Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment

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Word count: 4982 (excluding table, figure, text box and references)

Search strategy and selection criteria

For this Review, each contributing author selected references that s/he viewed as most relevant for their particular topic. The authors used systematic reviews and meta-analyses, where available, and also, expert reviews, classical articles, and recent articles that demonstrate cutting edge advances in the field. Dr Khandaker electronically searched the Medline-PubMed database from its inception until 22 September 2014 for studies of anti-inflammatory agents in schizophrenia and related psychosis. Search terms included Mesh terms: ("Schizophrenia"[Mesh] OR "Psychotic Disorders"[Mesh]) AND ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Anti-Inflammatory Agents"[Mesh] OR "Minocycline"[Mesh]). Selected studies were published in the English language, included cases of schizophrenia and related psychotic disorders, and were observational, clinical trial, case series or case report by design. Studies that did not report primary data, such as reviews or trial protocols were excluded. Studies of anti-inflammatory agents in disorders other than psychosis were also excluded. Electronic search identified 157 studies, of which 19 were selected after screening of title, abstract, and examination of full article content (see Table 1).

Summary

Complex interactions between the immune system and the brain may have important aetiological and therapeutic implications for neuropsychiatric brain disorders. A possible association between schizophrenia and the immune system was postulated over a century ago, and is supported by epidemiological and genetic studies pointing to links with infection and inflammation. Contrary to the traditional view that the brain is an immunologically privileged site shielded behind the blood-brain-barrier, recent studies have demonstrated complex interactions between the immune system, systemic inflammation and the brain that can lead to changes in mood, cognition, and behaviour. Here, we review some of the important areas of research regarding innate and adaptive immune response in schizophrenia and related psychotic disorders that, we think, will be of interest to psychiatric clinicians and researchers. We discuss potential mechanisms and therapeutic implications of these findings including studies of anti-inflammatory agents in schizophrenia, highlight areas for development, and offer testable hypothesis for future investigations.

Key words: Inflammation, infection, immunity, autoimmunity, inflammatory markers, C-reactive protein, CRP, Interleukin 6, IL-6, antibody, NMDA receptor, cytokine, lymphocyte, macrophage, microglia, microbiota, innate immunity, adaptive immunity, dopamine, glutamate, neurodevelopment, neurodegeneration, schizophrenia, psychotic disorders, treatment, anti-inflammatory agent, immuno-psychiatry

Introduction

Complex immune-brain interactions that affect neural development, survival, and function may have aetiological and therapeutic implications for a number of disorders of the central nervous system (CNS),[1-5] including psychiatric illness.[2] Multiple sclerosis, previously considered to be solely neurological, is increasingly recognised as secondary to immune dysfunctions.[3] Higher levels of the circulating proinflammatory cytokine interleukin (IL) 6 in childhood have been reported to be associated with increased risks of subsequent psychosis and depression in young adult life;[2] while elimination of auto-antibodies against neuronal cell surface proteins by immunotherapy has led to symptomatic improvement in some cases of first episode psychosis.[6] This review considers whether we are entering a new era of immuno-psychiatry that will change our understanding of the brain's maladies where manifestations include, but are rarely restricted to, mental symptoms. Accumulating evidence, of considerable breadth and depth, supports a role for immune system in the pathogenesis of depression and schizophrenia, which is consistent with the well-known clinical and aetiological (including genetic) overlap between these disorders. In this review, we highlight some of the important areas of research implicating the innate and adaptive immune response in the pathogenesis of schizophrenia and related psychotic disorders through effects on neurotransmitters, neurodevelopment, and degeneration. We discuss potential therapeutic implications of these findings as well as existing treatment studies of anti-inflammatory agents in schizophrenia.

The aim of this review is not only to summarise key evidence regarding the link between immune system and schizophrenia but also to identify gaps in knowledge, and to provide suggestions for improvement including testable hypothesis for future investigations. The aim

is also to give a holistic view, rather than an exhaustive review, of a landscape that may be of increasing relevance to people with schizophrenia and those who treat them.

The immune system and the brain share some fundamental characteristics. Both are highly integrated, complex systems with memory that develop through interactions with the external environment, able to distinguish between self and non-self, and respond adaptively.[7, 8] Historically, the brain has been considered as an immunologically privileged site shielded behind the blood-brain-barrier (BBB),[9] but immune components of the brain, such as microglia that constitute about 10% of the brain cell mass (equal to neurons), derive from the haematopoietic system beyond the CNS.[10] In response to systemic inflammation, microglia release cytokines which bind to specific receptors on neurons,[8] and affect neurotransmitters, synaptic plasticity, and cortisol levels, leading to changes in mood, cognition, and behaviour.[1, 5]

In the following section, we briefly summarise epidemiological and genetic studies that suggest a link between inflammation, immunity, and psychosis. Next, we review specific abnormalities of the immune system seen in schizophrenia and related psychosis. Finally, we discuss the potential role of these changes in pathogenesis and treatment of psychotic illness including existing studies of anti-inflammatory agents in schizophrenia.

The immune and infection link to psychosis

The immune system consists of a complex organisation of cells and mediators which has evolved largely to protect us from infection and malignancy.[8] It can be broadly conceptualised as consisting of an innate response, acting as a rapid, non-specific, first line of defence, and an adaptive response that is slower and antigen specific. The innate response is

mediated by neutrophils and macrophages that recognize and clear invading organisms. Inflammatory cytokines, secreted by macrophages and other cells, aid this process. The adaptive response involves immunological memory, and consists of T (thymic) lymphocytes that recognize antigen and cause lysis of infected cells, and B lymphocytes that secrete antibodies as part of the humoral response.[8]

Schizophrenia is a disabling disorder characterised by positive (delusions and hallucinations), negative (social withdrawal and apathy), and cognitive symptoms (poor executive function and memory). It affects around 1% of the population at some point in their life, with onset characteristically during the epoch of brain development that follows puberty and lasts until the end of the third decade.[11] Schizophrenia is multifactorial: it is associated with multiple genetic loci conferring risk as well as with developmental and postnatal risk factors.[12] A possible association between schizophrenia and the immune system was postulated more than a century ago (Box 1), and is supported by epidemiological studies pointing to links with infection and systemic inflammation.[13-16]

