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Circulating Cytokine, 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 cytokine, oxidative stress and cellular markers of inflammation in various stages on illness from drug naïve first episode psychosis to chronic schizophrenia. There is evidence that the acute psychotic episode is associated with low-grade systemic inflammation in some patients; reflected by increased concentrations of circulating inflammatory markers in peripheral blood. We discuss evidence from general population-based cohort studies reporting an association between inflammatory markers and subsequent risk of psychosis, which indicate that inflammation may be a causal risk factor for psychosis rather than simply be a consequence of illness. We discuss that an immunological understanding of schizophrenia could be clinically useful, as inflammation is associated with poor treatment response in first episode psychosis. We briefly present current evidence for effectiveness of anti-inflammatory treatment for psychosis, offer suggestions for future studies, and highlight notable gaps in current knowledge.

Introduction:

Schizophrenia can be understood as a neurodevelopmental disorder [1, 2], with onset usually in early adulthood [3]. Biological research into the pathogenesis of schizophrenia has focused on brain structure, function and neurotransmitter abnormalities [4] and genetic risk [5].

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. This includes childhood trauma, social and economic deprivation, minority status and stressful life events [6]. Increasing evidence suggests a role for the involvement of immunological processes in mediating the environmental risk and the pathophysiology at the onset and development of schizophrenia. Indeed, schizophrenia has been associated with an abnormal activation of the immune system for many years [7-9]. While previous reviews have summarised evidence linking schizophrenia with abnormalities in various components of the immune system [10, 11], here we focus primarily on circulating cytokine, oxidative stress and cellular markers of inflammation.

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 eosinophil's, monocytes and macrophages, dendritic cells and natural killer (NK) cells, which recognise and promote defence against pathogens but lack the sophistication to adapt compared to other more recent additions to the immune system [12]. See figure 1. The innate humoral component is made up of acute phase proteins such as C Reactive Protein (CRP) and the compliment cascade, which allow phagocytic cells to clear pathogens, as well as various cytokines (see below). Measurement of CRP as a marker of inflammation is common in other

branches of medicine, but with a lack of clinical significance readily apparent is not common practice in psychosis.

The second arm of our immune system is the “adaptive” system, which acts on re-exposure to a known pathogen, and has the ability to be conditioned. The prime cellular components of the adaptive system include T and B lymphocytes. There is considerable “cross-talk” 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 system (Th2). The Th1 system is polarised towards the production of pro inflammatory (activating) cytokines such as interleukin 2 (IL-2), interferon- γ (INF- γ), and tumour necrosis factor (TNF α). 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). 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 [13].

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. Changes in cytokines levels, their receptors and cytokine activity modifiers have been found in the blood and cerebrospinal fluid (CSF) of patients with schizophrenia [14]. Previously, the brain was thought to be protected from peripheral inflammatory responses; however, it is now clear that cytokines and other circulating inflammatory mediators can reach and influence the brain using a number of pathways. These pathways include direct entry through leaky circumventricular areas in blood-brain barrier (BBB), the lymphatic system as well as indirect pathways involving, for example, the Vagus nerve; for a review see [11]. Peripheral

or systemic inflammation is therefore relevant for neuropsychiatric disorders such as schizophrenia.

Inflammation might exert effects on dopamine via effect on cellular re-uptake and glutamatergic transmission and increased production of the tryptophan metabolite quinolinic acid, a powerful NMDA receptor agonist. Thus, the relationship of cytokines to known neurochemical changes in schizophrenia is of growing interest. Early changes in neurochemicals relevant to schizophrenia, such as glutamate or glutamine may occur in individuals with schizophrenia who have deficient defence against inflammatory challenge [16]. The effect of inflammation includes the generation of reactive oxygen species such as superoxide, hydroxyl and peroxy. They give rise to oxidative stress, which can damage tissues if defense mechanisms are inadequate. Oxidative stress occurs when there is an imbalance in the production of free radicals and the body's ability to counteract this insult via the action of antioxidants. Altered antioxidant enzyme response contributes to oxidative stress, and is inferred from higher tissue levels of reactive oxygen species (ROS) which leads to cell injury or death [15]. NMDA glutamate receptors are downregulated by oxidation [16], leading to disinhibition of pyramidal cells and unregulated glutamatergic excess. Thus, it is plausible that the response of brain glutamate to inflammation and associated oxidative stress will depend on the strength of defences against it. See figure 3.

There are notable difficulties with reported data around markers of inflammation in schizophrenia as, for example, studies have used patients in different stages of illness progression (prodrome vs. acute vs. chronic illness or active illness vs. remission). Levels of inflammatory markers could be also influenced by neuroleptic and other drugs, alcohol and illicit drug use, sex, smoking, body mass index (BMI), and co-morbid chronic physical

illness. The extensive list of potential confounds may be responsible for some of the discrepancies in reported studies [12]. In this chapter, we will review the evidence for aberrant circulating cytokines, cellular markers of inflammation and markers of oxidative stress in schizophrenia taking into account time and phase of illness, and provide a brief overview of CSF changes relevant to these markers. We will also discuss evidence from epidemiological cohort studies linking inflammation and psychosis, and the relevance of inflammation to treatment response, other risk factors such as early-life adversity, and common physical comorbidities for schizophrenia such as coronary heart disease and type-2 diabetes.

