

# Cytokines, Oxidative Stress and Cellular Markers of Inflammation in Schizophrenia



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**Abstract** In this article, we review current evidence linking immune dysfunction in schizophrenia and related psychotic disorders focusing particularly on circulating cytokines, oxidative stress and cellular markers of inflammation in various stages on illness from drug-naïve first episode psychosis to chronic schizophrenia. Acute psychotic episode is associated with low-grade systemic inflammation in some patients, as reflected by increased concentrations of cytokines and other inflammatory markers in peripheral blood. Evidence from general population-based

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longitudinal cohort studies reporting an association between elevated inflammatory markers in childhood/adolescence and risk of schizophrenia and related psychosis subsequently in adulthood suggest that inflammation could be a causal risk factor for psychosis rather than simply be a consequence of illness. Mendelian randomization studies also suggest that associations between IL-6, CRP and schizophrenia are likely to be causal. In addition, we discuss evidence for disruptions in oxidative stress markers and CSF cytokine levels in schizophrenia, and potential reasons for reported trans-diagnostic associations for inflammatory cytokines including role of early-life adversity/maltreatment. We argue that low-grade inflammation is a clinically useful feature, because it is associated with poor response to antipsychotic medication in first episode psychosis. We discuss clinical implications for immunological understanding of schizophrenia including scope for clinical trials of anti-inflammatory agents and notable gaps in current knowledge, and offer suggestions for future research.

**Keywords** Cytokine · Inflammation · Innate immunity · Schizophrenia · Psychotic disorder

## Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
BBB	Blood-brain barrier
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
FEP	First episode psychosis
Glx	Glutamate/glutamine ratio
GSH	Glutathione
HPA	Hypothalamic-pituitary-adrenal
IL-6	Interleukin-6
IL-8	Interleukin-8
MHC	Major histocompatibility complex
ROS	Reactive oxygen series
TNF- $\alpha$	Tumour necrosis factor alpha

## 1 Introduction

Schizophrenia can be understood as a neurodevelopmental disorder (Murray and Lewis 1987; Weinberger 1987), with onset usually in early adulthood (van Os et al. 2009). Biological research into the pathogenesis of schizophrenia has focused on brain structure, function and neurotransmitter abnormalities (Jones et al. 2005) and

genetic risk (Consortium 2011). However, there is also an accepted environmental impact, with a gene and environmental (GxE) combined effect related to increased risk, precipitation of illness and/or poorer outcomes. Notable environmental factors include childhood trauma, social and economic deprivation, minority status and stressful life events (van Os et al. 2010). Increasing evidence suggests a role for the involvement of immunological processes in mediating the genetic and environmental risk for schizophrenia. Indeed, schizophrenia has been associated with an abnormal activation of the immune system for many years (Dameshek 1930; Müller et al. 2012; Ganguli et al. 1994). Previous reviews have summarized evidence linking schizophrenia with abnormalities in various components of the immune system; see Khandaker et al. (2015) and Khandaker and Dantzer (2016), but here, we focus primarily on the evidence on circulating inflammatory cytokines, oxidative stress and cellular markers of inflammation.

## 2 Cytokines as Key Mediators of Immune Response

Cytokines are the key signalling molecules that coordinate both innate and adaptive arms of the immune system and exert effects in the periphery and the brain. The immune response is a highly coordinated process involving an array of cell types that protect the body from harm while maintaining tolerance to self-antigens and beneficial organisms. The first arm is our “innate” defence mechanisms, older in evolutionary terms, and considered to be a first-line defence. Its cellular components include neutrophils, basophils and eosinophils, monocytes and macrophages, dendritic cells and natural killer (NK) cells, which recognize and promote defence against pathogens but lack the sophistication to adapt compared to other more recent additions to the immune system (Uptegrove and Barnes 2014). The innate humoral component is made up of acute phase proteins such as C-reactive protein (CRP), cytokines such as interleukin-6 (IL-6) and the complement cascade, which allow phagocytic cells to clear pathogens (see below).

