 doi:10.20944/preprints201809.0289.v1

The role of aberrations in the immune-inflammatory reflex system (IRS) and the compensatory immune-regulatory reflex system (CIRS) in different phenotypes of schizophrenia: the IRS-CIRS theory of schizophrenia

Short title: The IRS-CIRS theory of schizophrenia

Chutima Roomruangwong, M.D. [a]; Cristiano Noto, M.D. [b,c]; Buranee Kanchanatawan, M.D. [a]; George Anderson [d]; Marta Kubera, Ph.D. [e]; Andre F. Carvalho, M.D.; Ph.D. [f,g], Michael Maes, M.D., Ph.D. [a,h,i]

[a] Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand;

[b] Schizophrenia Program (PROESQ), Department of Psychiatry, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil;

[c] GAPi (Early Psychosis Group), Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil;

[d] CRC, London & Scotland, UK;

[e] Department of Experimental Endocrinology Institute of Pharmacology, Polish Academy of Sciences, Poland;

[f] Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, ON, Canada;

[g] Centre for Addiction & Mental Health (CAMH), Toronto, ON, M6J 1H4, Canada;

[h] Department of Psychiatry, Medical University of Plovdiv, Plovdiv, Bulgaria;

[i] IMPACT Strategic Research Centre, Deakin University, Geelong, Vic, Australia.

Chutima Roomruanwong: chutima.room@gmail.com

Cristiano Noto: csnoto@gmail.com

Buranee Kanchanatawan: drburanee@gmail.com

George Anderson: anderson.george@rocketmail.com

Marta Kubera: kubera@if-pan.krakow.pl

Andre Carvalho: Andre.Carvalho@camh.ca

Michael Maes: dr.michaelmaes@hotmail.com

Address corresponding author:

Prof. Dr. Michael Maes, M.D., Ph.D.

Department of Psychiatry

Faculty of Medicine

Chulalongkorn University

Bangkok

Thailand

dr.michaelmaes@hotmail.com

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 doi:10.20944/preprints201809.0289.v1

Abstract

In this paper we propose a novel theoretical framework, which was previously developed for major depression and bipolar disorder, namely the compensatory immune-regulatory reflex system (CIRS), as applied to the neuro-immune pathophysiology of schizophrenia and its phenotypes, including first episode psychosis (FEP), acute relapses, chronic and treatment resistant schizophrenia (TRS), comorbid depression, and deficit schizophrenia. These schizophrenia phenotypes and manifestations are accompanied by increased production of positive acute phase proteins, including haptoglobin and α2-macroglobulin, complement factors, and macrophagic M1 (IL-1β, IL-6 and TNF-α), T helper (Th)-1 (interferon-γ and IL-2R), Th-2 (IL-4, IL-5), Th-17 (IL-17) and T regulatory (Treg; IL-10 and transforming growth factor (TGF)-β1) cytokines, cytokine-induced activation of the tryptophan catabolite (TRYCAT) pathway as well as chemokines, including CCL-11 (eotaxin), CCL-2, CCL-3 and CXCL-8. While the immune profiles in the different schizophrenia phenotypes indicate activation of the immune-inflammatory response system (IRS), there are simultaneous signs of CIRS activation, including increased levels of the IL-1 receptor antagonist (sIL-1RA), sIL-2R and tumor necrosis factor-α receptors, Th-2 and Treg phenotypes with increased IL-4 and IL-10 production, and increased levels of TRYCATs and haptoglobin, α2-macroglobulin and other acute phase reactants, which have immune-regulatory and anti-inflammatory effects. Signs of activated IRS and CIRS pathways are also detected in TRS, chronic and deficit schizophrenia indicating that these conditions are accompanied by a new homeostatic setpoint between upregulated IRS and CIRS components. In FEP, increased baseline CIRS activity is a protective factor which may predict favorable clinical outcomes. Moreover, impairments in the CIRS are associated with deficit schizophrenia and greater impairments in semantic and episodic memory. It is concluded that

CIRS plays a key role in the pathophysiology of schizophrenia by negatively regulating the primary IRS and contributing to recovery from the acute phase of illness. Components of the CIRS may offer promising therapeutic targets for schizophrenia.