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 *in vitro* studies showing that antipsychotic drugs affect immune cell function, which often occurs very shortly after initial exposure to drug [17]. However, there are mixed results and differing effects, including either stimulatory or inhibitory actions. Relatedly, other recent *in vitro* studies suggest that part of the efficacy of some antipsychotics may be through suppression of cytokine mediated microglial activity [18]. For example aripiprazole suppresses apoptosis of rodent oligodendrocytes by IFN- γ -activated microglia, and inhibition of TNF- α secretion from IFN- γ -activated microglia [19]. Clozapine, the most effective antipsychotic medication, influences the immune system. Its effects on white blood cell (WBC) count is well known. Roge *et al* suggest a ‘cytokine storm on initiation’ of clozapine in 50% of patients [20] with longer term effects on IL-6, CRP [21] and high sensitivity CRP (hs-CRP) levels [22].

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 diagnosis was schizophrenia or schizophreniform disorder (81%). Highly significant effect sizes emerged for IL-1 β , IL-6, sIL2r and TNF α , suggesting that an increase in these cytokines in first episode psychosis (FEP) compared with controls, is unrelated to medication effects. Non-significant effect size estimates were obtained for IL-2, IL-4, and IFN- γ ; these cytokines were measured in studies with small samples, and in fewer studies altogether, so the analysis were potentially underpowered. However, IL-1 β stimulates the production of IL-6 and acute phase proteins. sIL-2r flows into the blood during T-cell activation and is a common marker for cell mediated immune activation. IL-6 is again pro-inflammatory; inducing acute phase proteins, and late B-cell differentiation. TNF α we have known for some time is a key player in the inflammatory response and induces acute phase proteins such as CRP.

Since this review, a small number of studies have explored the medication naive first episode group. Notably, Noto *et al* reported on cytokine profile in 55 FEP patients, showing that the presence of co-morbid depression was a significant influence; increased levels of IL-6, IL-10 and TNF α in FEP patients was found, however FEP patients with depression showed higher IL-4 and TNF α levels versus those without depression [23].

Acute Psychosis

In a comprehensive meta-analysis published in 2011, Miller *et al* explored cytokine function by phase of illness in schizophrenia. Assessing 40 studies, they found IL-1 β , IL-6 and TGF- β were raised in the acute phase of illness, both in relapse patients and those with first episode psychosis, and reduced with treatment [24]. See figure 2. IL-6 correlated to total level of

psychopathology in 2 out of 5 studies [24]. TNF α and IL-6 were the subject of most studies (97 and 156 total studies respectively). Thus, there is a proposal that these are state dependant markers of inflammation, resolving with symptom reduction. In first episode psychosis, Mondelli *et al* measured BDNF, IL-6 and TNF in 46 patients. Compared to healthy controls patients had reduced BDNF gene expression, and increased IL-6 and TNF. A history of childhood trauma was associated with lower BDNF mediated through IL-6 [25]. 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 [26]. In meta-analysis, IL-6, sIL2r, IL-1RA and TNF α 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 [27]. This suggests a lack of specificity of inflammatory pathogenesis of psychosis, i.e., the effect of inflammation is trans-diagnostic (see below). As with Noto's paper above [23], the suggestion may be that there is an inflammatory pathway for a subset of psychosis patients, and perhaps those with more affective symptoms.

A recent meta-analysis by Fernandes *et al.*, they consistently found elevated serum levels of CRP in both first episode and chronic phase patients, irrespective of medication status [28]. Furthermore, an association between CRP levels and positive symptoms but not negative symptoms of psychosis was found, suggesting a relation with acute phase of illness. However, Johnsen *et al* investigated CRP in acute psychosis, finding a particular association with cognitive dysfunctions rather than positive symptoms [29]. So overall, findings from patient samples on the association of inflammatory cytokines with specific types of symptoms is mixed.

In terms of markers of oxidative stress, evidence of diminished levels of the anti-oxidant, glutathione (GSH) [30, 31] has been reported. GSH is an antioxidant which provides within cell protection, and when depleted contributes to oxidative stress. Flatlow, Buckly and Miller reported a decrease in GSH in acutely relapsed patients with schizophrenia together with other anti-oxidants such as superoxide dismutase (SOD) and catalase (CAT), however there was significant heterogeneity in reported studies such that SOD and CAT but not GSH was reduced in FEP[32]. This may suggest a more persevered oxidative defense earlier in the course of illness.