The second arm of our immune system is the “adaptive” system, which acts on re-exposure to a known pathogen. The prime cellular components of the adaptive system include T and B lymphocytes. Antibodies produced by B lymphocytes comprise the main humoral part of adaptive immunity. There is considerable “crosstalk” between the two major arms of the immune system. T cells comprise key components of the T helper 1 (Th1) system and the T helper 2 (Th2) system. The Th1 system is polarized towards the production of pro-inflammatory (activating) cytokines such as interleukin-2 (IL-2), interferon- $\gamma$  (INF- $\gamma$ ) and tumour necrosis factor (TNF $\alpha$ ). The Th2 system promotes the generation and maintenance of antibody-mediated immune responses as well as production of anti-inflammatory cytokines such as interleukin-4 (IL-4), interleukin-10 (IL-10) and interleukin-13 (IL-13). However, cytokines often have pleotropic effect, as, for example, IL-6 has both pro- and anti-inflammatory properties. More recently, a key role for the Th17 system has been discovered, in regulation of immune response, so this system is important for pathogenesis of a number of immune-related disorders

(Janeway et al. 2001). It is now understood that both innate and adaptive systems are able to form and retain memory, which influences immune response on re-exposure to a stimulus.

Changes in cytokines and their receptor levels have been reported in the blood and cerebrospinal fluid (CSF) of patients with schizophrenia (Upthegrove et al. 2014) – see below. Previously, the brain was thought to be protected from peripheral inflammatory responses due to the blood-brain barrier (BBB). However, it is now clear that cytokines and other circulating inflammatory mediators can reach and influence the brain in a number of ways. Peripheral immune-to-brain communication pathways include direct entry through leaky circumventricular areas in the BBB, the lymphatic system, infiltration of immune cells to the brain and retrograde axonal transport of immune signal via cranial nerves, for example, the vagus nerve (for a review, see Khandaker and Dantzer 2016). Peripheral or systemic inflammation is therefore relevant for neuropsychiatric disorders such as schizophrenia.

### **3 Evidence for Cytokine Alteration in Different Stages of Schizophrenia**

Here, we review the evidence for aberrant cytokines in peripheral blood and in CSF in patients with schizophrenia and related psychotic disorders. We also discuss evidence from epidemiological prospective cohort studies linking elevated inflammatory marker levels in childhood/adolescence with risk of psychosis subsequently in adulthood. There is notable heterogeneity in existing studies of inflammatory cytokines in schizophrenia as, for example, studies have used patients in different stages of illness. Levels of inflammatory markers could be influenced by neuroleptic and other drugs, alcohol and illicit drug use, sex, smoking, body mass index (BMI) and comorbid physical illness (Upthegrove and Barnes 2014). Therefore, we have put particular emphasis on stage of illness and effects of potential confounders such as those listed above.

#### **3.1 Drug Naïve Psychosis**

Studies of medication naive patients are particularly useful to gain a better understanding of inflammatory cytokine alteration in schizophrenia. It is well known that antipsychotic medication can influence the immune system. Drzyga and colleagues carried out an *in vitro* study showing that antipsychotic drugs affect immune cell function, which often occurs very shortly after initial exposure to drug (Drzyga et al. 2006). However, there are mixed results and differing effects, including either stimulatory or inhibitory actions. Relatedly, other *in vitro* studies suggest that suppression of cytokine mediated microglial activity may partly underpin the efficacy of some antipsychotic drugs (Bian et al. 2008). For example, aripiprazole

suppresses apoptosis of rodent oligodendrocytes by IFN- $\gamma$ -activated microglia and inhibition of TNF- $\alpha$  secretion from IFN- $\gamma$ -activated microglia (Seki et al. 2013). Clozapine, the most effective antipsychotic medication, influences the immune system. Its effects on white blood cell (WBC) count are well known. The drug may have immediate (Røge et al. 2012) and longer-term effects on IL-6, CRP (Kluge et al. 2009) and high-sensitivity CRP (hs-CRP) levels (Löffler et al. 2010) in schizophrenia patients.