Key words: schizophrenia, immune system, inflammation, cytokines, immune regulatory, CIRS, psychiatry, immunology, psychosis

List of abbreviations

TRYCAT = Tryptophan catabolite

NMDA = N-methyl-D-aspartate

Hp = Haptoglobin

Fb = Fibrinogen

C3C = complement component 3

C4 = complement 4

alpha 1S = Alpha 1-acid-glycoprotein

Hpx = Hemopexin

sIL-2R = soluble interleukin-2 receptor

IL = Interleukin

IRS = Immune-inflammatory response system

TNFα = Tumor necrosis factor-alpha

IFN-γ = Interferon-gamma

Th = T helper

iTreg = induced T regulatory

TGF = Transforming growth factor

CIRS = Compensatory immune-regulatory reflex system

FEP = First episode psychosis

TRS = Treatment resistant schizophrenia

LPS = Lipopolysaccharides

NK cells = Natural killer cells

CRP = C-reactive protein

CSF = cerebrospinal fluid

CC= Clara cell secretory protein

CXCL8= chemokine (C-X-C motif) ligand 8

CCL= chemokine ligands

MIP = macrophage inflammatory protein

IDO = Indoleamine 2,3-dioxygenase enzyme

PANSS = The Positive and Negative Syndrome Scale

NFκB = Nuclear factor kappa B

NDEL1= Nuclear distribution protein nudE-like 1

MBP = Myelin basic protein

COMT = catechol-O-methyltransferase

HERV = Human endogenous retrovirus

GM-CSF = Granulocyte-macrophage colony-stimulating factor

DCs = dendritic cells

1. Introduction

Schizophrenia is a major psychiatric disorder associated with meaningful disability [1-3]. The onset of schizophrenia typically occurs around late adolescent to early adulthood [4], with males having an earlier age of onset, whilst females exhibit a second post-menopausal peak [5]. A number of risk factors have emerged, including: being male [6]; an array of genetic susceptibility alleles [7-9]; immune-related processes and genes [10-12]; pre- and/or perinatal complications or exposure to environmental insults [13, 14], malnutrition [15], infections [16, 17], and exposure to neurotoxic infectious pathogens [18].

Although the role of immune dysregulation has been long investigated in schizophrenia [19], it was not until 1995, when Smith and Maes (1995) proposed the monocyte-T lymphocyte theory of schizophrenia that modern research in this area started to flourish [20]. The monocyte-T lymphocyte theory incorporated activated immune-inflammatory pathways, neurodevelopmental pathology associated with prenatal infections, activated microglia, increased nitro-oxidative stress, cytokine-induced activation of the tryptophan catabolite (TRYCAT) pathway, modulation of the N-methyl D-aspartate (NMDA) receptor and glutamate production [20]. In their studies, Maes and coworkers reported that the acute phase of schizophrenia is accompanied by an acute phase (inflammatory) response with significantly higher plasma haptoglobin (Hp), fibrinogen (Fb), complement component 3 (C3C), C4, alpha 1-acid-glycoprotein (alpha 1S), and hemopexin (Hpx) levels as compared with normal controls, with the levels of these factors being even higher in untreated patients [21]. Moreover, they also found significantly higher levels of soluble interleukin-2 receptor (sIL-2R), an indicator of T cell activation, and Interleukin 6 (IL-6) and sIL-1R antagonist (sIL-1RA), indicants of monocytic activation, in schizophrenia patients [22]. These early data pointed to an involvement of adaptive immunity, activation of the monocytic and T cells and an inflammatory response in schizophrenic patients. Since then many more results have been published confirming these earlier findings indicating immune-inflammatory processes in the peripheral blood [23], the brain [24-26] and genome-wide association studies as well [27, 28].

In the peripheral blood of patients with schizophrenia, there are validated findings on an activation of the immune-inflammatory response system (IRS), including M1 macrophagic activation, with increased production of IL-6 and tumor necrosis factor alpha (TNF)-α, T helper (Th)-1 activation, with increased levels of interferon (IFN) and IL-2, and activation of a Th-17 response with increased levels of IL-17 [29-31]. Schizophrenia patients also show increased levels of immune products which have immunosuppressive effects, for example the sIL-2R and sIL-1RA, to name a few [32]. In addition, schizophrenia patients exhibit signs of increased activity of immune cells with negative immune-regulatory effects, namely induced T regulatory (iTreg) cells (with increased levels of IL-10 and transforming growth factor (TGF)-β) and a Th-2 shift (with increased levels of IL-4) [29, 33, 34]

Therefore, schizophrenia is accompanied by activation of IRS (immune activation) and signs of counter-regulatory immune mechanisms, which are mounted following immune activation and tend to attenuate the detrimental effects of a primary IRS [32]. For example, the release of IL-1β by activated immune cells is accompanied by an increased release of the IL-1RA, which may attenuate IL-1 pro-inflammatory signaling (see below). Thus, increased levels of the sIL-1RA indicate immune activation, but at the same time inhibit the IRS. We named the aggregate of these immune-regulatory responses the “compensatory immune-regulatory reflex

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system" (CIRS) [32]. Nevertheless, no review has addressed the activity of the CIRS is relation to IRS activation in schizophrenia.