As a substantial minority of patients with FEP do not go on to develop an enduring mental illness, and it may be that those with a protective oxidative defense to cellular stress have better outcomes [33]. This 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 [34]. The functional consequences of increased oxidative stress or reduced defence against this oxidative stress in the brain are still to be fully understood. However, it is likely that changes in neuronal membrane permeability eventually causing cell death is a mechanism of effect which may lead to grey matter volume (GMV) loss [35]. In respect to neurochemical change known in psychosis, Berk *et al* (2008) described the process of oxidative stress resulting in over activation of NMDA and altered dopamine receptor function. Whilst 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 over active or more readily available dopamine may account for positive symptoms [36]. NMDA glutamate receptors are downregulated by oxidation leading to disinhibition of pyramidal cells and unregulated glutamatergic excess [16].

Chronic Schizophrenia

TNF α , IL-12, INF- γ and sIL2r group have been reported to be elevated in both acute illness and stable ‘outpatients’ with chronic schizophrenia. Goldsmith *et al* found that contrary to acute phases of illness there was more specificity to diagnostic groups: in chronically ill patients, the levels of IL-6 were significantly increased in schizophrenia, euthymic (but not depressed) bipolar disorder and major depressive disorder (MDD) compared with controls [26]. IL-1 β and sIL2R were significantly increased in chronic schizophrenia and euthymic bipolar disorder. TNF α has consistently been reported as a trait marker of neuroinflammation [27]. Goldsmith *et al* review confirmed evidence that TNF was raised in acute schizophrenia compared to controls and remained so after treatment; thus as a trait marker of inflammation.

In meta-analysis of 5 studies, Miller and Culpeper found that 28% of patients with chronic schizophrenia have an elevated CRP [37]. 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 [38]. The association between CRP levels and cognitive functioning in patients with predominantly chronic schizophrenia has been reported in one cross-sectional study [39]. Together these studies suggest a poorer cognitive deficit course may be associated with enduring neuroinflammation.

There is substantial evidence of impaired oxidative defense in chronic schizophrenia, as reviewed by Flatlow *et al* in 2013 [32]. 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 [40]. Thus, the deficit state of some patients with schizophrenia may be related to a specific lack of defence against oxidative stress.

We have also previously reported significant clinical and phenomenological commonality between schizophrenia and depression [41]. In schizophrenia the dysfunction of glutamate is substantial: with 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 [42]. Just as in schizophrenia, there is substantial evidence for increase in peripheral markers of inflammation in MDD. In schizophrenia, it may be that the presence of depression is a key component explaining the cytokine imbalance responsible for the immune-inflammatory abnormalities described. However there is also evidence that immune dysfunction is present in samples of patients with schizophrenia even when depression is excluded or controlled for [43]. Thus models may include dual pathways for psychosis and depression, both of which have dysfunctional immune profiles, or that the presence of both has greater impact than the sum of each individually. The poorer outcome, increased risk of relapse, quality of life and functional outcome for those patients with both depression and schizophrenia may speak to the latter possibility [44]. Early changes in neurochemicals such as Glx may result in more significant impact for those individuals with deficient defence against this inflammatory challenge [16]. The effect of inflammation includes the generation of reactive oxygen species such as superoxide, hydroxyl and peroxy. The substantial evidence of impaired oxidative defense in early psychosis with diminished levels of GSH [30, 31, 45] 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.

Longitudinal studies

Psychological stress can activate innate immune response [46], so cytokine elevation during acute psychosis could be a consequence of illness rather than be its cause. Longitudinal studies are needed 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 [47-49]. Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a general population birth cohort, we have reported that higher levels of IL-6 in childhood is associated with increased risk of psychotic symptoms at early adulthood in a linear dose-response fashion [47]. See Figure X. 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, in the Northern Finland Birth Cohort 1986 (NFBC 1986) higher levels of CRP in adolescence was associated with increased risk of hospitalisation with a diagnosis of schizophrenia subsequently in adulthood. Furthermore, there was evidence that higher CRP levels in adolescence was associated with

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earlier age at illness onset [49]. 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 [50]. More recently a longitudinal study based on Swedish male conscripts reported that higher ESR, a marker of systemic inflammation, in early-adulthood is associated with increased risk of schizophrenia subsequently in adulthood [48]. Together these studies suggest that reverse causality is an unlikely explanation for previously observed association between inflammatory markers and psychosis. Inflammation could be a cause for psychosis rather than simply being a consequence of illness.

Although previous longitudinal studies have controlled for key confounders such as sex, BMI, social class, residual confounding still might explain the association between inflammatory markers and psychosis. Recently, we 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 [51]. Using data from the ALSPAC birth cohort, we have shown that a genetic variant in the IL-6 receptor gene (*IL6R* Asp358Ala; rs2228145) that is known to dampen down inflammation by impairing the activity of IL-6 is protective for severe depression and/or psychosis [52]. 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 body mass. 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.