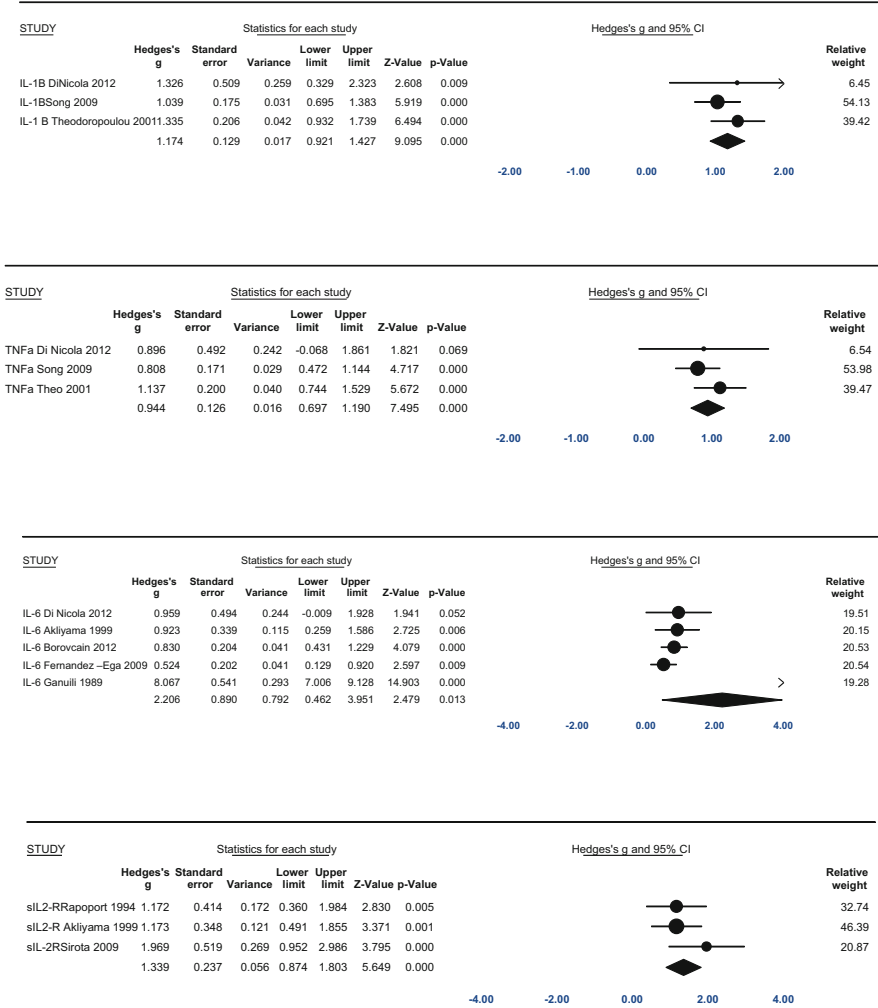
In a systematic review and meta-analysis published in 2014, we included 14 studies that together assessed levels of 20 different cytokines and cytokine receptors in 570 neuroleptic naive patients. The majority of these patients had a diagnosis of schizophrenia or schizophreniform disorder (81%). Highly significant effect sizes were seen for IL-1 $\beta$ , IL-6, sIL2r and TNF $\alpha$ , suggesting that an increase in these cytokines in first episode psychosis (FEP) patients, compared with controls, is unrelated to antipsychotic drugs (Fig. 1). These cytokines play key roles in orchestrating innate immune response; IL-1 $\beta$  and TNF- $\alpha$  are responsible for stimulating IL-6 production, while IL-6 signals hepatocytes to produce acute phase proteins such as CRP. Some increase in levels of IL-2, IL-4 and IFN- $\gamma$  were also seen, but differences in these cytokine levels were not statistically significant. These cytokines were measured in studies with small samples and in fewer studies altogether leading to low statistical power.

More recently, a study by Noto et al. reported that comorbid depression might influence cytokine levels in FEP patients. While increased levels of IL-6, IL-10 and TNF $\alpha$  were found in 55 FEP patients overall, compared with controls, patients with depression showed higher IL-4 and TNF $\alpha$  levels compared with those without depression (Noto et al. 2015).

### 3.2 *Acute Psychosis*

In an extensive meta-analysis published in 2011, Miller et al. explored cytokine function by phase of illness in schizophrenia. Assessing 40 studies, they found IL-1 $\beta$ , IL-6 and TGF- $\beta$  were raised in the acute phase of illness (both in relapse patients and in first episode psychosis) and reduced with successful treatment (Miller et al. 2011). IL-6 correlated to total level of psychopathology in two out of five studies (Miller et al. 2011). TNF- $\alpha$  and IL-6 levels were analysed in most studies (97 and 156 total studies, respectively). It was proposed that these cytokines could be state-dependent markers of inflammation, resolving with symptom reduction. However, elevated levels of IL-6 in childhood measured years before onset of psychosis is associated with psychotic symptoms in early-adulthood (Khandaker et al. 2014) (see below). Levels of IL-6 and TNF- $\alpha$  are also associated with childhood maltreatment (Baumeister et al. 2016), so these cytokines could also be trait markers for psychosis.