Schizophrenia is a heterogeneous phenotype and recent research showed that different phenotypes of schizophrenia may exhibit distinct immune profiles and even different IRS and CIRS profiles. For example, a series of studies conducted by Noto and colleagues between 2014-2018 (see below) reported different immune profiles in different schizophrenia subtypes, including first episode psychosis (FEP), treatment resistant schizophrenia (TRS) and chronic schizophrenia. A meta-analysis shows that acute exacerbations of schizophrenia are accompanied by activation of the IRS, with increased levels of M1 macrophagic and Treg cytokines, while Th-1 activation with increased levels of IL-12, interferon-gamma (IFN-γ) and sIL-2R, may constitute a trait marker of schizophrenia [35]. Patients with deficit schizophrenia show specific alterations in the CIRS as compared to patients with non-deficit forms of schizophrenia. However, no research has addressed whether schizophrenia phenotypes, including FEP, relapses of acute psychoses, chronic schizophrenia, treatment resistant schizophrenia and deficit schizophrenia present with different IRS and CIRS profiles.

2. Aims of the review

The aims of this narrative review are a) to summarize the immune findings in different phenotypes and dimensions of schizophrenia with reference to IRS and CIRS components in the peripheral blood and examine which component prevails in these different forms of schizophrenia; and b) to propose a new immune-pathological framework for schizophrenia based on aberrations in the IRS and CIRS.

3. Methods

We performed a narrative review by searching Google Scholar, PubMed and Scopus for articles published in English from 1991 to present, using combinations of the words schizophrenia, FEP, treatment resistant schizophrenia, chronic schizophrenia and deficit schizophrenia with immune, inflammation, adaptive immunity, humoral immunity, acute phase response, interleukins, cytokines, chemokines, M1 macrophagic, T helper (Th)-1, Th-2, Th-3, and T regulatory (Treg).

4. Basics on IRS versus CIRS

Macrophages and lymphocytes exist in distinct functional states such as inflammatory versus anti-inflammatory or negative immune-regulatory effects, including macrophage polarization into M1 (classically activated) and M2 (alternatively activated) macrophages, and T helper (Th) polarization into Th-1, Th-2, and Th-17 phenotypes [32]. Thus, M2 macrophages display immune-regulatory effects (Th-2 and Treg-like activities by producing IL-10 and TGF-β1, inhibiting IL-1 release, elevating IL-1RA production), while M1 macrophages are pro-inflammatory (produce IL-1β, IL-6 and TNF-α, activate Th-1 responses with IFN-γ production) [36, 37]. Naive T (T0) cells can be primed to differentiate into different Th phenotypes with different activities such as: a) Th-1 phenotype (immune activation, pro-inflammatory) through activation by IL-12; b) Th-2 phenotype (anti-inflammatory and producing IL-4 and IL-5) through activation by IL-4; and c) Th-17 phenotype (involved in autoimmunity and pro-inflammatory) through activation by IL-6, IL-1β and TGF-β.

Figure 1 shows that IL-1β, IL-6 and TNF-α are predominantly produced by activated M1 (and other immune) cells and play a key role in orchestrating the immune-inflammatory response

 doi:10.20944/preprints201809.0289.v1

as well as the acute phase response in the liver. The same immune cells that release IL-1β also release IL-1RA following stimulation by M1 and Th-1 products such as IL-1, IL-6 and IFN-γ. Importantly, once released in the blood, sIL-1RA inhibits IL-1β signaling by binding to the IL-1 cell receptor [36]. Therefore increased plasma levels of sIL-1RA indicate immune activation including monocytic / macrophagic activation with increased IL-1β release, but at the same time indicate increased regulation of the IL-1 signaling pathway [36].