Cerebrospinal fluid (CSF) studies

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 β , IL-6 and IL-8 were significantly elevated in schizophrenia patients compared with controls [53]. Similar findings were also observed for depression. Whether levels of inflammatory markers in peripheral blood corresponds 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 [53]. 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 18k Da (TSPO), a marker of microglial activation using [^{11}C] DPA-713[54]. Whilst 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.

Trans-diagnostic effect of inflammation

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 [10, 14, 53, 55, 56], depression [57, 58], anxiety [59], post-traumatic stress disorder (PTSD) [60], autism [61], Alzheimer's disease and other dementias [62]. 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

[63]. Using a symptom-level data on 10 positive and 10 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 [64]. Anhedonia is both an important negative symptom for psychosis and a core feature of depression [64].

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 [65]. In healthy volunteers, inflammation induces hedonic alterations (decreased preference for reward and increased avoidance of punishment) [66], which resemble anhedonia. Other reasons for this apparent trans-diagnostic effect could be shared genes that contributes 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 program the immune system leading with increased concentrations inflammatory markers in adulthood [67], 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 [68]. 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 [69]. Early-life adversity is associated with coronary heart disease, type-two diabetes, which are common co-morbidities for schizophrenia and depression. Young adults with psychotic symptoms display evidence of dysglycaemia, which is linked with levels of IL-6 in childhood [70]. Therefore, whether programming of innate immune response by early-life adversity may explain the comorbidity between schizophrenia, depression, coronary heart disease and type-two diabetes is an interesting hypothesis that needs investigating.

Association with treatment response and novel therapeutic options

Mondelli *et al* have reported an association between innate immune activation and poorer treatment response in 57 patients with FEP: non-responders (as defined by an absence of clinically significant symptom response in keep in with remission criteria at 12 weeks) had a significantly higher IL-6 and INF- γ at baseline. They also reported an aberrant cortisol wakening response and suggest this combination of markers may be an early signal of poor outcome [71]. Indeed, inflammatory mechanisms, as outlined above, have been cited as one of the potential mechanism of effect of Clozapine in treatment resistant schizophrenia.

As well as poor treatment response, makers 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 dyslipidemia, independent of weight-gain [72]. As mentioned earlier, in the ALSPAC birth cohort young adults with psychotic symptoms displayed evidence of dysglycasemia which was associated with childhood IL-6 levels [70]. 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. Clinical trials indicate anti-inflammatory drugs may be helpful for patients with depression who show evidence of inflammation [73, 74]. However results are mixed: as demonstrated by the recent large negative BeneMin trial [75] and therefore, patients with psychosis who do show evidence of inflammation may be more suitable candidate for RCTs of anti-inflammatory drugs in future.

Conclusion and future research

See key findings and challenges box below. 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. Some aspects are becoming clearer: there is good evidence of longitudinal association of inflammatory markers with psychosis prior to the onset of clinical disorder; elevated markers of inflammation and reduced oxidative stress in medication naive and first episode subjects. Evidence for treatment response prediction of outcome is also promising. However, there remain significant challenges: the heterogeneity of studies pulled into meta-analysis, a lack of replication in a number of studies and a significant heterogeneity of results with other major mental disorders. This may speak to a lack of specificity of the

inflammatory makers; a signal of any major brain illness, or to the lack of specificity in diagnostic groups. Indeed, the Kraepelinian dichotomy is challenged on many fronts; yet often remains set within biological research. Therefore, shifting the focus of research from syndrome to symptom (or constellation of symptoms) may help to elucidate the role of inflammation more fully. The use of the research domain criteria (RDoC) could lead to a better understanding of the mechanisms of psychopathology; as demonstrated the effects of inflammation are likely to cut-across traditional diagnostic categories. This framework would allow examining how inflammation influences developmental trajectories of neuropsychiatric symptoms, cognition or functional outcome over the life course.

An ambition would be phenotyping of patients based on their immunological characteristics, prior to choosing a tailored treatment approach including antipsychotic, anti-inflammatory and other novel neuroprotective medication and the length of monitoring and psychological interventions needed in those at most risk of cognitive decline or negative symptoms. Thus, if a subset of severe mental illness is characterised by an inflammatory profile, then anti-inflammatory agents may be more effective if targeted specifically to these patients. Presently Celecoxib has the strongest evidence base for interventions[76]; this may be larger still if tailored to those with active inflammatory pathway.

Many of the major advances in our understanding of the pathophysiology of schizophrenia suggest immune dysfunction as a novel and promising finding. The potential for translation in to treatment advances may be within our grasp. Our understanding of both the nosological boundaries and “end phenotypes” of psychotic disorders advances, and this together with our increasing knowledge of the complexities of the cellular and humoral immune system and its genetic coding, provide major advances in our understanding of neurobiological process in

psychotic illness. The investigation of immune dysfunction in psychosis offers the greatest potential to advance our understanding of schizophrenia in the 21st century.

