

Immunopsychiatry: important facts

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Accumulating evidence indicate a role for the immune system particularly inflammation and autoimmunity in the aetiology of major psychiatric disorders such as depression and schizophrenia. In this paper, we discuss some of the key advances in immunopsychiatry in order to highlight to psychiatrists and other health professionals how an increased understanding of this field might enhance our knowledge of illness mechanism and approaches to treatment. We present a brief overview of clinical research that link inflammation and autoimmunity with depression and psychosis, including potential role of inflammation in treatment response, current evidence for the effectiveness of immune-modulating treatment for depression and psychosis, and possible role of inflammation in common physical comorbidities for these disorders such as coronary heart disease and diabetes mellitus. Gaining a better understanding of the role of immune system could be paradigm changing for psychiatry. We need collaborations between clinicians and scientists to deliver high-quality translational research in order to fully realise the clinical potential of this exciting and rapidly expanding field.

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Introduction

There are intricate interactions between the immune system and the brain that may offer new mechanistic understanding and insights for novel therapies for psychiatric disorders. In particular, proinflammatory cytokines and circulating autoantibodies can influence the brain leading to changes in mood, cognition and behaviour; so may be relevant for the pathogenesis and treatment of depression, psychosis and other major psychiatric disorders (Raison *et al.* 2006; Dantzer *et al.* 2008; Khandaker *et al.* 2015). In this paper, we present a brief overview of clinical research that link inflammation and autoimmunity with depression and psychosis. We discuss potential role of inflammation in treatment response, current evidence for the effectiveness of immune-modulating treatment for depression and psychosis, and possible role of inflammation in common physical comorbidities for these disorders. Our aim is to inform psychiatrists and other health professionals about a few key advances (see Textbox) in the field of immunopsychiatry that could impact on clinical practice rather than providing a comprehensive literature review regarding

the immune system and mental disorders. Unless specified otherwise, in this context inflammation refers to chronic, low-grade systemic inflammation as reflected by increased concentrations of circulating inflammatory markers in peripheral blood such as cytokines and acute phase proteins, rather than inflammation in the classical sense, which is clinically manifest by the so-called cardinal signs.

Evidence for a role of inflammation in depression

Depression is common in people with a chronic inflammatory illness such as rheumatoid arthritis (Dickens & Creed, 2001). About 30–50% of patients with hepatitis C virus develop depression following treatment with interferon (Bonaccorso *et al.* 2002), which is a potent inducer of inflammatory cytokines. These clinical observations provide clues that inflammation may play a role in depression. Indeed, inducing inflammation in healthy volunteers in experimental setting with a typhoid vaccine leads to depressive symptoms and reduced cognitive performance, which is mediated by increase in circulating interleukin 6 (IL-6) levels (Harrison *et al.* 2009), a pleiotropic, proinflammatory cytokine. Furthermore, systematic reviews and meta-analyses of cross-sectional studies have confirmed that the levels of circulating proinflammatory cytokines such as IL-6, IL-1 β , tumour necrosis factor alpha (TNF- α) and acute phase proteins such as

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C-reactive protein (CRP) are elevated in acutely depressed patients, which are largely normalised after recovery (Howren *et al.* 2009; Haapakoski *et al.* 2015; Goldsmith *et al.* 2016). However, a limitation of the cross-sectional studies is that they cannot determine whether increase in inflammatory markers is a cause or consequence of illness (i.e. reverse causality).

Recently, longitudinal studies have shown that elevated cytokine levels precede, and so could potentially cause, depressive symptoms. Based on over 4000 participants from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we have shown that elevated serum levels of IL-6 in childhood increase risks of developing depressive and psychotic symptoms subsequently in adulthood in a linear, dose-response fashion (Khandaker *et al.* 2014a). In this study, evidence for an association persisted after taking into account effects of sociodemographic factors, maternal depression and other potential confounders. A longitudinal association between circulating IL-6 and CRP levels and subsequent development and persistence of depressive symptoms have been reported from other cohorts (Gimeno *et al.* 2009; Zalli *et al.* 2016). Taken together the current evidence indicates that inflammation is unlikely to be merely a consequence of depression or stress (which can cause immune-activation). Inflammation precedes depression so could be a causal risk factor for the illness.