Text box 1: The link between immune system and psychosis has a long history

- 1870, Alexander Rosenbilum published a case series of psychotic states in febrile episodes of malarial infection.
- 1910, Julius Wagner-Jauregg was awarded the Nobel Prize for medical inoculation of malarial parasites as a treatment for syphilitic psychosis.
- 1926, Karl Menninger published a case series of post-influenzal psychosis in the American Journal of Psychiatry.
- 1929, Moritz Tramer reported an association between schizophrenia and winter or spring birth.
- 1937, Lehman Facius described auto antibodies against brain structures in CSF of patients with schizophrenia.
- 1988, Sarnoff Mednick and colleagues reported increased risk of schizophrenia in adult offspring of women pregnant during the 1957 influenza pandemic. Although subsequent meta-analysis of ecological studies did not find an association between pandemic influenza and schizophrenia, these findings spurred a great deal of research leading to some important discoveries regarding early-life infection and schizophrenia using serological data of prenatal maternal infection (see below).
- 1992, Ronald Smith proposed a macrophage-T-lymphocyte theory of schizophrenia.

Serologically confirmed prenatal maternal infection with any of several pathogens, including influenza, herpes simplex virus type 2, cytomegalovirus, and the intracellular parasite *Toxoplasma gondii,* clinically diagnosed non-specific viral and bacterial infections, elevated maternal CRP levels during pregnancy, all have been associated with schizophrenia in the adult offspring.[15, 17] Lower levels of acute phase proteins in neonates might increase the risk of adult psychosis by increasing susceptibility to infections in the early-life.[18] Acute phase proteins are released as part of the innate immune response, and consist of several mediators with different physiological functions.[8] Exposure to neurotropic virus in early childhood is associated with increased risk of sub-clinical psychotic experiences in adolescence.[19] The finding that the risk of schizophrenia is almost doubled in adult survivors of childhood CNS viral infection demonstrates that the period during which infection may increase the risk of future neuropsychiatric disorders is not confined to prenatal period.[14] Adult schizophrenia is also associated with increased rates of various infections, including those caused by *Toxoplasma gondii*.[20]

Childhood auto-immune conditions are associated with sub-clinical psychotic experiences in adolescents[21] and schizophrenia in adults.[22] The prevalence of auto-immune conditions is increased in people with schizophrenia and their unaffected first degree relatives.[23] Besides, risk of schizophrenia increases in a linear fashion with the number of severe infections in individuals with a previous history of auto-immune disease.[22] Thus, the links between schizophrenia and a range of infections and autoimmune conditions suggest a common underlying pathway, most likely involving the inflammatory immune response. In addition to its own effects on the brain, inflammation is thought to increase the permeability of the BBB and to facilitate penetration of immune components into the brain.[24]

Support for an immune-mediated aetiology in schizophrenia comes from genome wide association studies (GWAS), reporting significant associations between schizophrenia and markers close to the major histocompatibility complex (MHC) region on chromosome six.[25, 26] This region contains many immune-related genes, including those involved in antigen presentation and inflammatory mediators. A recent GWAS has identified 108 genetic loci (83 previously undetected) associated with schizophrenia: broadly, these represent genes expressed in the brain, and immune cells involved in adaptive immunity (CD19 and CD 20 B-lymphocytes) as well as the MHC.[27] Moreover, associations for the immune related genes remained significant after the MHC region was excluded suggesting these findings were not driven by the strong association at the MHC. Another GWAS found significant genetic overlap involving the MHC region between schizophrenia and multiple sclerosis, a condition characterised by immune dysfunction.[28]

The immune system in the pathogenesis of schizophrenia and related psychosis

The abnormalities of the immune system seen in schizophrenia and related psychosis are diverse and overlapping, involving a number of immune components. Here, we first consider the components of the innate immune response, including cytokines and microglia; second, we describe components of the adaptive immune response, including lymphocyte subsets and anti-neuronal cell surface antibodies. We do not cover autoimmunity involving various brain regions, thyroid, thymus, and antibodies to dietary antigens such as gliadin and casein. Key questions pertaining to the entire field have been summarised in box 2.

Heterogeneity between studies may point towards uncertainty or may reflect heterogeneity in the causes and pathogenesis of the schizophrenia syndrome. Changing the focus of research from syndrome to symptom or constellation of symptoms would be helpful to fully

understand the role of inflammation and immunity in neuropsychiatric disorders. Many current studies have inadequately accounted for confounding factors such as body mass and smoking. More have focused on blood rather than CNS immune markers while few have examined relationships between immune markers and either symptoms or cognition in schizophrenia. Rarer still are longitudinal studies of immune markers and schizophrenia that comment on cause and effect between immunity and psychiatric syndrome. Relationships between immune markers, stress, and cortisol in schizophrenia are also poorly understood. We have highlighted these issues along with suggestions for development in relevant sections. Despite these lacunae in the literature, current knowledge is consistent with a role for the immune system in the pathophysiology of schizophrenia and related psychotic disorders.