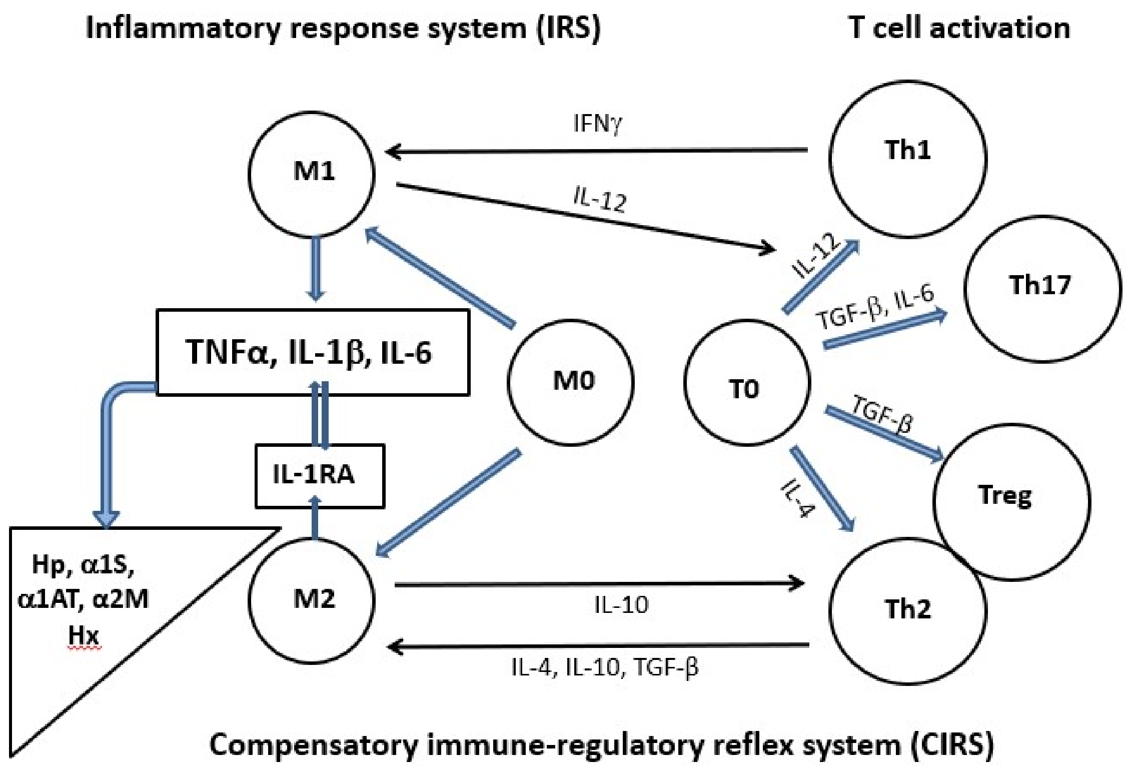

Figure 1. Key immune cell phenotypes and its products belonging to the immune-inflammatory response system (IRS) and the compensatory immune-regulatory reflex system (CIRS).

IL-6 has several pro-inflammatory effects including induction of Th-17 differentiation [38]. Nevertheless, IL-6 also exhibits immune-regulatory effects for example by promoting iTreg ($CD4^+$ $CD25^+$ $Foxp3^+$) activation by TGF-β and increasing sIL-1RA and sTNF-R production (both of which have immune-regulatory effects). Here, a differentiation should be made between

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classical IL-6 signaling pathway and IL-6 trans-signaling [38]. IL-6 may bind to its membrane receptor, namely the IL-6R, thereby forming a complex with gp130 and activating the classical IL-6 signaling pathway, which is frequently immune-regulatory. Activated immune cells release (through shedding) the IL-6R into the plasma thereby binding to IL-6 and forming an IL-6-sIL-6R complex, which may subsequently bind to membrane gp130 and induce IL-6 trans-signaling, which has predominant pro-inflammatory activities [38].

TNF-α is another pro-inflammatory cytokine, which is produced mainly by macrophages, monocytes and T cells [39]. TNF-α and other immune signals, including increased levels of IL-1, IL-6, IL-2, IL-10 and lipopolysaccharides (LPS) may cause shedding of TNF-α receptors in the plasma leading to increased levels of sTNF-R1 and sTNF-R2 [40]. Therefore, elevated plasma concentrations sTNF-Rs can be regarded as surrogate biomarkers of an ongoing immune-inflammatory response [41]. However, both receptors concomitantly act as decoy receptors thereby attenuating TNF-α signaling and protecting against TNF-α-related toxicity [32].

Figure 1 further shows that cytokines such as IL-4 (Th-2-like), TGF-β and IL-10 (Treg) may have immune-regulatory effects and are major players of the CIRS and that iTreg cells are major components of the CIRS. iTreg cells exert immune-regulatory in part by enhancing the production of IL-10 and TGF-β thereby inducing tolerance by regulating Th-1, Th-17 and Th-2 cells [32]. IL-4 activates M2 macrophages, which also play a role in the CIRS by activating IL-10, TGF-β and the sIL-1RA and suppressing IL-1β, IL-6 and TNF-α production [32]. TGF-β and IL-10 may also induce T0 cells which in turn differentiate into iTreg cells, whilst IL-10 enhances the release of IL-1RA from macrophages and also suppresses Th-1-like, M1, dendritic, effector and cytotoxic cells, as well as B and natural killer (NK) cells [32]. TGF-β attenuates pro-inflammatory cytokine-production by M1 macrophages and proliferation of other immune cells (e.g. B cells). As such, increased levels of IL-10, IL-4 and TGF-β occur during an immune-inflammatory response, but those actors regulate and counteract the IRS response and therefore may be key players together with Th-2 and iTreg cells in the CIRS.