However, observed association between inflammatory markers and depression could still be due to residual confounding, so more definitive studies, such as Mendelian randomization and randomised controlled trials (RCTs), are needed to establish whether the association between inflammation and depression is causal. Elevated CRP levels are associated with somatic (e.g. fatigue, anorexia, altered sleep) rather than psychological symptoms of depression in general population (Jokela *et al.* 2016) and in cancer patients who develop depressive symptoms after interferon treatment (Capuron *et al.* 2002). Therefore, focusing on specific symptoms/group of symptoms might help to elucidate further the role of inflammation in depression. Animal experimental studies suggest that inflammatory cytokines communicate with the brain using a number of pathways, and affect mood, cognition and behaviour by altering neurotransmitter metabolism, activating the hypothalamic-pituitary-adrenal (HPA) axis, increasing oxidative stress, and reducing synaptic plasticity possibly as a result of activation of microglia (a marker of neuroinflammation) (Raison *et al.* 2006; Dantzer *et al.* 2008). It remains to be seen whether neuroinflammation corresponds with severity of depression or response to antidepressant treatment in humans.

Evidence for a role of inflammation, atopy and autoimmunity in psychosis

Epidemiological studies indicate a role of infection, inflammation and autoimmunity in schizophrenia (Khandaker *et al.* 2015; Khandaker & Dantzer, 2016). Schizophrenia is associated with increased prevalence of various infections, including neurotropic viruses from the *Herpesviridae* family, and the intracellular parasite, *Toxoplasma gondii*. However, it is unclear whether increased infection is a result of poor lifestyle, so more convincing results have come from longitudinal studies. Exposure to a variety of infection during foetal development, including herpes simplex virus type 2 (HSV-2), cytomegalovirus (CMV), influenza, *T. gondii*, non-specific viral/bacterial infection and elevated maternal inflammatory marker levels, is associated with risk of schizophrenia and related psychotic illness in adult life, though the strength of association for each of these exposures vary; reviewed (Brown & Derkits, 2010; Khandaker *et al.* 2012, 2013). A linear, dose-response relationship has been reported between hospitalisation with a serious infection (CNS or non-CNS) during childhood and risk of adult psychotic disorders (Benros *et al.* 2011).

Similar to depression, antipsychotic 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 tend to normalise after remission of symptoms with antipsychotic treatment (Miller *et al.* 2011; Uptegrove *et al.* 2014; Goldsmith *et al.* 2016). Serum cytokine levels, including IL-6 are associated with illness severity, duration and anti-psychotic treatment (Maes *et al.* 1994; Miller *et al.* 2011). 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). However, it is not clear to what extent peripheral inflammation is related to inflammatory activity in the CNS, so further studies are needed. Recently population-based longitudinal studies have shown that elevated IL-6 and CRP levels in childhood or adolescence are associated with increased risk of developing psychotic symptoms (Khandaker *et al.* 2014a) and schizophrenia (Metcalf *et al.* 2017) subsequently in adulthood. As with depression, the longitudinal studies indicate that inflammation could be a causal risk factor for psychosis. Adverse experiences in early-life could be a source of low-grade systemic inflammation in healthy people, as levels of circulating inflammatory markers in adults are associated with childhood adversity/maltreatment (Baumeister *et al.* 2016) and sub-optimal foetal environment as indexed by low birth weight (Tzoulaki *et al.* 2008). Therefore,

whether low-grade systemic inflammation mediates the relationship between early-life adversity and adult depression or psychosis is a hypothesis that needs testing.

Further support for a role of the immune system in schizophrenia comes from studies pointing to links with atopy and autoimmunity (Benros *et al.* 2011). There is some evidence that childhood atopic disorders such as asthma, eczema are associated with increased risk of psychotic symptoms in adolescence (Khandaker *et al.* 2014b) and schizophrenia in adulthood (Pedersen *et al.* 2012). The prevalence of autoimmune 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 & McKenzie, 2014). Increased autoantibodies 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 in some (Zandi *et al.* 2011; Steiner *et al.* 2013), but not all studies (de Witte *et al.* 2015); reviewed (Pollak *et al.* 2014). Anti-NMDAR antibodies have been typically associated with the eponymous encephalitis, which is often associated with psychotic symptoms. Not all anti-NMDAR antibody positive cases of psychosis have classic features of encephalitis, suggesting these antibodies might be a cause of psychosis in some people. Similarly, elimination of autoantibodies by plasmapheresis improves psychotic symptoms in some cases of first episode psychosis (Zandi *et al.* 2011, 2014). However, anti-NMDAR antibodies are also increased in depression and bipolar disorder (Pearlman & Najjar, 2014). It remains to be established whether antibody positive patients differ from antibody-negative patients in terms of underlying pathology and response to antipsychotic treatment, and whether immunomodulatory treatments are effective in alleviating psychotic symptoms in this group using RCT. There is limited data on the relationships between neuronal autoantibodies and other aspects of immunity such as cytokines and microglial activation. Nevertheless, given these antibodies are present in about 5% of patients with first episode psychosis (Zandi *et al.* 2011), some psychiatric services in the UK now screen for these antibodies in new onset cases.