Text box 2: A few key research questions regarding immunological aspects of schizophrenia, related psychosis and other mental illness

1. Is elevated serum concentration of proinflammatory cytokines a cause or consequence of schizophrenia?
2. Could systemic inflammatory markers be used to identify prodromal cases of schizophrenia, to predict disease progression, response to antipsychotic treatment and recovery?
3. Could inflammatory processes explain cognitive deficits, progressive cognitive decline and brain volume loss in some cases of schizophrenia?
4. Could inflammatory processes explain the association between early-life adversity and risk of psychiatric disorders in adult life?
5. Does activation of microglia correspond with clinical severity of schizophrenia and response to antipsychotic treatment?
6. What is the role of neuronal cell surface auto-antibodies in schizophrenia and other psychiatric disorders?
7. What is the prevalence of neuronal cell surface antibodies in schizophrenia, other psychiatric disorders and healthy controls?
8. Does the prevalence of neuronal cell surface antibodies depend on the phase of the illness? Are there clinical signs that predict a positive test?
9. Are there other peripheral biomarkers associated with neuronal cell surface antibodies which could form therapeutic targets?
10. What is the relationship between intestinal microbiota and inflammatory, behavioural, cognitive and neurochemical phenotypes seen in schizophrenia and other psychiatric disorders?
11. What is the response of antibody associated psychosis to immunosuppression or antipsychotic treatment?
12. Does controlling inflammation lead to clinical improvement in psychosis and other mental illness?
13. Is stratification of patients based on their immune phenotype helpful with regards to predicting response to conventional and/or novel treatments?

Inflammatory cytokines

Meta-analyses of many cross-sectional studies show that schizophrenia is associated with disruption of the cytokine milieu and the propensity for the production of proinflammatory cytokines.[16, 29, 30] Longitudinal studies of inflammatory markers and subsequent psychotic disorders are scarce. Recent findings from the ALSPAC birth cohort suggest that higher serum levels of the proinflammatory cytokine IL-6 at age 9 years confers a two-fold risk of developing psychotic disorder at age 18 years.[2] The study also reports a robust, dose-response relationship between higher IL-6 levels in childhood and subsequent risk of sub-clinical psychotic experiences in young adulthood, which persists after taking into account a number of potential confounders including gender, body mass, and psychological and behavioural problems preceding the measurement of childhood IL-6.[2] No associations between serum CRP levels at baseline and future psychiatric disorders were observed, but another longitudinal study reported increased risk of late or very late onset schizophrenia for higher serum CRP levels at baseline.[31] Further longitudinal studies are needed to confirm whether the increase in serum levels of proinflammatory cytokines in schizophrenia and related psychosis is the cause or consequence of illness, though these findings suggest they point towards causal mechanisms.

Antipsychotic naïve first episode psychosis[30] and acute psychotic relapse[16] are also associated with increased serum levels of IL-6 and other proinflammatory cytokines, such as tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and decreased serum levels of anti-inflammatory cytokine IL-10, which are normalised after remission of symptoms with antipsychotic treatment.[16] Reduced IL-2 production in vitro by T cells collected from schizophrenia patients has been reported,[32] but acute psychosis is associated with no significant changes in serum IL-2 levels.[16] There is an increase in levels of soluble IL-2

receptor (sIL-2R),[16, 30] which is likely to be a compensatory mechanism inhibiting IL-2 production. Thus, the data are consistent with an increase in proinflammatory cytokines in acute psychosis. However, a few studies have adjusted for important immune-modulatory factors such as body mass or smoking,[16] or examined cytokines in CSF where increase in IL-6[33, 34] has been reported in schizophrenia. One study has reported increased serum IL-6 concentration in people with at-risk mental state for psychosis compared with healthy controls.[35] Some data suggest that serum cytokine concentrations including IL-6 are associated with illness severity, duration, and antipsychotic therapy,[16, 36, 37] but we know little regarding the associations between stress, cortisol and cytokine levels in different stages of schizophrenia. Therefore, more studies are required to understand the relationships between cytokine levels, disease prodrome, progression and treatment response. Longitudinal studies of first episode psychosis, individuals at clinical high risk for developing psychosis as well as those with treatment refractory illness would be useful to examine these issues. Rather than merely demonstrating group differences in cytokine serum or CSF levels, future studies should examine associations between cytokines, cognitive and social functioning, comorbid physical illness, and structural and functional brain indices in people with psychosis and healthy controls.

In rodents studies have demonstrated physiological roles of cytokines in memory and learning, including long-term potentiation, synaptic plasticity and neurogenesis (for review see).[38] Recently, 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.[39] Whether cytokine-mediated inflammatory processes underlie cognitive dysfunction in schizophrenia, an integral part of the syndrome, is an important hypothesis that requires investigation.

Longitudinal associations between IL-6 and both psychosis and depression may indicate a trans-diagnostic effect.[2] A longitudinal association between serum C-reactive protein, a marker of systemic inflammation, and subsequent symptoms of post-traumatic stress disorder has been reported.[40] Thus, understanding the early-life bio-psycho-social determinants of cytokine serum concentrations would be crucial in order to elucidate whether increased levels of cytokines could explain the association between early-life adversity and the risk of various psychiatric illnesses in adulthood.[41]

Studies using mouse models have demonstrated how peripheral cytokines, such as IL-6, can affect the brain (figure 1) (for reviews see).[1, 4] Circulating IL-6 binds to receptors on the vagus nerve, and the signal reaches hypothalamic brain nuclei via brainstem by retrograde axonal transport. Once within the CNS, the cytokine signal is amplified, which activates microglia, leading to the secretion of proinflammatory cytokines, chemokines, and proteases within the brain.[1] These messengers activate indoleamine 2, 3 dioxygenase, an enzyme that metabolizes tryptophan along the kynurenine pathway, leading to increased levels of kynurenic acid and its metabolite quinolonic acid, both of which are involved in glutamatergic neurotransmission.[42] Cytokines also increase oxidative stress by raising the concentration of toxic nitric oxide, and activate the hypothalamic-pituitary-adrenal axis leading to the release of cortisol.[1, 5] 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 other psychiatric disorders. Indeed non-specific peripheral immune activation caused by injection of lipopolysaccharide in healthy volunteers increases serum IL-6 levels as well as inducing low mood, anxiety and reduced cognitive performance.[43] Furthermore, cytokines have significant effects on microglia that, in turn, are crucial for the maintenance of effective neuronal and synaptic health.[10]

--- Insert Figure 1 here ---

Figure 1: How peripheral immune signals reach the brain to contribute to neuropsychiatric symptoms