Figure 1 also shows that IL-6, IL-1β and TNF-α promote the production of acute phase proteins by the liver, including C-reactive protein (CRP), Hp, alpha 1S, Hpx, alpha-1 antitrypsin and alpha-2 macroglobulin. As previously explained, Hp, alpha 1S, Hpx, alpha-1 antitrypsin (but not CRP) have significant anti-inflammatory effects through different mechanisms. For example, those acute phase proteins stimulate the production of IL-10 and heme-oxygenase-1, they have anti-protease activities, attenuate the production of IL-8 and Th-17-associated inflammation and bind hemoglobin [32]. In addition, alpha-2 macroglobulin shows potent anti-inflammatory, anti-oxidant and anti-fibrosis effects for example by capturing nearly all proteinase activity, promoting DNA repair mechanisms and binding to IL-6, IL-1β and TNF-α [42, 43]. This latter activity may induce latency of cytokines and thus exert immune-regulatory effects by protecting against the toxic effects of these cytokines and targeting these cytokines to cells bearing the alpha-2 macroglobulin-receptor, a mechanism that ultimately results in increased production of alpha-2 macroglobulin [43]. In other words, IL-6 and other pro-inflammatory cytokines induce the acute phase response in the liver and therefore increased levels of these proteins indicate the presence of an inflammatory response, but at the same time some of these proteins exert potent anti-inflammatory and anti-oxidative effects and thus are part of the CIRS.

Table 1 displays an overview of the major chemokines and cytokines and their receptors, which are reported to be altered across schizophrenia phenotypes. This table also shows the type of cells producing these molecules as well as the predominant functions of these immune products.

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Table 1. Biomarkers of the immune-inflammatory response system (IRS) and compensatory immune-regulatory reflex system (CIRS) in schizophrenia.

Cytokine / chemokine / soluble receptors	**Predominant Type**	**IRS / CIRS function**	**Main IRS and CIRS functions**
Interleukin (IL)-1β	M1	IRS	Pro-inflammatory cytokine
Soluble IL-1 receptor antagonist (sIL-RA)	M2	CIRS	Attenuates IL-1 signaling; promotes tissue repair and resolution of inflammation
Tumor necrosis factor (TNF)-α	M1	IRS	Pro-inflammatory cytokine
sTNF-R60 (R1) and sTNF-R80 (R2)	-	CIRS	Act as decoy receptors and reduce TNFα bioactivity and signaling
IL-6	M1	IRS	Pro-inflammatory cytokine
sIL-6R	-	IRS	Binds IL-6 and causes IL-6 trans-signaling
Granulocyte-macrophage colony stimulating factor (GM-CSF)	M1	IRS	Stimulates development of immune cells
IL-2	Th-1	IRS	A Th-1-like cytokine
sIL-2R	Th-1	CIRS	Lowers IL-2 levels; suppresses IL-2-induced proliferation; promotes differentiation into Treg cells
Interferon-γ (IFN-γ)	Th-1	IRS	Th-1-like cytokine
IL-12	Th-1	IRS	Differentiates naïve T cells into Th-1 cells
IL-17	Th-17	IRS	Pro-inflammatory cytokine
IL-4	Th-2	CIRS	Suppresses M1 and Th-1 cytokines, promotes M2 macrophages; activates sIL-1RA and IL-10 production
IL-5	Th-2	-	Growth factor for B cells and eosinophils
IL-13	Th-2	CIRS	Regulator of IgE synthesis; has CIRS functions comparable to those of IL-4 but less potent
Transforming growth factor (TGF-β1)	Treg	CIRS	Inhibits Th-1 and Th-17 cells; stimulates sIL-1RA; Lowers production of IL-1∃, IL-12, IFN(and TNFα
IL-10	Treg	CIRS	Major immune-regulatory cytokine
IL-3	Activated T cells	IRS	Activates macrophages and granulocytes and thus immune

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			cell production
IL-7	Bone marrow and thymus cells	IRS	Activates the differentiation of lymphoid progenitor cells and T and B cell development; induces Th-1 subsets; decreases TGF-β1 production
IL-15	Macrophages, dendritic cells, epithelium cells	IRS	Pro-inflammatory, pleiotropic cytokine; costimulates IFN-γ; expansion and survival of immune cells
IL-18	Antigen presenting cells	IRS	Pro-inflammatory cytokine; differentiates naïve T cells into Th-1; activates macrophages; increases IFN-γ; host defense
Uteroglobin or CC16	-	CIRS	Anti-cytokine and immunomodulation
CCL-2 or monocyte chemoattractant protein (MCP1)	macrophages, monocytes and dendritic cells	IRS	Recruits T cells and monocytes
CCL-3 or macrophage inflammatory protein (MIP-1α)	M1	IRS	Recruits mononuclear cells, activates granulocytes and induces the production of IL-1, IL-6 and TNF-α
CCL-11 or eotaxin	Th-2, eosinophils	IRS	Recruits eosinophils
CXCL-8 or IL-8	M1	IRS	Induces neutrophil chemotaxis and promotes phagocytosis
C-Reactive Protein	M1-acute phase	IRS	Acute phase reactant
Haptoglobin	M1-acute phase (liver)	CIRS	Captures HMGB1 and complexes hemoglobin; stimulates a Th-2 phenotype, IL-10 and heme-oxygenase-1 (HO-1); inhibits cyclooxygenase 2 and effector cells; potent anti-oxidant
α1 Anti-trypsin	M1-acute phase (liver)	CIRS	Has anti-protease activity (e.g. elastase) Inhibits the production of IL-8 Regulates neutrophil chemotaxis, T and B cell proliferation, cytokine production by monocytes and macrophages
Alpha-2 macroglobulin	M1-Acute phase (liver)	CIRS	Induces latency of IL-6, TNF-α and IL-1β and has immune-regulatory effects by protecting against the toxic effects of these cytokines; panproteinase inhibitor
Hemopexin	Acute phase (liver)	CIRS	Inhibits Th-17 associated inflammation; binds haem; inhibits synergy with HMGB1
Alpha 1-acid-glycoprotein	M1-Acute phase (liver)	CIRS	Attenuates mitogen-induced T cell proliferation; prevents Gram-negative bacteria infections; promotes wound healing