In first episode psychosis, Mondelli et al. measured BDNF, IL-6 and TNF- $\alpha$  in 46 patients. Compared to healthy controls, patients had reduced BDNF gene expression and increased IL-6 and TNF- $\alpha$ . History of childhood trauma was



**Fig. 1** Cytokine profile in medication-naive first episode psychosis: patients have higher IL-1β, TNF-α, IL-6 and sIL-2r levels compared with controls. Modified from Uptegrove et al. (2014)

associated with lower BDNF mediated through IL-6 (Mondelli et al. 2015). In a more recent review, Goldsmith et al. investigated acute and chronic cytokine changes in schizophrenia, bipolar disorder and depression, which included 40 studies on acute schizophrenia (Goldsmith et al. 2016). In meta-analysis, IL-6, sIL2r, IL-1RA and TNFα were all significantly raised in acute schizophrenia, bipolar disorder and depression. There was more heterogeneity in FEP samples than acute relapse of established schizophrenia. No publication bias was reported for IL-6 (Goldsmith et al. 2016). These findings suggest that the association of increased inflammatory cytokines transcend traditional diagnostic boundaries; for a discussion on the trans-diagnostic effect of inflammation please, see below.

Another meta-analysis reported elevated serum levels of CRP in FEP and chronic schizophrenia irrespective of medication status (Fernandes et al. 2016). With regard to association with specific symptoms, an association between CRP levels and positive symptoms, but not negative symptoms of psychosis, was found. However, Johnsen et al. investigated CRP in acute psychosis, reporting a particular association with cognitive dysfunctions rather than positive symptoms (Johnsen et al. 2016). Studies in healthy volunteers and non-human primates have reported association of inflammatory markers with anhedonia-like behaviour and reward alterations (Harrison et al. 2016; Capuron et al. 2012). So overall, patient and animal studies indicate an association of inflammatory markers with positive, negative and cognitive symptoms.

### **3.3 Chronic Schizophrenia**

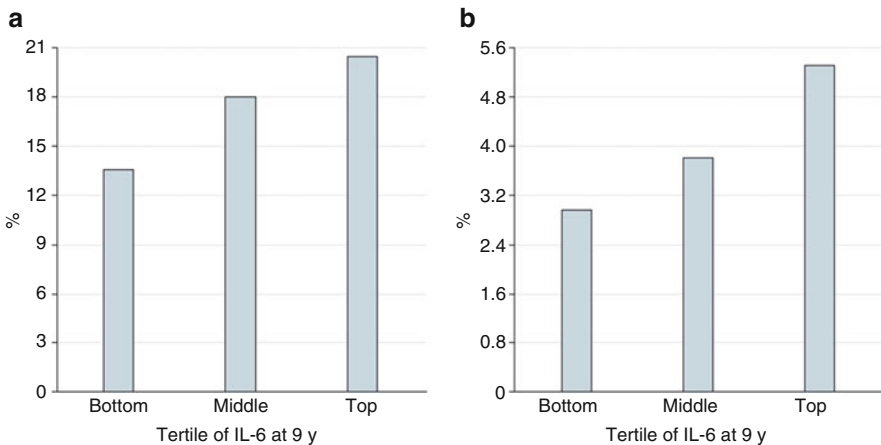
TNF- $\alpha$ , IL-12, INF- $\gamma$  and sIL2r have been reported to be elevated in both acute illness and stable “outpatients” with chronic schizophrenia. Goldsmith et al. found that, compared with controls, the levels of IL-6 were significantly increased in chronic schizophrenia, euthymic (but not depressed) bipolar disorder and major depressive disorder (Goldsmith et al. 2016). IL-1 $\beta$  and sIL2R were significantly increased in chronic schizophrenia and euthymic bipolar disorder. TNF- $\alpha$  has been suggested as a trait marker of neuroinflammation (Goldsmith et al. 2016). Goldsmith et al. review confirmed that TNF- $\alpha$  was raised in acute schizophrenia compared to controls and remained so after treatment.

In meta-analysis of five studies, Miller and Culpeper found that 28% of patients with chronic schizophrenia have an elevated CRP (Miller et al. 2013). In a recent study of 295 patients with schizophrenia and 192 with bipolar disorder, CRP was elevated in the schizophrenia even after adjusting for age, gender, race, maternal education, smoking status and BMI, but this was not found in bipolar disorder (Dickerson et al. 2013). The association between CRP levels and cognitive functioning in patients with predominantly chronic schizophrenia has been reported in one cross-sectional study (Dickerson et al. 2007). Together these studies suggest poorer cognitive function may be associated with enduring neuroinflammation.