Microglia

Microglia, the resident immune cells of the brain, constitute 10% of all non-neuronal or glial cells which, in turn, constitute 90% of the adult human brain.[10] Similar to macrophages, these cells originate from myeloid precursor cells and are thought to migrate into the CNS during the early neonatal period.[44] Within the normal brain, microglia retain a down-regulated phenotype ('resting state'),[45] yet continue to survey and respond to the surrounding brain micro-environment (see **video** – http://www.nature.com/news/microglia-the-constant-gardeners-1.10732). If the brain is subject to injury, inflammation, or in response to systemic inflammation, microglia develop an 'activated' phenotype characterised by morphological changes, up-regulation of surface receptors, the potential to activate T cells, and the release of various inflammatory mediators including cytokines.[46]

Neuroinflammation is characterised by the activation of microglia cells, which show an increase in the expression of the peripheral benzodiazepine receptor. Neuroimaging studies using positron emission tomography and a peripheral benzodiazepine receptor ligand provide evidence for neuroinflammation in recent onset schizophrenia,[47] and in acute exacerbations of schizophrenia.[48] They indicate increased binding of this ligand in the entire grey matter and the hippocampus, suggesting that neuroinflammation might contribute to grey matter volume loss and cognitive deterioration in schizophrenia.[47, 48] However, such studies are limited in

number and the existing studies have included small numbers of people with schizophrenia and healthy controls. An alternative explanation for increased binding of the benzodiazepine receptor ligand could be its affinity for activated astrocytes, which are seen in schizophrenia but are unrelated to neuroinflammation.[48] Many patients with schizophrenia are treated with benzodiazepines, which can also influence binding of this ligand. Thus, there is a need for identifying reliable markers of microglial activation that can be used for *in vivo* imaging or measured in blood in order to investigate whether microglial activation corresponds with clinical severity and treatment response.

Previously activated microglia may respond more strongly to a new stimulus.[49] Microglia are likely to retain an immune memory of the neuropathology, which, in turn, is associated with heightened responsiveness to new systemic inflammation.[46] Thus, early developmental insults such as childhood CNS or severe systemic infection may have a priming effect on microglia,[49] increasing microglial activation and psychosis risk following subsequent infections. Whether the association between early-life CNS infection and adult schizophrenia[14] could be explained by changes in microglia can be tested using longitudinal birth cohorts. Induced pluripotent stem cell technology has been successfully used to create neurons by reprogramming human fibroblast cells: neurons derived from schizophrenia patients have diminished neuronal connectivity, decreased neurite number and glutamate receptor expression compared with neurons derived from healthy controls.[50] It remains to be seen whether this technology can be utilized to study non-neuronal brain cells such as microglia.

Anti-neuronal cell surface auto-antibodies

A possible role of brain reactive auto-antibodies in the aetiology of schizophrenia has been discussed since the early twentieth century.[51] Auto-antibodies against components of various brain regions, cellular proteins, and dietary antigens such as gliadin and casein in serum and cerebrospinal fluid have been demonstrated in schizophrenia and related psychosis (for reviews see).[52, 53] More recently, antibodies against neuronal cell surface targets, N-methyl-D-aspartate receptor (NMDAR) and components of the voltage-gated potassium channel complex, have been reported in some patients with first episode psychosis and DSM-IV schizophrenia.[6, 54-57] Some of these antibodies have been typically associated with anti-NMDAR encephalitis, a progressive illness that often starts with psychotic symptoms and/or seizures, and subsequently manifests other neurological and autonomic features.[58] When present in patients with encephalitis, the antibodies are considered pathogenic, and removal of the antibodies is associated with clinical improvement. Early identification of the antibodies and treatment with immunotherapy has been reported to predict good clinical outcome.[59] It remains to be tested whether this is also the case for patients with antibodies and a purely psychiatric presentation, although there are a few case descriptions to support this.[6] Randomised controlled trials (RCT) of immuno-therapy as an adjunct of standard antipsychotic treatment for antibody-associated cases of psychosis are required to examine this question.

It is possible that NMDAR antibody seropositivity in some people with psychosis is in fact undiagnosed anti-NMDAR encephalitis. However, it has been argued that diagnostic misclassification is unlikely to be the sole explanation for this because almost none of the NMDAR antibody seropositive cases of psychosis has IgG class NMDAR antibodies against the NR1 subunit alone (one of the subunits of the NMDAR antibody).[57, 60] An association

between NMDAR antibody and schizophrenia is biologically plausible. In healthy volunteers, NMDAR blockade with ketamine produced psychotic symptoms.[61] Furthermore, a recent study has shown that *de novo* mutations, in the form of chromosomal copy number changes, affect glutamatergic post-synaptic proteins that form part of the NMDAR.[62]

NMDAR antibody seropositivity is not limited to patients with schizophrenia alone. Patients with psychiatric disorders such as schizophrenia, depression, and bipolar disorder are collectively about three times more likely to have elevated NMDAR antibody titers compared with controls based on high-specificity (but not low-specificity) seropositivity thresholds.[60] This underscores the need for further cross-sectional and longitudinal studies of psychiatric cases and healthy controls employing standardized assay methods and seropositivity threshold definitions. Preclinical studies are also needed to elucidate pathogenic mechanisms of these antibodies in psychosis and other mental illness.

T lymphocytes

T cells are thymus derived lymphocytes which, very simply, can be considered as either 'CD8 expressing' cytotoxic cells or 'CD4 expressing' helper cells, and may have both proinflammatory and anti-inflammatory roles. Recent evidence suggests a role for T cells in the aetiology of schizophrenia. Acute psychosis is associated with the activated phenotype of lymphocytes within the CNS compared with controls.[63] In post mortem studies, immunohistology has allowed direct visualisation of increased T cell as well as B cell numbers within the hippocampus in patients with schizophrenia.[64] These changes were particularly evident in those with predominantly negative, compared with positive symptoms.[65] However, there are inconsistencies between studies as to whether schizophrenia is associated with increased or decreased numbers of lymphocytes in the peripheral

circulation. A recent meta-analysis has reported increased numbers of cells positive for CD56 (a marker of natural killer cells and activated T cells), and a higher CD4/CD8 T cell ratio in schizophrenia.[66] It also highlighted important limitations of the existing data. Many studies do not control for immune-mediating variables, such as smoking, body mass, stress-associated cortisol levels, and medication. Findings from individual studies are difficult to compare because they report percentages rather than cell numbers.