Abbreviations

BBB: Blood–brain barrier

CRP: C-reactive protein

TNF- α : Tumour necrosis factor alpha

IL6: Interleukin-6

IL-8: Interleukin 8

CNS: Central nervous system

MHC: Major histocompatibility complex

ALSPAC: Avon longitudinal study of parents and children

CSF: Cerebrospinal fluid

HPA: Hypothalamic-pituitary-adrenal

ROS: Reactive Oxygen Series

Glx: Gutamate/Glutamine ratio

GSH: Glutathione

FEP: First Episode Psychosis

Key Findings

- Consistent evidence suggests patients with schizophrenia have elevated peripheral markers of inflammation
- Peripheral markers of inflammation appear to pre-date the onset of illness and be independent to medication.
- Depression and Schizophrenia both have elevated pro-inflammatory profiles: understanding the co-morbidity in psychosis is important.
- Physical health outcomes may be poorer in those with psychosis and immune dysfunction

Key Gaps

- Future research should elucidate further the relationship between peripheral markers of inflammation and structural or functional brain changes
- It remains unclear whether inflammation may be an effective target for novel therapies: anti-inflammatory and repurposed medication trials have produced mixed results
- A key question remains as to whether it is possible to stratify or better target those patients with psychosis and immune dysfunction.

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Declaration of Interest

The authors have no competing financial interests in relation to the work described.

References

1. Murray, R.M. and S.W. Lewis, *Is schizophrenia a neurodevelopmental disorder?* BMJ (Clinical Research Edition), 1987. **295**(6600): p. 681- 682.
2. Weinberger, D.R., *Implications of normal brain development for the pathogenesis of schizophrenia.* Arch Gen Psychiatry, 1987. **44**(7): p. 660-9.
3. Van Os, J., et al., *A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder.* Psychological medicine, 2009. **39**(2): p. 179.
4. Jones, A.L., et al., *Immune dysregulation and self-reactivity in schizophrenia: do some cases of schizophrenia have an autoimmune basis?* Immunology and Cell biology, 2005. **83**(1): p. 9-17.
5. Consortium, S.P.G.-W.A.S., *Genome-wide association study identifies five new schizophrenia loci.* Nature genetics, 2011. **43**(10): p. 969-976.
6. van Os, J., G. Kenis, and B.P. Rutten, *The environment and schizophrenia.* Nature, 2010. **468**(7321): p. 203-212.
7. Dameshek, W., *White blood cells in dementia praecox and dementia paralytica.* Arch Neurol Psychiatry, 1930. **24**: p. 855.
8. Müller, N., et al., *Impaired monocyte activation in schizophrenia.* Psychiatry Research, (0).
9. Ganguli, R., et al., *Serum interleukin-6 concentration in schizophrenia: elevation associated with duration of illness.* Psychiatry Res, 1994. **51**(1): p. 1-10.
10. Khandaker, G.M., et al., *Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment.* The Lancet Psychiatry, 2015. **2**(3): p. 258-270.
11. Khandaker, G.M. and R. Dantzer, *Is there a role for immune-to-brain communication in schizophrenia?* Psychopharmacology (Berl), 2016. **233**(9): p. 1559-73.
12. Upthegrove, R. and N.M. Barnes, *The immune system and schizophrenia: an update for clinicians.* Advances in Psychiatric Treatment, 2014. **20**(2): p. 83-91.
13. Janeway, C.A., et al., *Immunobiology: The Immune System in Health and Disease.* 5th ed. 2001, New York: Garland Science.
14. Upthegrove, R., N. Manzanares-Teson, and N.M. Barnes, *Cytokine function in medication-naïve first episode psychosis: a systematic review and meta-analysis.* Schizophrenia research, 2014. **155**(1-3): p. 101-108.
15. Mahadik, S.P., D. Evans, and H. Lal, *Oxidative stress and role of antioxidant and ω -3 essential fatty acid supplementation in schizophrenia.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2001. **25**(3): p. 463-493.
16. Traynelis, S.F., et al., *Glutamate receptor ion channels: structure, regulation, and function.* Pharmacological reviews, 2010. **62**(3): p. 405-496.
17. Drzyzga, Ł., et al., *Cytokines in schizophrenia and the effects of antipsychotic drugs.* Brain, behavior, and immunity, 2006. **20**(6): p. 532-545.
18. Bian, Q., et al., *The effect of atypical antipsychotics, perospirone, ziprasidone and quetiapine on microglial activation induced by interferon- γ .* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2008. **32**(1): p. 42-48.
19. Seki, Y., et al., *Pretreatment of aripiprazole and minocycline, but not haloperidol, suppresses oligodendrocyte damage from interferon-gamma-stimulated microglia in co-culture model.* Schizophr Res, 2013. **151**(1-3): p. 20-8.
20. Røge, R., et al., *Immunomodulatory effects of clozapine and their clinical implications: what have we learned so far?* Schizophrenia research, 2012. **140**(1): p. 204-213.
21. Kluge, M., et al., *Effects of clozapine and olanzapine on cytokine systems are closely linked to weight gain and drug-induced fever.* Psychoneuroendocrinology, 2009. **34**(1): p. 118-128.