## **4 Population-Based Longitudinal and Mendelian Randomization Studies Examining Causality**

Psychological stress can activate an innate immune response (Maes et al. 1998), so cytokine elevation during acute psychosis could be a consequence of illness rather than be its cause (i.e., reverse causality). Therefore, longitudinal studies need to establish, or refute, a potentially causal role of inflammation in the pathogenesis

of psychosis. Evidence from population-based longitudinal cohort studies from the UK, Finland and Sweden has linked higher levels of IL-6, CRP and erythrocyte sedimentation rate (ESR) in childhood/adolescence with risk of psychotic symptoms or diagnosis of schizophrenia subsequently in adulthood (Khandaker et al. 2014; Kappelmann et al. 2018a; Metcalf et al. 2017). Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a general population-representative birth cohort, Khandaker et al. have reported that higher levels of IL-6 in childhood at age 9 years are associated with increased risk of psychotic symptoms at early adulthood at age 18 years in a linear dose-response fashion (Khandaker et al. 2014) (Fig. 2). Evidence for this association remained after controlling for sex, BMI, social class, ethnicity and childhood psychological and behavioural problems preceding the measurement of IL-6. Although, in ALSPAC, CRP was not associated with psychosis risk, Khandaker and colleagues found that in the Northern Finland Birth Cohort (NFBC) 1986, higher levels of CRP in adolescence were associated with increased risk of hospitalization with a diagnosis of schizophrenia subsequently in adulthood. Furthermore, there was evidence that higher CRP levels in adolescence were associated with earlier age at illness onset (Metcalf et al. 2017). These findings are consistent with a Danish study reporting that higher CRP at baseline is associated with increased risk of late- and very-late-onset schizophrenia subsequently at follow-up (Wium-Andersen et al. 2014). More recently, we have conducted a longitudinal study based on Swedish male conscripts which found that higher ESR, a marker of systemic inflammation, in early adulthood is associated with increased risk of schizophrenia subsequently in adulthood (Kappelmann et al. 2018a).



**Fig. 2** Depression and psychotic experiences at age 18 years in the Avon Longitudinal Study of Parents and Children. Reproduced with permission from: Khandaker et al. (2014). Note: Samples of depression (a) and psychotic experiences (b) were divided by tertiles of interleukin-6 (IL-6) in participants 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 noncases combined) were 1.08 and 0.57 pg/mL, respectively



Although previous longitudinal studies have controlled for key confounders such as sex, BMI, and social class, residual confounding still might explain the association between inflammatory markers and psychosis. Recently, Khandaker and colleagues have used genetic association analysis informed by Mendelian randomization (MR) which indicates that residual confounding is unlikely to explain the association between IL-6 and psychosis fully. MR is based on the idea that if a biomarker is causally related to an illness, genetic variant(s) regulating levels/activity of that biomarker should also be associated with the illness (Davey Smith and Ebrahim 2003). Using data from the ALSPAC birth cohort, we have shown that a genetic variant in the IL-6 receptor gene (*IL-6R* Asp358Ala; rs2228145) that is known to dampen down inflammation by impairing the activity of IL-6 is protective for severe depression and/or psychosis (Khandaker et al. 2018a). The genetic variant is strongly associated with serum IL-6 and CRP levels, but not with any common confounders of the inflammation-psychosis relationship such as sex, social class, ethnicity and BMI. Genetic variants segregate at random during meiosis and are unrelated to sociodemographic and other confounders. Therefore, an association between psychosis and a genetic variant that regulates IL-6 activity strongly indicates that the IL-6/IL-6R pathways are causally linked to psychosis. Similarly, using MR analysis of psychiatric genomic consortium (PGC) data, Hartwig et al. has reported that IL-6 and CRP are likely to be causally linked with schizophrenia (Hartwig et al. 2017).

Together these studies suggest that reverse causality and residual confounding are unlikely explanations for previously observed association between inflammatory markers, particularly IL-6, CRP and psychosis. These associations are likely to be causal, so these biomarkers could be novel targets for intervention and prevention of psychotic disorders.