Well-controlled studies reporting absolute cell numbers are required to fully understand any associations between T cells and schizophrenia. Since schizophrenia is a heterogeneous condition, one might speculate that different T cell subtypes are associated with differing symptomatology. Thus studies of T cells after stratification of cases by symptom profile may be more informative. In order to fully understand the role of T cells in schizophrenia, an understanding of the function of these cells is also required. Future studies should assess the cytokine profile of these cells, their activation status, and gene expression profile.

How might immune dysregulation lead to the manifestation of schizophrenia?

Effects on neurotransmitters

Studies in animal models suggest an association between prenatal infection/ inflammation and disturbance of neurotransmitter systems (glutamate, dopamine and GABA) in the offspring,[67] but little is known about the direct effects of the inflammatory immune response on neurotransmitter systems in humans. NMDAR antagonism and glutamatergic hypofunction have long been proposed as underlying mechanisms for psychotic symptoms and cognitive dysfunction in schizophrenia.[61, 68] There is evidence that proinflammatory cytokines increase the concentration of kynurenic acid, which is a metabolite of tryptophan and the only naturally occurring NMDAR antagonist in the human CNS (figure 2).[69, 70]

--- Insert Figure 2 here ---

Figure 2: Possible mechanisms of immune-mediated aetiology of psychosis

Studies of the cyclooxygenase (COX) pathway may lead to a better understanding of the role of kynurenic acid in psychosis. COX-1 inhibition increases levels of kynurenic acid while COX-2 inhibition decreases them.[71] This might explain some of the side effects of COX-1 inhibitors, such as psychotic symptoms and cognitive dysfunction. On the other hand, Celecoxib (a selective COX-2 inhibitor) has been reported to improve clinical symptoms in schizophrenia.[72, 73] Thus, systematic evaluation of the neuropsychiatric side-effects of COX-1 and COX-2 inhibitors from existing RCT data would be useful.

The relationship between neurotransmitters and immune mediators may be reciprocal with a few publications reporting immunoregulatory functions for dopamine; for review see.[74] T cells express dopamine receptors, the stimulation of which promotes up-regulation of adhesion molecules and cytokine production.[75, 76] Increased expression of the dopamine D3 receptor and increased synthesis of the pro-inflammatory cytokine IFN-γ by lymphocytes have been reported in un-medicated patients with schizophrenia.[77] The opposite has been observed in Parkinson's disease,[78] a condition characterised by CNS dopamine depletion. Further studies are required to understand the effects of inflammation on neurotransmission and *vice versa* in healthy people and those with psychiatric disorders.

Effects on neurodegeneration

Progressive clinical deterioration, cognitive decline, loss of cortical grey matter along with histopathological evidence of neuronal atrophy and reductions in the number of neuronal synapse and dendrites, all suggest a neurodegenerative process is active in schizophrenia beyond that seen in healthy subjects.[79-81] Activated microglia are increasingly being recognised as an important component in the pathogenesis of other degenerative brain conditions, such as Alzheimer's disease, where they appear to have wide ranging effects.[46] Is this also the case in schizophrenia? Microglial activation interferes with neuronal survival by increasing oxidative stress and decreasing neurotrophic support.[5] Schizophrenia is associated with changes in serum, plasma, and red blood cell markers of oxidative stress.[82] Recently a population-based longitudinal study has reported a strong association between delirium and subsequent dementia and cognitive decline in older adults, which is not mediated by classical neuropathologies associated with dementia.[83] It is possible systemic inflammation, a common cause of delirium, underlies this association. Indeed severe systemic illness in the elderly has been reported to be associated with subsequent cognitive decline and functional deterioration.[84, 85] In the future, studies should examine whether inflammatory processes could explain progressive cognitive decline and brain volume loss in some cases of schizophrenia.

Effects on neurodevelopment

Interference with brain development from early-life infection/inflammation is consistent with a neurodevelopmental view of schizophrenia.[86, 87] Given the association of adult schizophrenia with a variety of early-life infections, (for reviews see)[14, 15] it is likely that a common pathway, the proinflammatory immune response, is involved. This notion is supported by animal model studies. 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.[88] Some of these phenotypes, such as deficits in sensory gating and abnormal latent inhibition, are reversible by treatment with clozapine.[89] Since infections are widespread in the general population, interactions with genetic or other factors are likely. Indeed an additive effect of family history of psychosis and prenatal infection in the causation of schizophrenia has been reported in a Finnish cohort.[90] In the future studies should examine gene-infection interaction, and whether there is a 'sensitive period' during development when exposure to infection is more harmful.

GWAS and epidemiological studies indicate some overlap of genetic susceptibility between schizophrenia and serious infection.[26, 91] Childhood infection may have a priming effect on microglia (discussed above). Thus, it is possible that early-life infection, by affecting gene expression or in the presence of pre-existing genetic liability, can lead to a distinct or pathological immune response. This may, in turn, lead to CNS alterations making these individuals susceptible to developing psychotic illness later in life. Studies with detailed phenotypic characterisation of early development as well as immune and genetic data are necessary to test this hypothesis.