Neuroimaging and genome wide association studies (GWAS) support a role for the immune system in schizophrenia. Neuroimaging studies using PET provide evidence for neuroinflammation in patients with schizophrenia and in persons with subclinical symptoms, who are at high risk of psychosis and are related to at-risk symptom severity (Bloomfield *et al.* 2016). Evidence of microglial activation in the entire grey

matter and hippocampus indicates that neuroinflammation might contribute to grey matter volume loss and cognitive deterioration in schizophrenia (Doorduyn *et al.* 2009). The largest GWAS of schizophrenia to date has shown that in addition to genes expressed in the brain, schizophrenia is associated with genes involved in adaptive immunity (CD19 and CD 20 B-lymphocytes) and the major histocompatibility complex (MHC) region on chromosome six (Schizophrenia Working Group of the Psychiatric Genomics, 2014). The association between schizophrenia and the MHC locus arises in part from variations of the complement component 4 (*C4*) genes. *C4* is a critical component of the classical complement cascade, an innate immune system pathway that recognizes and eliminates pathogens and cellular debris. The brain expression of *C4A* is increased in schizophrenia (Sekar *et al.* 2016). In mice, *C4* tags synapses to be eliminated by microglial cells (synaptic pruning) that express *C4* receptors during postnatal development. Excessive complement activity could lead to altered neurodevelopment as a result of excessive synaptic pruning.

Inflammation and response to psychotropic treatments

Inflammation is associated with poor response to antidepressant and antipsychotic treatments. About a third of depressed patients have elevated circulating CRP levels (Wium-Andersen *et al.* 2013) while a third of patients are antidepressant resistant (Nemeroff, 2007) – this may not be a coincidence. Indeed, activation of the inflammatory system as reflected by elevated serum concentrations of IL-6 and other cytokines predicts poor response to antidepressants (O'Brien *et al.* 2007; Carvalho *et al.* 2013). Patients who do not respond to selective serotonin reuptake inhibitors and other antidepressants continue to show elevated levels of IL-6, CRP and other inflammatory markers (Maes *et al.* 1997). Findings from patients with psychosis are similar. Patients with first episode psychosis who do not respond to antipsychotic drugs have elevated levels of IL-6 and INF- γ at the start of treatment compared with responders (Mondelli *et al.* 2015). Furthermore, non-responders continue to show elevated levels of these inflammatory markers after 3 months of antipsychotic treatment compared with responders (Mondelli *et al.* 2015). While these findings are illuminating, longitudinal studies of inflammation and treatment response based on incident cases are limited. Inflammatory marker levels can be influenced by psychological stress, body mass, life style (e.g. smoking, alcohol use) and some psychotropic drugs. So further research is needed to understand whether

and how measuring inflammation in clinical setting could be useful for predicting response to antidepressant/antipsychotic treatment, and for identifying patients who are likely to benefit from immunomodulatory treatments.

It is thought that depressed patients with elevated inflammatory markers display resistance to antidepressants because these drugs do not rectify inflammation-related pathologies such as activation of the kynurenine pathway (Christmas *et al.* 2011). Inflammatory cytokines such as IFN and IL-6 activate indoleamine 2,3-dioxygenase (IDO), an enzyme that shifts metabolism of tryptophan towards kynurenine (Haroon *et al.* 2012). Further metabolism of kynurenine in the brain leads to increased production of neurotoxic and potentially depressogenic metabolites such as 3-hydroxykynurenine (3-HK) and quinolinic acid. In mice, lipopolysaccharide-induced systemic inflammation leads to depression-like behaviour through activation of IDO (O'Connor *et al.* 2009). Blocking inflammation with minocycline (a broad spectrum antibiotic) (O'Connor *et al.* 2009) or an anti-IL-6 monoclonal antibody (Hodes *et al.* 2014) prevents development of depression-like behaviour. Pertinent to psychosis, kynurenic acid is the only naturally occurring NMDAR antagonist in the human CNS (Schwarcz & Pellicciari, 2002). NMDAR antagonism and glutamatergic hypofunction have long been proposed to underlie psychotic symptoms and cognitive dysfunction in schizophrenia (Carlsson & Carlsson, 1990). Indeed, there is evidence that levels of kynurenine and kynurenic acid are elevated in the CSF and brain tissue of schizophrenia patients compared with healthy controls (Erhardt *et al.* 2001; Schwarcz *et al.* 2001). In future, examination of markers of inflammation and IDO activation in peripheral blood and in CSF in different stages of illness, their relationship with treatment response would be helpful to understand fully the implications of these findings for depression and psychosis.