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5. IRS and CIRS in schizophrenia

The role of immune-inflammation in schizophrenia has attracted considerable research with data generally supporting a role for increased peripheral and central inflammatory responses in schizophrenia [35, 44-47]. The first study which attributed immune findings in schizophrenia to an ongoing inflammatory response, was published in 1997 [21]. These authors reported that patients with schizophrenia have significantly increased plasma levels of acute phase proteins, such as Hp, Fb, alpha 1-antitrypsin, alpha 1S and Hpx, as well as complement factors C3C and C4. This study also reported that aberrations in acute phase reactants were more pronounced in patients with schizophrenia than in patients with major depression. Furthermore, there was also a significant association between schizophrenia and Hp-2 gene frequency and Hp 2-2 phenotype in schizophrenia as compared with controls [48]. This is of relevance as Hp genotypes/phenotypes have different immune-inflammatory and pro-oxidant effects, which may differently influence the pathophysiology of medical conditions [49, 50]. Hence, the Hp 2 gene and 2-2 genotype is associated with increased inflammatory potential and related carotid artery intima-media thickness [51] and poorer disease outcomes [52]. This together with prior results showing increased cerebrospinal fluid (CSF) levels of IL-1, and plasma/serum levels of IL-6, sIL-1RA, IL-2 and sIL-2R indicate an immune-inflammatory (IL-6 and sIL-1RA) and Th-1-like (IL-2 and sIL-2R) response in schizophrenia [22, 53-57]. Interestingly, Maes et al. (1996) also reported lowered levels of Clara cell secretory protein 16 (CC16) or uteroglobulin, an endogenous anti-inflammatory protein, which inhibits the production of pro-inflammatory cytokines and thus acts as an anti-cytokine mediator [58]. As such, already in the 1990ties it was established that schizophrenia is characterized by an immune-inflammatory response and simultaneous signs of a

CIRS as indicated by higher sIL-2R and sIL-1RA levels [22, 58] and a relative deficit in CC16, an endogenous CIRS component [58].

These early findings on IRS activation in schizophrenia are now well replicated and synthesized in meta-analytic studies. A meta-analysis suggested that changes in IL-1β, IL-6, and TGF-β to be state-related markers of schizophrenia, whilst alterations in peripheral levels of IL-12, INF-γ, TNF-α, and sIL-2R may be trait markers for schizophrenia [35]. Moreover, findings on an acute phase responses in schizophrenia were replicated for example by [59] who found elevated serum levels of CRP in schizophrenia and a positive correlation between CRP and symptom severity. Increased TNF-α levels are now established as one of the most frequently reported findings in schizophrenia [35, 45], while also its soluble receptors, sTNF-R1 and sTNF-R2, are also frequently increased in this disorder [33, 60-63]. Again, these findings show that schizophrenia is accompanied by IRS activation (increased serum levels of TNF-α and its receptors) and increased CIRS activity due to the immune-regulatory effects of sTNF-R1 and sTNF-R2.

A relatively more recent new direction in schizophrenia research is the examination of alterations in the production and signaling of chemokines, which are immune mediators that display chemotactic activity attracting various types of immune effector and inflammatory cells. Thus, the first reports that emerged in the literature pointed to a significant increase in peripheral levels of C-X-C motif ligand 8 (CXCL8) or IL-8 in schizophrenia relative to healthy controls [64-66]. CXCL8 is predominantly produced by macrophages and endothelial cells and may induce neutrophil chemotaxis and promote phagocytosis [64].