22. Löffler, S., et al., *Clozapine therapy raises serum concentrations of high sensitive C-reactive protein in schizophrenic patients*. International clinical psychopharmacology, 2010. **25**(2): p. 101-106.
23. Noto, C., et al., *Effects of depression on the cytokine profile in drug naive first-episode psychosis*. Schizophrenia research, 2015. **164**(1): p. 53-58.
24. Miller, B.J., et al., *Meta-Analysis of Cytokine Alterations in Schizophrenia: Clinical Status and Antipsychotic Effects*. Biological Psychiatry, 2011. **70**(7): p. 663-671.
25. Mondelli, V., et al., *Cortisol and Inflammatory Biomarkers Predict Poor Treatment Response in First Episode Psychosis*. Schizophrenia Bulletin, 2015. **41**(5): p. 1162-1170.
26. Goldsmith, D.R., M.H. Rapaport, and B.J. Miller, *A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression*. Mol Psychiatry, 2016.
27. Goldsmith, D., M. Rapaport, and B. Miller, *A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression*. Molecular psychiatry, 2016. **21**(12): p. 1696-1709.
28. Fernandes, B., et al., *C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications*. Molecular psychiatry, 2016. **21**(4): p. 554-564.
29. Johnsen, E., et al., *The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis*. BMC psychiatry, 2016. **16**(1): p. 60.
30. Wood, S.J., et al., *Neurobiology of schizophrenia spectrum disorders: the role of oxidative stress*. Ann Acad Med Singapore, 2009. **38**(5): p. 396-401.
31. Raffa, M., et al., *Decreased glutathione levels and impaired antioxidant enzyme activities in drug-naive first-episode schizophrenic patients*. BMC psychiatry, 2011. **11**(1): p. 1.
32. Flatow, J., P. Buckley, and B.J. Miller, *Meta-analysis of oxidative stress in schizophrenia*. Biological psychiatry, 2013. **74**(6): p. 400-409.
33. Lally, J., et al., *Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies*. The British Journal of Psychiatry, 2017: p. bjp. bp. 117.201475.
34. Wang, L.-J., et al., *Increased serum levels of cysteine in patients with schizophrenia: A potential marker of cognitive function preservation*. Schizophrenia Research, 2017.
35. Mahadik, S.P. and S. Mukherjee, *Free radical pathology and antioxidant defense in schizophrenia: a review*. Schizophrenia research, 1996. **19**(1): p. 1-17.
36. Howes, O.D. and S. Kapur, *The dopamine hypothesis of schizophrenia: version III—the final common pathway*. Schizophrenia bulletin, 2009. **35**(3): p. 549-562.
37. Miller, B.J., N. Culppepper, and M.H. Rapaport, *C-reactive protein levels in schizophrenia: a review and meta-analysis*. Clinical schizophrenia & related psychoses, 2013. **7**(4): p. 223-230.
38. Dickerson, F., et al., *C-reactive protein is elevated in schizophrenia*. Schizophrenia research, 2013. **143**(1): p. 198-202.
39. Dickerson, F., et al., *C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia*. Schizophrenia research, 2007. **93**(1): p. 261-265.
40. Fraguas, D., et al., *Decreased glutathione levels predict loss of brain volume in children and adolescents with first-episode psychosis in a two-year longitudinal study*. Schizophrenia research, 2012. **137**(1): p. 58-65.
41. Upthegrove, R.M., S; Birchwood, Max, *Depression and schizophrenia: cause, consequence or trans-diagnostic issue?* Schizophrenia Bulletin, 2016. **online ahead of print**.
42. Marsman, A., et al., *Glutamate in schizophrenia: a focused review and meta-analysis of 1H-MRS studies*. Schizophrenia bulletin, 2013. **39**(1): p. 120-129.
43. Khandaker, G.M., R. Dantzer, and P.B. Jones, *Immunopsychiatry: important facts*. Psychological medicine, 2017. **47**(13): p. 2229-2237.