Effectiveness of immunomodulatory treatment in depression and psychosis

Anti-inflammatory drugs may be helpful for patients with depression and psychosis. A meta-analysis of RCTs of non-steroidal anti-inflammatory drugs (NSAIDs), administered as sole treatment or as adjunct to antidepressants, indicates that they are more effective than placebo in treating depression (Kohler *et al.* 2014). The effect size for Celecoxib (a selective cyclooxygenase 2 inhibitor) based on 10 RCTs was $SMD = -0.29$ (95% CI -0.49 to -0.08). However, cyclooxygenase-2 inhibitors increase risk of cardiovascular disease (Mukherjee *et al.* 2001), a known comorbidity for

depression, so their use in this patient group may be problematic. Besides, it unclear whether improvements in mood is due to improvements in physical illness or due to the effect of NSAIDs on pathways other than inflammation such as glucocorticoid receptor (Nikkheslat *et al.* 2015).

More recently studies have examined the effectiveness of cytokine modulators (e.g. anti-cytokine monoclonal antibodies and cytokine inhibitors) for depression. We have conducted a systematic review and meta-analysis of secondary outcome data on depressive symptoms from clinical trials of cytokine modulators in patients with chronic inflammatory illnesses. Based on seven RCTs, we have found that cytokine modulators have a significant antidepressant effect; effect size, $SMD = 0.40$ (95% CI $0.22-0.59$) (Kappelmann *et al.* 2016). Crucially, improvements in depressive symptoms are independent of improvements in physical illness, suggesting mood improvement is not merely a by-product of physical improvement; cytokines may indeed be causally related to depressive symptoms. Only one RCT to date has investigated the effectiveness of a monoclonal antibody using depression as a primary outcome (Raison *et al.* 2013). Although overall no benefit of infliximab (anti-TNF monoclonal antibody) was observed, the study found that the higher the level of inflammation at the start of trial the greater the improvement in depressive symptoms by the end of trial (Raison *et al.* 2013). Together, these findings indicate that cytokine modulating drugs could be useful for depressed patients, particularly those with evidence of inflammation, but further work is needed to establish their efficacy, safety and cost-benefit for treating depression.

In schizophrenia, a meta-analysis of RCTs of NSAIDs as adjuncts to antipsychotics has shown promising results especially for aspirin and non-acetyl cysteine (Sommer *et al.* 2014). Dopaminergic drugs, which include all anti-psychotics currently in use, are effective in controlling positive symptoms, but cognitive dysfunction and negative symptoms rarely respond to these drugs. This may indicate fundamental differences in the mechanism underlying different types of symptoms. Preclinical studies of peripheral immune-to-brain communication lend support for a role of inflammation in the pathogenesis of these difficult-to-treat symptoms (Khandaker *et al.* 2015; Khandaker & Dantzer, 2016). In future, targeting these symptoms with immunological treatment could be a clinically fruitful strategy. Indeed, minocycline, a centrally acting tetracyclic anti-inflammatory agent, improves negative symptoms and cognitive function in schizophrenia (Chaudhry *et al.* 2012). Celecoxib may improve cognitive function in early stages of

schizophrenia (Muller *et al.* 2002). Recently, a small, proof-of-concept, open-label study of tocilizumab (anti-IL-6 receptor monoclonal antibody) as adjunct to antipsychotic treatment showed improvements in cognitive function in schizophrenia (Miller *et al.* 2016), but more definitive trials are needed. A subgroup of patients with depression (Wium-Andersen *et al.* 2013) and psychosis (Mondelli *et al.* 2015) show evidence of inflammation, so RCTs of anti-inflammatory drugs based on ‘inflamed’ rather than all patients of depression/psychosis are likely to be useful.

Transdiagnostic effect of inflammation and the common cause hypothesis

The association between inflammation and psychiatric disorders transcends traditional diagnostic boundaries. In addition to depression and psychosis, evidence for a link with inflammation exists for a number of disorders, including anxiety (Rossi *et al.* 2012; Khandaker *et al.* 2016), post-traumatic stress disorder (Eraly *et al.* 2014), autism (Brown *et al.* 2014) and dementias (Schmidt *et al.* 2002). Inflammation is likely to be relevant for some, *not all*, cases of depression/psychosis, because, as with most chronic illnesses, no risk factor alone is necessary or sufficient for causing an illness. Inflammation is no different in this regard; evidence for inflammation is seen in a sub-group of patients with depression and psychosis (Wium-Andersen *et al.* 2013; Mondelli *et al.* 2015). One explanation for the transdiagnostic effect could be that inflammation contributes to features common to different psychiatric syndromes such as fatigue, anhedonia and cognitive difficulties. Furthermore, this lack of specificity is not unique to inflammation. It is well known that there is overlap in the genetic risk for depression, schizophrenia and bipolar disorder. Psychological stress is a common risk factor for many physical and psychiatric illnesses.