The human microbiome and the gut-brain axis: an emerging area of interest

The intestinal microbiota consists of a vast bacterial community that resides primarily in the lower gut and lives in a symbiotic relationship with the host. A bidirectional neurohumoral communication system, known as the gut-brain axis, integrates the host gut and brain activities. The intestinal microbiota is thought to influence brain development and function via this axis, and thus, may be relevant for neuropsychiatric disorders.[92, 93] Bacterial colonization of germ-free mice increases metabolism of tryptophan leading to over two-fold

increase in concentrations of 5-hydroxy tryptophan and its metabolites including kynurenic acid (relevant for psychosis; see above). An animal study suggests that manipulation of the intestinal microbiota can alter host cognitive function and behaviour.[94]

The vagus nerve, which plays a central role in relaying the systemic cytokine signal to the brain (discussed above), may be also important for gut-brain communication. In mice, anxiolytic and antidepressant effects of feeding a specific strain of *Lactobacillus* can no longer be seen after vagotomy.[95] There is evidence of greater intestinal inflammation in individuals with schizophrenia compared with controls, and similarly, in people with first episode psychosis who have not taken antipsychotics compared with those receiving antipsychotics.[96] Studies in animals[97] and humans[98] suggest that manipulation of the gut microbial composition influences systemic cytokine levels. Thus, it is possible that intestinal microbiota affect the brain and behaviour by influencing systemic cytokine levels in schizophrenia. This is an important hypothesis that warrants examination. In the future, studies should examine the relationships between intestinal microbiota and behavioural, cognitive and neurochemical phenotypes in psychiatric disorders and healthy controls.

Therapeutic implications of an immunological and inflammatory understanding of schizophrenia and other mental disorders

Current understanding of the association between the immune system and risk of psychotic disorders hold promise for novel approaches for detection, treatment and prevention. These may include developing or 'repurposing' drugs to target inflammatory pathways, immunotherapy for antibody-associated cases of psychosis and other mental illness, and stratification of patients by their immune phenotype in order to inform treatment decision and to measure treatment response. Indeed, a recent molecular study has reported two distinct

subgroups of schizophrenia patients characterised by predominant abnormalities in either immune molecules or growth factors and hormones.[99]

RCTs of anti-inflammatory agents as adjunct to standard therapy have shown promising results in schizophrenia (table 1), although such trials are few and have often involved small samples.[100] Celecoxib has been reported to improve cognitive function in early stages of schizophrenia,[101, 102] but the use of COX-2 inhibitors is problematic as they can increase risk of heart disease.[103] Recently, Minocycline, a centrally acting tetracyclic anti-inflammatory agent, has been reported to improve negative symptoms and cognitive function in schizophrenia.[104, 105] Large multi-centre trials are required, with stratification of patients by their immune phenotype. This approach proved useful in a recent RCT of infliximab (a TNF-α antagonist) in treatment-resistant depression, in which no overall efficacy was observed but it improved depressive symptoms in patients with high concentrations of inflammatory markers at the start of the trial.[106] It has been suggested that lack of clinical benefit from conventional antidepressants may be related to activation of the inflammatory system.[107] In the future, RCTs should focus on specific patient groups characterised by, for example, resistance to conventional antipsychotics, presence of a defined pattern of immune activation, such as a predominantly proinflammatory molecular signature, or symptom profile, such as predominant negative symptoms or cognitive dysfunction.

Identification of specific inflammatory pathways for neuropsychiatric symptoms would provide novel targets for therapeutic intervention.[108] Animal studies suggest a mechanistic role of quinolonic acid, an NMDAR agonist, for inflammation-induced depression.[42] Indeed RCTs of NMDAR antagonists, ketamine and compound AZD6765, have shown promising results for treatment resistant depression.[109-111] Whilst safety and tolerability of ketamine may

limit its applicability in clinical setting, these findings provide further support for a role of inflammation in major mental illness.

New therapeutics for immunologically stratified psychosis might be based on molecules and targets that are already well known in other therapeutic areas, allowing 'repurposing' of existing anti-inflammatory agents.[112] Collaboration between industry and academia would be important to realise the potential of immune modulatory agents for the treatment of major mental illness. In the future studies should assess the prophylactic potential of immunological agents in individuals at high risk of developing psychosis. Longitudinal associations between higher levels of IL-6 and subsequent risks of psychosis,[2] depression,[2] heart disease,[113] and type-two diabetes[114] suggest that controlling inflammation might reduce the risk of a number of chronic adult diseases, and thus, have a huge beneficial effect at the population level.

Conclusion

Inflammation and immune dysfunction might contribute to cognitive, negative and positive symptoms in schizophrenia. We have highlighted several hypotheses and potential areas of interest for future research regarding the immunological aspects of schizophrenia. Addressing these issues would contribute to understanding disease mechanism and the development of effective new interventions, but requires integrated working between several disciplines. While animal model studies have much to offer in terms of understanding specific biological systems, these findings need to be confirmed in human subjects. This highlights the scope for translational research in schizophrenia over the coming years encompassing immune, genetic, microbiological, and other biomarkers.

Contributors' statement

Golam Khandaker designed the review, carried out literature search including data presented in Table 1, adapted Figure 1, drafted Figure 2, and wrote the first draft. Lesley cousins revised the initial manuscript, carried out literature search, adapted Figure 1, and drafted Figure 2. Julia Deakin contributed to the section on anti-neuronal cell surface antibodies, carried out literature search relevant to the section, provided links for the videos, and revised the manuscript. Belinda Lennox contributed to the section on anti-neuronal cell surface antibodies, carried out literature search relevant to the section, and revised the manuscript. Robert Yolken contributed to the section on human microbiome and the gut-brain axis, carried out literature search relevant to the section, and revised the manuscript. Peter Jones contributed to designing the review, carried out literature search, and revised the manuscript including the Figures and Table 1. Golam Khandaker and Lesley Cousins have contributed equally to this paper.

Declaration of interests

The authors have no conflicts of interest to disclose regarding the content of this study. 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. Peter Jones received an honorarium that he donated to his department from Roche for taking part in an advisory board to advise on education about schizophrenia to psychiatrists.

