RCT of infliximab (a TNF- α antagonist) in treatment-resistant depression. In this trial, no overall efficacy of infliximab was observed but it improved depressive symptoms in patients with higher levels of CRP at the start of the trial (Raison et al. 2013).

Immunological treatment could be helpful for specific types of symptoms. Minocycline, a centrally acting tetracyclic anti-inflammatory agent, has been reported to improve negative symptoms and cognitive function in schizophrenia (Chaudhry et al. 2012; Levkovitz et al. 2010). Dopaminergic drugs, which include all anti-psychotics currently in use, are effective

in controlling hallucinations and other positive symptoms, but negative symptoms and cognitive dysfunction rarely respond to these drugs. This may indicate fundamental differences in the mechanisms underlying different types of symptoms. The data on peripheral immune-to-brain communication on the whole lend support for a role of inflammation in the pathogenesis of these difficult-to-treat symptoms. In future, targeting these symptoms with immunological treatment could be a clinically fruitful strategy. Peripheral inflammatory makers could provide accessible biomarkers to study effects of experimental drugs and to measure treatment response. Efforts for the development of novel therapeutic agents could target different parts of the immune-to-brain communication pathways. For example, selectin-mediated adhesion of leukocytes to the BBB endothelial cells is a key event that contributes to neuroinflammation by facilitating transmigration of inflammatory cells into the brain tissue. Animal and human healthy volunteer studies have identified promising new selectin inhibitors, which might be clinically useful to prevent acute and chronic inflammation; reviewed (Nagy et al. 2012). Indeed, clinical trial of a selectin inhibitor has shown promising results in patients with asthma where it reduced airway recruitment of eosinophils (Romano 2005). Therefore, the potential for immunological treatment for psychiatric disorders is not limited to repurposing of existing drugs but includes development of novel agents.

Conclusions

Epidemiological and genetic studies strongly indicate a role of inflammation and immunity in schizophrenia. Schizophrenia is associated with alteration in important components of immune-to-brain communication pathways, which include increased serum levels of proinflammatory cytokines and markers of endothelial cell activation. Immune-to-brain communication could contribute to a number of important features of the schizophrenia syndrome including positive symptoms, negative symptoms, cognitive dysfunction, impaired neurodevelopment and accelerated neurodegeneration. A clearer understanding of the immunological aspects of schizophrenia could lead to new treatment, especially for the difficult-to-treat negative symptoms and cognitive dysfunction, which would require joint working between several disciplines such as immunobiology, clinical neuroscience and psychiatry. Persistent low-grade activation of the innate immune response as a result of developmental programming following early-life adversity might contribute to the high comorbidity between schizophrenia, depression, heart disease and type-two diabetes. Public health interventions aimed at controlling inflammation by promoting simple yet effective means, such as healthy diet and exercise, might have a huge beneficial effect at the population level.

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Abbreviations

BBB	Blood–brain barrier
HSV-2	Herpes simplex virus type-2
HSV-1	Herpes simplex virus type-1
CRP	C-reactive protein
TNF-α	Tumour necrosis factor alpha
IL-8	Interleukin 8
CNS	Central nervous system
NMDAR	<i>N</i> -methyl-D-aspartate receptor
GWAS	Genome-wide association studies
MHC	Major histocompatibility complex
ALSPAC	Avon longitudinal study of parents and children
PAMPs	Pathogen-associated molecular patterns
CVOs	Circumventricular organs
DSM-IV	Diagnostic and Statistical Manual Fourth Revision
ICD-10	International Classification of Disease Tenth Revision
STAT	Signal transducer and activator of transcription
CSF	Cerebrospinal fluid
NDST3	Bifunctional heparan sulphate <i>N</i> -deacetylase/ <i>N</i> -sulfotransferase 3
COX	Cyclooxygenase
11β-HSD2	11beta-hydroxysteroid dehydrogenase type 2
HPA	Hypothalamic-pituitary-adrenal

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Fig. 1.

Associations between serum IL-6 levels at age 9 years, and psychotic disorder, psychotic symptoms and depression at age 18 years in the ALSPAC cohort. Samples of psychotic disorder (a), psychotic symptoms (b) and depression (c) at age 18 years were divided by tertiles of interleukin 6 (IL-6) at age 9 years. Cut-off values for the top and bottom thirds of the distribution of IL-6 values in the total sample (cases and non-cases combined) were 1.08 and 0.57 pg/mL, respectively. Adapted with permission (Khandaker et al. 2014a)

Fig. 2. Peripheral immune system-to-brain communication pathways. CVO=circumventricular organ, PGE2=prostaglandins, NO=nitric oxide, NTS=nucleus tractus solitaries, MCP-1=monocyte chemoattractant protein-1, IL-6=interleukin-6, IL-1 β =interleukin-1 β , TNF α =tumor-necrosis factor alpha. Reprinted with permission (Capuron and Miller 2011)

Fig. 3.

IDO and the kynurenine pathway in inflammation-induced CNS pathology. Cytokine-induced activation of IDO in peripheral immune cells (e.g. macrophages and dendritic cells) or cells in the brain (e.g. microglia, astrocytes, and neurons) leads to the production of kynurenine, which is converted to kynurenic acid (KA) by the enzyme KAT-II in astrocytes, or quinolinic acid by the enzymes kynurenine-3-monooxygenase (KMO) and 3-hydroxy-anthranilic acid oxygenase (3 HAO) in microglia or infiltrating macrophages. Through blockade of the alpha 7 nicotinic acetylcholine receptor ($\alpha 7$ nAChR), KA can contribute to cognitive dysfunction. Quinolinic acid can contribute to excitotoxicity, oxidative stress, and

neurodegeneration. Reprinted by permission from Macmillan Publishers Ltd (Haroon et al. 2012)