Later, schizophrenia was found to be associated with a specific chemokine profile, comprising increased plasma levels of CXCL8, chemokine ligand (CCL)-11 or eotaxin, CCL-3 or macrophage inflammatory protein (MIP)1α, and CCL-2 or monocyte chemoattractant protein (MCP)-1 [33, 67-70]. CCL-11 is an eosinophil chemotactic factor released by different cell types including eosinophils, fibroblasts, endothelial and epithelial cells, macrophages, lymphocytes, and B cells [71]. CCL-11 is induced by cytokines belonging to the Th-2 lineage, including interleukin IL-4, IL-10 and IL-13 [71]. CCL-3 is another chemokine, predominantly produced by macrophages, that recruits mononuclear cells, activates granulocytes and induces the production of IL-1, IL-6 and TNF-α thereby playing a key role in inflammation [72]. CCL-2 is secreted by macrophages, monocytes and dendritic cells and recruits T cells and monocytes at inflammatory sites [73]. Thus, the increased levels of these four chemokines in schizophrenia indicate the presence of IRS activation with macrophagic / monocyte (increased CCL-2, CCL-3 and CXCL8) and Th-2 (eotaxin) activation.

There is now also evidence that schizophrenia is accompanied by increased activity of the tryptophan catabolite (TRYCAT) pathway. This pathway is induced by IRS activation, through increased production of Th-1 (IFN-γ) and M1 macrophagic (IL-1β) cytokines, which stimulate indoleamine-2,3-dioxygenase (IDO) thereby lowering tryptophan and increasing the production of TRYCATs [74, 75]. Schizophrenia is accompanied by an activated TRYCAT pathway as indicated by lowered plasma tryptophan levels and increased levels of TRYCATs, such as kynurenine and kynurenic acid, in plasma, CSF and brain tissues [76-78]. More recently, Kanchanatawan et al. (2017) reported that schizophrenia is accompanied by increased IgA responses directed to different TRYCATs including xanthurenic acid, picolinic acid, 3-OH-kynurenine and quinolinic acid [79]. In addition, Sirivichayakul et al. [72] found highly significant associations between indicants of immune activation (increased IL-10, MIP1 and sIL-1RA plasma levels) and the activity of the TRYCAT pathway in schizophrenia. These findings suggest that IRS activation in schizophrenia induces the TRYCAT pathway leading to an increased production of different TRYCATs. However, IDO activation is a key immune-regulatory process that has an established CIRS role in pregnancy, transplantation, cancer, infections and autoimmune conditions [80]. Indeed, decreased plasma tryptophan contributes to a tolerogenic environment, metabolic shutdown and starvation thereby attenuating T cell activation and proliferation [81]. Moreover, TRYCATs, including kynurenine and xanthurenic acid, may have immune-regulatory effects by suppressing T cell proliferation and the production of Th-1 cytokines including IFN-γ [82]. Thus, IRS activation is accompanied by over-activation of the TRYCAT pathway, which in turn exerts a negative feedback control over T cell activation thereby attenuating the primary immune response through the effects of tryptophan depletion and TRYCAT formation.

6. IRS and CIRS in patients at high risk for psychosis and first episode psychosis (FEP)

Several studies have reported biological abnormalities even before the onset of psychotic symptoms. Individuals with prodromic symptoms, who later convert to psychosis may present immune-inflammatory imbalances. Khoury and Nasrallah (2018) reviewed 15 studies and found a possible role of plasma levels of IL-1β, IL-7, CXCL-8, matrix metalloproteinase (MMP)-8 and albumin as predictors of psychotic transition [83]. Other studies found higher IL-6 and lower IL-17 levels compared to healthy controls [84] and higher IL-6 levels when comparing who convert to psychosis with those who did not convert [85]. Kappelmann et al. (2018) in a large population study with 638,213 men in Sweden found associations between erythrocyte sedimentation rate (ESR), a marker of low-grade inflammation, IQ, and subsequent psychosis, suggesting that inflammatory abnormalities may influence schizophrenia risk by affecting neurodevelopment [86].

Patients in a first episode of psychosis (FEP) differ from their chronic psychosis counterparts in various aspects, including symptom patterns [87], cognitive impairments [88], neuroanatomical and functional changes [89, 90], and response to antipsychotic treatment as well [90, 91]. FEP also shows a specific immune-inflammatory profile. Thus, a recent study reports that FEP is associated with an increased expression of the Hp gene and that there are significant associations between the Positive and Negative Syndrome Scale (PANSS), depression, and excitement symptoms and peripheral levels of Hp, alpha-1 antitrypsin and alpha-2 macroglobulin [92]. These data show that not only schizophrenia [21] but also FEP is accompanied by an inflammatory response. These findings are further supported by results showing that the production of nuclear factor kappa B (NFκB), which is a major inflammatory regulator, is elevated in FEP [93].