## 5 CSF Cytokine Alteration in Schizophrenia

Meta-analysis of studies of CSF from patients with schizophrenia suggests that levels of inflammatory cytokines are increased in patients with psychosis. A meta-analysis of 16 studies published in 2018 by Wang et al. reported that CSF levels of IL-1 $\beta$ , IL-6 and IL-8 were significantly elevated in schizophrenia patients compared with controls (Wang and Miller 2018). Similar findings were also observed for depression. Whether levels of inflammatory markers in peripheral blood correspond with neuroinflammation is an important question. This meta-analysis also reported that many CSF alterations are also concordant with those in the peripheral blood, particularly for schizophrenia (Wang and Miller 2018). This provides some validity to the use of peripheral markers of inflammation in schizophrenia research. This finding is consistent with a study by Coughlin et al. that measured IL-6 in the CSF of patients with recent-onset schizophrenia

also undergoing a positron emission tomography (PET) study of translocator protein 18 kDa (TSPO), a marker of microglial activation using [<sup>11</sup>C] DPA-713 (Coughlin et al. 2016). While non-significant results were seen in the TSPO analysis, IL-6 levels were significantly raised in patients compared to controls. Furthermore, the study found IL-6 levels in the CSF correlated significantly with circulating IL-6.

## **6 Oxidative Stress Markers in Acute and Chronic Schizophrenia**

### **6.1 First Episode Psychosis**

Decreased levels of the antioxidant, glutathione (GSH), have been reported in patients with acute psychosis compared with controls (Wood et al. 2009; Raffa et al. 2011). GSH is an antioxidant which provides within cell protection and when depleted contributes to oxidative stress. Flatlow, Buckley and Miller reported a decrease in GSH in acutely relapsed patients with schizophrenia together with other antioxidants such as superoxide dismutase (SOD) and catalase (CAT); however, there was significant heterogeneity in reported studies such that SOD and CAT but not GSH were reduced in FEP (Flatow et al. 2013). This may suggest a more persevered oxidative defence earlier in the course of illness.

As a substantial minority of patients with FEP do not go on to develop an enduring mental illness, it may be that those with a protective oxidative defence to cellular stress have better outcomes (Lally et al. 2017). This hypothesis remains to be tested. However Wang et al. investigated cysteine, a semi-essential amino acid and a precursor of GSH glutathione, as a potential indicator of preserved cognitive function in FEP with some positive findings (Wang et al. 2018). The functional consequences of increased oxidative stress or reduced defence against this oxidative stress in the brain are still to be fully understood. Changes in neuronal membrane permeability eventually leading to cell death could contribute to grey matter volume (GMV) loss seen in schizophrenia (Mahadik and Mukherjee 1996). In respect to known neurochemical changes in psychosis, it has been proposed that oxidative stress results in over activation of NMDA and altered dopamine receptor function. While schizophrenia is no longer understood within a simplistic conclusion of hyperdopaminergia, rather consisting of regionally specific prefrontal hypodopaminergia and subcortical hyperdopaminergia, the cumulative effect of overactive or more readily available dopamine may account for positive symptoms (Howes and Kapur 2009). NMDA glutamate receptors are downregulated by oxidation leading to disinhibition of pyramidal cells and unregulated glutamatergic excess (Traynelis et al. 2010).

## **6.2 *Chronic Schizophrenia***

There is substantial evidence of impaired oxidative defence in chronic schizophrenia, as reviewed by Flatlow et al. (2013). Negative symptoms have been associated with low levels of GSH, and positive symptoms have been positively correlated with SOD activity. A study by Fraguas et al. assessed the relationship between GMV and GSH in the brains of patients with schizophrenia, with a progressive decline in GMV correlated to declining circulating GSH (Fraguas et al. 2012). Thus, the deficit state of some patients with schizophrenia may be related to a specific lack of defence against oxidative stress.

There is a great deal of clinical and phenomenological commonality between schizophrenia and depression (Uptegrove et al. 2017). In schizophrenia, there is substantial glutamate dysfunction including clear evidence for Glx abnormality in brain areas such as the posterior medial prefrontal cortex (pmPFC). Increased Glx is seen in younger patients or more acute phases of illness, whereas reduced Glx has been reported in patients who are older and have residual negative symptoms (Marsman et al. 2013). Just as in schizophrenia, there is substantial evidence for increase in peripheral markers of inflammation in MDD. However, comorbid depression doesn't solely account for increased inflammation in schizophrenia, as evidence for association persists after excluding or controlling for depression (Khandaker et al. 2017). Nevertheless, it is possible that the presence of both psychosis and depression has a greater impact on immune dysfunction than the sum of each individually. Poorer clinical outcomes including increased risk of relapse, low quality of life and poor functional outcomes for patients with comorbid depression and schizophrenia support this idea (McGinty et al. 2018).