44. McGinty, J., M.S. Haque, and R. Upthegrove, *Depression during first episode psychosis and subsequent suicide risk: A systematic review and meta-analysis of longitudinal studies*. Schizophrenia research, 2017.
45. Jiménez-Fernández, S., et al., *Oxidative stress and antioxidant parameters in patients with major depressive disorder compared to healthy controls before and after antidepressant treatment: results from a meta-analysis*. The Journal of clinical psychiatry, 2015. **76**(12): p. 1658-1667.
46. Maes, M., et al., *The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety*. Cytokine, 1998. **10**(4): p. 313-8.
47. Khandaker, G.M., et al., *Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study*. JAMA Psychiatry, 2014. **71**(10): p. 1121-8.
48. Kappelmann, N., et al., *Systemic inflammation and intelligence in early adulthood and subsequent risk of schizophrenia and other non-affective psychoses: a longitudinal cohort and co-relative study*. Psychol Med, 2018: p. 1-8.
49. Metcalf, S.A., et al., *Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: A prospective birth cohort study*. Brain Behav Immun, 2017. **59**: p. 253-259.
50. Wium-Andersen, M.K., D.D. Orsted, and B.G. Nordestgaard, *Elevated C-reactive protein associated with late- and very-late-onset schizophrenia in the general population: a prospective study*. Schizophr Bull, 2014. **40**(5): p. 1117-27.
51. Davey Smith, G. and S. Ebrahim, 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol, 2003. **32**(1): p. 1-22.
52. Khandaker, G.M., et al., *Association between a functional interleukin 6 receptor genetic variant and risk of depression and psychosis in a population-based birth cohort*. Brain Behav Immun, 2017.
53. Wang, A.K. and B.J. Miller, *Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons Between Schizophrenia, Bipolar Disorder, and Depression*. Schizophr Bull, 2018. **44**(1): p. 75-83.
54. Coughlin, J., et al., *In vivo markers of inflammatory response in recent-onset schizophrenia: a combined study using [11 C] DPA-713 PET and analysis of CSF and plasma*. Translational psychiatry, 2016. **6**(4): p. e777.
55. Miller, B.J., et al., *Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects*. Biol Psychiatry, 2011. **70**(7): p. 663-71.
56. Upthegrove, R., N. Manzanarez-Teson, and N.M. Barnes, *Cytokine function in medication-naïve first episode psychosis: a systematic review and meta-analysis*. Schizophr Res, 2014. **155**(1-3): p. 101-8.
57. Dantzer, R., et al., *From inflammation to sickness and depression: when the immune system subjugates the brain*. Nat Rev Neurosci, 2008. **9**(1): p. 46-56.
58. Miller, A.H., V. Maletic, and C.L. Raison, *Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression*. Biol Psychiatry, 2009. **65**(9): p. 732-41.
59. Wohleb, E.S., et al., *Re-establishment of anxiety in stress-sensitized mice is caused by monocyte trafficking from the spleen to the brain*. Biol Psychiatry, 2014. **75**(12): p. 970-81.
60. Eraly, S.A., et al., *Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk*. JAMA Psychiatry, 2014. **71**(4): p. 423-31.
61. Brown, A.S., et al., *Elevated maternal C-reactive protein and autism in a national birth cohort*. Mol Psychiatry, 2014. **19**(2): p. 259-64.
62. Schmidt, R., et al., *Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study*. Ann Neurol, 2002. **52**(2): p. 168-74.

63. Khandaker, G.M., et al., *Positive and Negative Symptoms of Psychosis Associated with Circulating C-Reactive Protein: Unravelling Trans-diagnostic Effect of Inflammation* (under review), 2018.
64. APA, *Diagnostic and statistical manual of mental disorders (5th ed.)*. 2013, American Psychiatric Publishing: Arlington, VA.
65. Felger, J.C., et al., *Chronic interferon-alpha decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in nonhuman primates*. Neuropsychopharmacology, 2013. **38**(11): p. 2179-87.
66. Harrison, N.A., et al., *A Neurocomputational Account of How Inflammation Enhances Sensitivity to Punishments Versus Rewards*. Biol Psychiatry, 2016. **80**(1): p. 73-81.
67. Baumeister, D., et al., *Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha*. Mol Psychiatry, 2016. **21**(5): p. 642-9.
68. Khandaker, G.M., et al., *Influence of Prenatal Maternal Depression on Circulating Inflammatory Markers and Risks of Depression and Psychosis in Offspring: a prospective birth cohort study*. Psychoneuroendocrinology, 2018 (in press).
69. Barker, D.J.P., *Fetal and Infant Origins of Adult Disease*. 1993, London: British Medical Journal.
70. Perry, B.I., et al., *Dysglycaemia, Inflammation and Psychosis: Findings From the UK ALSPAC Birth Cohort*. Schizophr Bull, 2018.
71. Mondelli, V., et al., *Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis*. Schizophrenia bulletin, 2015. **41**(5): p. 1162-1170.
72. Russell, A., et al., *Inflammation and metabolic changes in first episode psychosis: preliminary results from a longitudinal study*. Brain, behavior, and immunity, 2015. **49**: p. 25-29.
73. Raison, C.L., et al., *A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers*. JAMA Psychiatry, 2013. **70**(1): p. 31-41.
74. Kappelmann, N., et al., *Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions*. Mol Psychiatry, 2018. **23**(2): p. 335-343.
75. Deakin, B., et al., *The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomised, double-blind, placebo-controlled trial*. The Lancet Psychiatry, 2018. **5**(11): p. 885-894.
76. Zheng, W., et al., *Adjunctive celecoxib for schizophrenia: a meta-analysis of randomized, double-blind, placebo-controlled trials*. Journal of psychiatric research, 2017. **92**: p. 139-146.