Acknowledgements

The authors thank Professor Ed Bullmore (University of Cambridge, UK), Dr Alasdair Coles (Addenbrooke's hospital, Cambridge, UK), Dr Claire Dibben (Norfolk and Suffolk NHS

Foundation Trust, UK), and Dr Nicola Kalk (Imperial College London, UK) for their helpful comments on a previous version of this manuscript. The work was supported by a doctoral clinical research training fellowship grant from the Wellcome Trust to Golam Khandaker (094790/Z/10/Z; 2010-‘13), grants from the Stanley Medical Research Institute and the National Institutes of Mental Health (grant# MH-94268) to Robert Yolken, and grants from the Wellcome Trust (095844/Z/11/Z & 088869/Z/09/Z), and the NIHR (RP-PG-0606-1335) to Peter Jones.

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Figure 1: How peripheral immune signals reach the brain to contribute to neuropsychiatric symptoms

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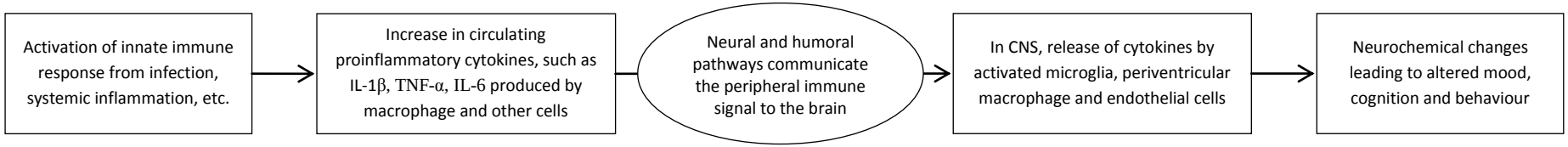

Figure 1 will appear here

Please see attached hand drawn Figure 1, which will be created as an artwork with the help of an illustrator from the Journal.

Figure 2: Possible mechanisms of immune-mediated aetiology of psychosis

Figure 2 will appear here

Please see attached slide

Table 1: Anti-inflammatory agents in the treatment of schizophrenia and related psychosis

Study	Design and setting	Sample and source	Outcome and exposure measurement	Main findings	Strengths and limitations
Longitudinal study of treatment with Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and schizophrenia risk					
Laan *et al* 2007[115]	Nested case control design; compares incidence of schizophrenia in users and non-users of prescribed NSAIDs	82 schizophrenia and 359 controls from routine register	Outcome: new prescription for antipsychotics for ≥3 months as proxy for incident schizophrenia. Exposure: prescription for NSAIDs in the preceding four years.	No association overall, but after adjusting for age and prescription frequency, protective effect of NSAID use in men, OR for schizophrenia 0.41 (95% CI 0.17- 0.97)	Strengths: large population-based study Limitations: no direct assessment for schizophrenia or NSAID use; short follow-up; included young individuals
Stolk *et al* 2007[116]	Nested case control design; compares exacerbation of schizophrenia in users and non-users of prescribed NSAIDs	Exacerbation of psychotic symptoms (case event; n=1443) compared with non-exacerbation (control event; n=1443) in ICD-9 schizophrenia cases receiving antipsychotic therapy +/- NSAIDs from routine register	Case event: change of antipsychotic, increase in dose, use of combination or parenteral treatment Exposure: NSAIDs use 90 days prior to case event	No association overall; Cox-2 inhibitors led to exacerbation of symptoms, OR=2.56 (95% CI 1.35-4.87)	Strengths: large population-based study Limitation: no direct assessment for exacerbation of symptoms, prescription as proxy for NSAIDs use
Randomised Controlled Trial (RCT) of NSAIDs as adjunct of antipsychotic treatment in schizophrenia					
Laan *et al* 2010[117]	Double blind RCT of antipsychotic plus Aspirin (1 gram daily) or placebo Trial duration: 90 days Analysis: Intention to treat (ITT)	37 Aspirin vs. 33 placebo Inclusion criteria: DSM-IV schizophrenia, aged 18- 55 years, illness duration <10 years. Exclusion criteria: contraindication to or chronic use of NSAIDs, stomach illness, corticosteroid use, pregnancy	Outcome measures: PANSS total, positive, negative, and general psychopathology sub-scores, cognitive tests, immunologic markers	In the Aspirin group, statistically significant improvement in total and positive PANSS score (Cohen's *d* 0.47 and 0.39, respectively)	Strengths: double blind RCT, included both in and outpatient cases, and various clinical outcome measures Limitations: Small sample, short duration, high attrition
Baheti *et al* 2013[118]	Open labelled trial of Celecoxib (400mgs daily). Trial duration: 42 days Analysis: study completers	31 Celecoxib + Olanzapine vs. 31 Olanzapine only Inclusion criteria: ICD-10 schizophrenia with acute relapse Exclusion criteria: comorbid physical or other psychiatric illness, treatment-resistant schizophrenia, PANSS score	Outcome measures: PANSS total, positive, negative, and general psychopathology sub-scores	Significantly lower positive, negative and general psychopathology scores at 3 and 6 weeks in the Celecoxib, compared with Olanzapine only group.	Strength: objective outcome measure Limitations: small sample, short duration, no placebo or blinding of assessment