Taking a broader perspective on causal models for illness, the idea of *specificity of association* between a risk factor and a disease fits well causal models for some illnesses (e.g. Koch’s postulates and Tuberculosis), but might be problematic in the case of chronic illnesses. Smoking is associated with numerous illnesses, including cancers and cardiovascular diseases. Similarly, inflammation might be a common underlying mechanism for a number of chronic illnesses of adult life such as depression, schizophrenia, coronary heart disease and diabetes mellitus that are highly comorbid with each other. All of these illnesses are associated with inflammation (Pradhan *et al.* 2001; Danesh *et al.* 2004; Khandaker *et al.* 2014a; Metcalf *et al.* 2017), which 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 by David Barker (Barker *et al.* 1993a). Developmental programming refers to permanent alteration in physiological system(s) following exposure to adversity during a specific ‘developmental window’. The resulting physiological alterations, in combination with genetic and/or other environmental factors, can increase risks of several diseases in adulthood. Empirical evidence from longitudinal studies supports the developmental programming hypothesis. Low birth weight (a marker of suboptimal foetal development) and childhood maltreatment are associated with increased circulating CRP levels (Tzoulaki *et al.* 2008) as well as risks of heart disease, diabetes mellitus, depression and schizophrenia (Barker *et al.* 1993b; Abel *et al.* 2010). Indeed, there is evidence that inflammation moderates the association between childhood maltreatment and risk of depression in adulthood (Danese *et al.* 2008). In future, population-based epidemiological, clinical and experimental studies are needed to understand whether and how inflammation contributes to the comorbidity between chronic cardio-metabolic and psychiatric illnesses of adult life. Experimental studies would be particularly useful to understand how early-life adversity might ‘programme’ the immune system.

Conclusions

Pathophysiologic explanations and pharmacotherapy for major psychiatric disorders such as depression and schizophrenia are predicated on monoamine neurotransmitters. However, heterogeneity in clinical presentation, illness course and treatment response suggest other mechanisms are involved. A better understanding of the role of immune system could be paradigm changing for psychiatry by providing novel mechanisms and treatments for these disorders, which are among leading causes of disability worldwide. The field now needs studies to investigate causality of association and RCTs of novel immunotherapies for depression and psychosis. In future, immunotherapeutic strategies could include immune-phenotyping of patients to predict treatment response and anti-inflammatory treatment for patients with evidence of inflammation. Shifting the focus of research from syndrome to symptom (or constellation of symptoms) may help to fully elucidate the role of immune system in the aetiology of psychiatric disorders. Accumulating evidence from preclinical studies suggests inflammation is a key mechanism underlying cognition and behaviour, which needs to be translated into human studies of affective and cognitive neuroscience. A clearer understanding of the immunological aspects of psychiatric disorders may lead to novel approaches to diagnosis and treatment but would require close

collaborations between clinicians and researchers to deliver high-quality translational research.

Immunopsychiatry: Key facts

- Depression is common in people with a chronic inflammatory illness, and immuno-activation leads to depressive symptoms in patients and healthy volunteers
- Schizophrenia and related psychotic disorders are associated with prenatal and childhood infections, atopic disorders and autoimmunity
- Elevated circulating inflammatory markers increase future risk of depression and psychosis in healthy people suggesting inflammation might cause these disorders
- Circulating inflammatory markers are elevated in acute depression and psychosis, which tend to normalise after recovery, but continue to be elevated in treatment resistant cases
- There is evidence of neuroinflammation in schizophrenia as demonstrated by activation of microglia in patients as well as those who are at risk of developing the illness
- Anti-NMDA receptor and anti-VGKC antibodies may be responsible for about 5% of all cases of psychosis
- Elevated circulating inflammatory markers are associated with poor response to antidepressant and antipsychotic treatment
- Measuring circulating inflammatory markers may aid treatment decisions
- Emerging evidence indicates anti-inflammatory agents may be effective treatments for patients with depression and psychosis particularly those with evidence of inflammation
- Inflammation might be a common mechanism underlying the comorbidities between depression, schizophrenia, coronary heart disease and diabetes mellitus

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