Figure 1 Cytokine profile in medication naive first episode psychosis: Modified from Upthegrove et al 2014 (14). Increased IL-6, TNF- α , IL-1 β and sIL-2r

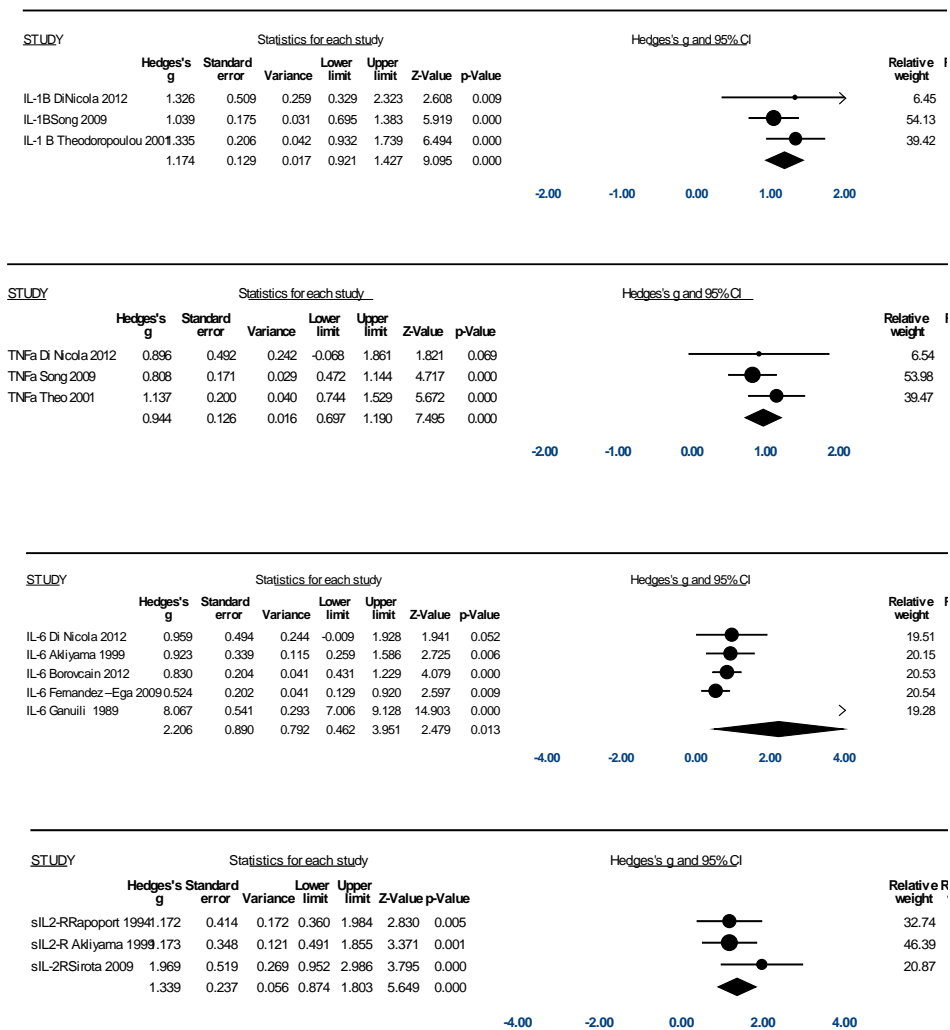


Figure2: From Upthegrove and Barnes 2015

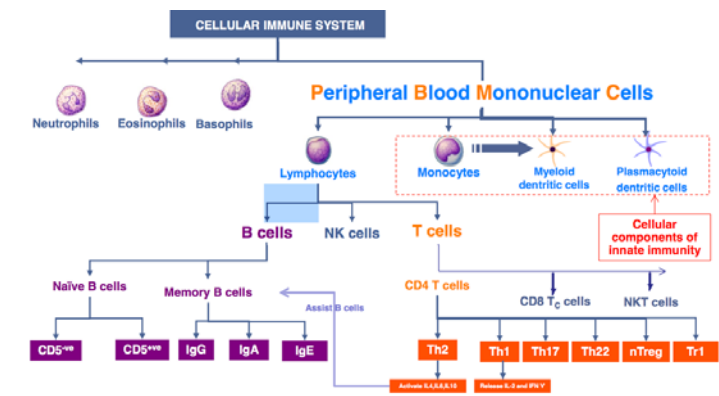


Figure 3:Depression, psychosis, inflammation and oxidative defence Title needed