		< 80 or > 120.			
Muller *et al* 2002[101]† Muller *et al* 2004[119]† Muller *et al* 2005[102]†	Double blind RCT of Risperidone (2-6mgs daily) plus Celecoxib (400mgs daily) or placebo Trial duration: 35 days Analysis: ITT	25 Celecoxib vs. 25 placebo Inclusion criteria: DSM-IV schizophrenia, aged 18- 65 years	Outcome measures: PANSS scores; cognitive factor of the PANSS scale; serum immunologic measures	Total PANSS score lower in the Celecoxib arm; no difference on cognitive measures; lower baseline TNF-R1 predicted better response to Celecoxib	Strengths: double blind RCT, use of plasma drug levels for monitoring Limitations: Small sample, and short duration
Rapaport *et al* 2005[120]‡ Bresee *et al* 2006[121]‡	Double blind RCT of Risperidone/ Olanzapine plus Celecoxib (400mgs daily) or placebo Trial duration: 56 days	18 Celecoxib vs. 17 placebo Inclusion criteria: stable outpatient cases of DSM-IV schizophrenia. Exclusion criteria: use of other antipsychotics, other criteria similar to Laan *et al* 2010.	Outcome measures: PANSS, SANS, CGI, CDS, HAM-A scales; serum cytokine levels	No difference between groups on any measures	Strengths: RCT, used various outcome measures Limitations: only included stable cases, analysed trial completers, small sample, and short duration
Akhondzadeh *et al* 2007[72]	Double blind RCT of Risperidone (6mgs daily) plus Celecoxib (400mgs daily) or placebo Trial duration: 56 weeks Analysis: ITT	30 Celecoxib vs. 30 placebo Inclusion criteria: inpatient DSM-IV schizophrenia, aged 19-44 years. Exclusion criteria: organic disease or substance dependence, other psychotic illness, peptic ulcer, GI bleeding, pregnancy or lactation	Outcomes: PANSS scores	Statistically significant improvement in PANSS total, positive, and general scores in the Celecoxib arm	Strengths: double blind RCT, low drop out Limitations: small sample, short duration of trial
Muller *et al* 2010[73]	Double blind RCT of Amisulpride plus Celecoxib (400mgs daily) or placebo Trial duration: 42 days	25 Celecoxib vs. 25 placebo Inclusion criteria: inpatient cases of DSM-IV schizophrenia or schizophreniform disorder, aged 19-44 years, illness duration <2 years	Outcomes: PANSS and CGI	Statistically significant global clinical improvement in the Celecoxib arm using ITT analysis	Strength: double blind RCT Limitations: small sample, short duration, and high attrition
RCT of Minocycline as an adjunct of antipsychotic treatment in schizophrenia					
Levkovitz *et al* 2010[105]	Double blind RCT of antipsychotic plus Minocycline (200mgs daily) or placebo Trial duration: 26 weeks	36 Minocycline vs. 18 placebo Inclusion criteria: DSM-IV schizophrenia, aged 18- 35 years, illness duration <5 years. Exclusion criteria: contraindication to or use of Minocycline in last 6 months, compulsory hospitalization, others similar to Akhondzadeh *et al*	Outcomes: SANS, PANSS, CGI, CDS, ITAQ, CANTAB	In the minocycline arm, statistically significant improvement in negative symptoms, executive function, clinical status, and general functioning starting from week 14.	Strength: double blind RCT, use of clinical, cognitive, and functional outcome measures, long duration Limitation: small sample, high attrition

Chaudhry *et al* 2012[104]	Double blind RCT of standard antipsychotic treatment plus Minocycline (200mgs daily) or placebo Trial duration: 52 weeks Analysis: ITT	71 Minocycline vs. 73 placebo Inclusion criteria: DSM-IV in or outpatient cases of schizophrenia, and related psychosis, aged 18–65 years, diagnosis <5 years, stable on medication. Exclusion criteria: similar to Levkovitz *et al*	Outcomes: PANSS, CGI, GAF, CANTAB	In the Minocycline arm, statistically significant improvement in negative symptoms	Strength: double blind RCT, use of clinical, cognitive, and functional outcome measures, long trial duration Limitation: small sample, high attrition
Case reports of Minocycline and Aspirin as an adjunct of antipsychotic treatment in schizophrenia					
Webb *et al* 2013[122]	Aspirin (650mgs daily) plus Aripiprazole 20mgs daily	A 13 year old Hispanic male with schizophrenia	Outcome: PANSS score and clinical impression	Hallucinations, speed and social communication improved in a few days.	Strength: early-onset case Limitation: only one case, no control group
Jhamnani *et al* 2013[123]	Minocycline (10mgs daily) plus atypical antipsychotic for 2-3 months	Two cases of ICD-10 schizophrenia with persistent negative symptoms	Outcome: SANS and SAPS	Improvement in negative symptoms and serum CRP levels compared with baseline	Strength: use of CRP and psychopathology measures Limitation: no control group
Miyaoko *et al* 2008[124]	Minocycline (200-450mgs daily) plus atypical antipsychotic for 4 weeks	22 in or outpatient cases of DSM-IV schizophrenia not responding to current treatment	Outcome: PANSS	Significant decrease in positive and negative symptoms after 4-8 weeks	Strength: large case series Limitation: no control group
Miyaoko *et al* 2007[125]	Minocycline (150mgs daily) plus Haloperidol/ Risperidone for 10-11 weeks	Two male DSM-IV schizophrenia cases with prominent catatonic features and concurrent infection	Outcome: clinical impression	Clinical improvement in both cases	Limitation: only two cases, no control group
Chaves *et al* 2010[126]	Minocycline (200mgs daily) plus Haloperidol for 8 weeks	One, 19 year old man with a five year history of treatment resistant DSM-IV schizophrenia	Outcome: PANSS score, and brain scan	Improvement in positive symptoms, and decrease in hyperperfusion of posterior cingulate gyrus	Strength: use of neuroimaging data Limitation: only one case, no control group
Kelly *et al* 2011[127]	Minocycline (200mgs daily) plus Clozapine for up to 16 weeks	Two cases of schizophrenia with catatonic symptoms	Outcome: BPRS, SANS, CDS	In both cases, improvement in negative and positive symptoms	Limitation: only two cases, no control group

Note: ‡, †= articles share the same sample but focus on different outcomes; PANSS= Positive and negative syndrome scale; DSM-IV= Diagnostic and statistical manual of mental disorders fourth edition; TNF= Tumour necrosis factor alpha; SANS= Scale for the Assessment of Negative Symptoms; SAPS= Scale for assessment of positive symptoms ;CGI= Clinical Global Impressions Scale; HAM-A= Hamilton Anxiety Rating Scale; CDS= Calgary depression scale for schizophrenia; ITAQ= Insight and treatment attitude questionnaire; CANTAB= Cambridge neuropsychological test automated battery; GAF= Global Assessment of Functioning; BPRS= Brief Psychiatric Rating Scale