Early changes in neurochemicals such as Glx may result in more significant impact for those individuals with deficient defence against this inflammatory challenge (Bian et al. 2008). The effect of inflammation includes the generation of reactive oxygen species such as superoxide, hydroxyl and peroxy. The substantial evidence of impaired oxidative defence in early psychosis with diminished levels of GSH (Wood et al. 2009; Raffa et al. 2011; Jiménez-Fernández et al. 2015) show that the response of brain glutamate to inflammation and associated oxidative stress will also depend on the strength of defences against it. Thus, clinically poorer outcomes, such as seen with some subjects with depression and schizophrenia, may be related not just to the effect of chronic inflammation but also impaired defence against this.

## **6.3 *Trans-diagnostic Effect of Inflammation and Potential Role of Early-Life Adversity***

Studies of inflammatory markers in peripheral blood and CSF suggest that inflammation is associated with a number of psychiatric disorders including schizophrenia and related psychoses (Khandaker et al. 2015; Uptegrove et al. 2014; Wang and Miller 2018; Miller et al. 2011), depression (Dantzer et al. 2008; Miller et al. 2009),

anxiety (Wohleb et al. 2014), post-traumatic stress disorder (PTSD) (Eraly et al. 2014), autism (Brown et al. 2014), Alzheimer's disease and other dementias (Schmidt et al. 2002). However, possible reasons for this apparent trans-diagnostic association of inflammation are unknown. We have recently reported that the apparent trans-diagnostic effect may arise from association of inflammation with symptoms that are commonly shared between disorders (Khandaker et al. 2018b). Using a symptom-level data on ten positive and ten negative symptoms of psychosis assessed in adolescent participants from the ALSPAC birth cohort, we have shown at the group level positive and negative symptom dimension scores were associated with serum CRP levels in a similar fashion. At individual symptom level, CRP was associated with particularly auditory hallucinations and anhedonia. Auditory hallucinations can occur in psychosis, depression and anxiety disorders (APA 2013). Anhedonia is both an important negative symptom for psychosis and a core feature of depression (APA 2013).

Association between inflammation and anhedonia is supported by experimental studies. In non-human primates, chronic, low-dose peripheral interferon administration reduces striatal dopamine release in association with anhedonia-like behaviour (Felger et al. 2013). In healthy volunteers, inflammation induces hedonic alterations (decreased preference for reward and increased avoidance of punishment) (Harrison et al. 2016), which resemble anhedonia. Other reasons for this apparent trans-diagnostic effect could be shared genes that contribute to inflammation and risk of depression and schizophrenia. Genetic overlap between schizophrenia, bipolar disorder and depression is well established.

Shared risk factors, particularly early-life adversity, could be another explanation for the apparent trans-diagnostic effect of inflammation. Childhood abuse/maltreatment may programme the immune system leading with increased concentrations inflammatory markers in adulthood (Baumeister et al. 2016), which, in turn, may increase psychiatric risk. In the ALSPAC birth cohort, maternal/parental depression is associated with higher levels of IL-6 and CRP in childhood and with higher risk of depression and psychosis in early adulthood in offspring (Khandaker et al. 2018c). Furthermore, childhood IL-6 levels mediate the association between prenatal depression and offspring psychosis risk. These findings are consistent with the developmental programming hypothesis by David Barker, which posits that exposure to stress during critical period of development may program certain physiological system(s) leading to increased risk of chronic illnesses of adult life (Barker 1993). Early-life adversity is associated with coronary heart disease and type 2 diabetes, which are common comorbidities for schizophrenia and depression. Young adults with psychotic symptoms display evidence of dysglycaemia, which is linked with levels of IL-6 in childhood (Perry et al. 2018). Therefore, whether programming of innate immune response by early-life adversity may explain the comorbidity between schizophrenia, depression, coronary heart disease and type 2 diabetes is an interesting hypothesis that needs investigating.

## **6.4 Therapeutic Implications for Low-Grade Inflammation in Schizophrenia**

Mondelli et al. have reported an association between innate immune activation and poorer treatment response in 57 patients with FEP: nonresponders (as defined by an absence of clinically significant symptom response in keep with remission criteria at 12 weeks) had a significantly higher IL-6 and INF- $\gamma$  at baseline. They also reported an aberrant cortisol wakening response and suggest this combination of markers may be an early signal of poor outcome (Mondelli et al. 2015). Indeed, inflammatory mechanisms, as outlined above, have been cited as one of the potential mechanisms of effect of clozapine in treatment-resistant schizophrenia.

As well as poor treatment response, markers of inflammation may indicate poorer physical health outcomes. Russell et al. investigated 53 FEP patients and showed that FEP patients with raised CRP were at more risk of developing short-term metabolic abnormalities including dyslipidaemia, independent of weight gain (Russell et al. 2015). As mentioned earlier, in the ALSPAC birth cohort, young adults with psychotic symptoms displayed evidence of dysglycaemia, which was associated with childhood IL-6 levels (Perry et al. 2018). Thus, the potential for stratifying treatment approach; early targeting of potential treatment resistance or heightened monitoring from adverse effects of antipsychotics shows some promise in a personalized approach to FEP and schizophrenia.

Because inflammation is associated with BMI, smoking, alcohol use, physical comorbidity, antipsychotic treatment and treatment-induced weight gain, further work 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.

Inflammation is unlikely to be relevant for illness pathogenesis in all patients with psychosis. For depression, clinical trials indicate that anti-inflammatory drugs may be helpful for patients who show evidence of inflammation (Raison et al. 2013; Kappelmann et al. 2018b). Existing RCTs of anti-inflammatory drugs for schizophrenia have yielded mixed results (Deakin et al. 2018; Girgis et al. 2018; Miller et al. 2016), possibly due to imprecise targeting of patients. Patients with psychosis who do show evidence of inflammation may be more suitable candidate for RCTs of anti-inflammatory drugs in future.

## **7 Conclusions and Future Directions**

For a number of years now, there have been considerable efforts to have a better understanding of the immunological and inflammatory aspects of schizophrenia, in the hope that this might lead to novel approaches to diagnosis and treatment. See Boxes 1 and 2 for key clinical findings and questions for future research. Some aspects are becoming clearer. For example, accumulating evidence now

confirms that inflammation could play a causal role in psychosis rather than being an epiphenomenon or result of treatment, other confounders or illness itself. An immunological understanding of schizophrenia could be clinically useful. Inflammation is associated with poor response to antipsychotics; comorbid physical illness, such as type 2 diabetes mellitus (Pradhan et al. 2001); and increased all-cause mortality (Zacho et al. 2010). Therefore, measuring inflammation levels (e.g. CRP test) as part of routine clinical assessment of psychosis could identify treatable causes of inflammation and potentially guide antipsychotic treatment decision. However, the “one-size-fits-all” approach to drug therapy is unlikely to be effective for immune therapies, so more personalized approach is needed.

### **Box 1 Key Clinical Findings**

- Patients with schizophrenia show evidence of low-grade inflammation detectable in peripheral blood.
- Inflammation appears to predate the onset of illness and be independent of medication treatment.
- Inflammation is associated with poor response to antipsychotic medication.

### **Box 2 Key Clinical Questions**

- What are the relationships between peripheral markers of inflammation and structural or functional brain changes?
- Which patients could benefit from anti-inflammatory therapies?
- Could measuring inflammation levels in clinical practice help better monitoring of psychiatric and physical health?

A key challenge for future is to determine precisely which patients are likely to benefit from anti-inflammatory therapies. This would require a concerted approach including immune target identification using genomic and other methods, deep immuno-phenotyping of psychosis patients to identify cellular source of inflammation and clinical studies to identify effect of inflammation on symptom dimensions, followed by experimental medicine and animal studies to examine the effects of novel immune-modulating agents on the brain and behaviour. With regard to certain pathways where there is sufficient evidence for a causal association with schizophrenia, e.g. IL-6/IL-6R pathway, the field now needs experimental medicine studies based on selected patient groups to test whether targeting these pathways with immuno-modulating drugs improves clinical/clinically relevant outcome measures.

Another important avenue for future research would be to understand how inflammation influences developmental trajectories of neuropsychiatric symptoms, cognition or functional outcome over the life course. Population-based prospective studies and animal experiments would be useful for this purpose.

In summary, many of the major advances in our understanding of the links between immune system and schizophrenia suggest that immuno-psychiatry is a promising field, which could transform our understanding of illness pathogenesis and approaches to treatment and prevention for schizophrenia. To be successful, the field requires collaborative working among many experts including those from psychiatry, neuroscience, immunology, neurobiology, genomics, data science, epidemiology and clinical trial.

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