There are recent reports on increased levels of IL-6, TNF-α and IL-10 in drug-naïve FEP patients, indicating monocytic (IL-6 and TNF-α) and Treg (IL-10) activation [94]. Kubistova et al. (2012) found significantly increased plasma levels of IL-6 and TNF-alpha, suggesting a proinflammatory state in the FEP [95]. de Witte et al. (2014) measured levels of 9 cytokines in antipsychotic-naïve first-episode schizophrenia patients and age and gender-matched controls using a multiplex immunoassay and found significantly increased levels of IL-1RA, IL-10 and IL-15 in FEP patients, again indicating signs of both IRS and CIRS activation in FEP (CIRS activation being indicated by increased sIL-1RA and IL-10 levels) [96]. Zhang et al. (2013) found increased levels of IL-18, a pro-inflammatory cytokine, in FEP and a significant association between IL-18 and neurocognitive deficits in the visuospatial and constructional

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domains [97]. Fu et al. (2016) reported significantly lowered IL-3 levels in FEP patients when compared with chronic schizophrenia patients and healthy controls, suggesting signs of immunosuppression [98]. Borovcanin et al. (2012) detected decreased levels of IL-17 and increased levels of IL-4 and TGF-β in FEP, indicating a suppressed Th-17 response, but elevated Th-2 and Treg responses [99]. Moreover, other studies found that, when compared to healthy controls, FEP patients show higher levels of IL-4, IL-10 and TNF-α [33, 100]. Interestingly, some studies reported significantly decreased levels of IL-10 levels in FEP [101-103]. IL-10 is a Treg cytokine which inhibits macrophage/monocyte and T-cell lymphocyte replication and the production of some inflammatory cytokines (including IL-1, TNF-α, IL-6, IL-8 and IL-12) [104], thus indicating that there is a lowered immune-regulatory potential in some patients with FEP. A recent meta-analysis shows that serum IL-6 and TNF-α are significantly higher in FEP patients than in normal controls [105].

All in all, recent studies and meta-analyses found significantly higher levels of IL-1β, sIL-1RA, IL-6, TNF-α, sTNF-R1, sTNF-R2, IL-12, IFN-γ, IL-2, sIL-2R, IL-18, IL-4, IL-5, IL-13, IL-10, and TGF-β in drug-naïve FEP patients compared to healthy controls [33, 35, 45, 99, 106, 107]. These data point towards an activation of macrophagic M1 (IL-1β, sIL-1RA, IL-6, TNF-α), Th1 (IL-12, IFN-γ, IL-2 and sIL-2R), Th-2 (IL-4, IL-5) and Treg (IL-10, TGF-β) cells during a first psychotic episode, including in drug-naive patients.

IL-6 and IL-10 may significantly contribute to the immunepathogenesis of FEP. Thus, Noto et al. (2016), in a gene expression study, found an up-regulation of protein nudE-like 1 (*NDEL1*) and myelin basic protein (*MBP*) genes in FEP, while *DROSHA* (which encodes a class 2 ribonulease III enzyme), catechol-O-methyltransferase (*COMT*), and disrupted in schizophrenia 1 *(DISC1)* were downregulated as compared to controls [108]. In addition, IL-6

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levels in FEP were associated with lowered *AKT1* (which encodes RAC-alpha serine/threonine-protein kinase) and *DROSHA* expression, whereas increased IL-10 levels were associated with increased *NDEL1*, *DISC1* and *MBP* expression [108]. Importantly, these genes play a key role in neuronal processes and therefore changes in the equilibrium between IL-6 and IL-10 in FEP may regulate miRNA machinery and neuronal functions, including intracellular signaling, neuroplasticity, neurogenesis and neuroprogression. For example, elevated levels of IL-6 in FEP may dysregulate the miRNA machinery (lowered *DROSHA* expression) and downregulate AKT-mediated cellular functions, while increased levels of IL-10 may have neuroprotective effects by increasing *NDEL1*, *MBP* and *DISC1* expression [108].

It should be noted that the CSF levels of kynurenic acid are increased in patients with FEP [109]. There are also reports that patients with FEP show elevated levels of human endogenous retrovirus (HERV) transcripts, which are endogenous viral elements in the human genome [110-114], as well as increased levels of antibodies against those retroviral proteins [115]. HERVs glycoproteins may contribute to neuro-inflammation and neurodegeneration, which could increase vulnerability to develop schizophrenia [116-119]. Moreover, copies of HERV elements are activated by some infectious pathogens including *T. gondii* and influenza virus [120, 121], whilst there is evidence of increased levels of antibodies against *T. gondii* in schizophrenia [122]. The derived hypothesis is that envelope proteins released due to pathogenic activation of HERVs may activate the innate immune system thereby inducing production of pro-inflammatory cytokines, for example by activating the CD14 / TLR4 pathway [123].

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7. IRS and CIRS in acute episodes and relapses

As in FEP, recent meta-analyses indicate increased levels of IRS cytokines, including IL-1β and IL-6, during an acute episode of psychosis, which is frequently normalized with treatment [35, 45]. Indicants of Th-1 activation (including increased IFN-γ and sIL-2R levels) may be trait markers of schizophrenia [23, 35]. Kubistova et al. (2012) found increased levels of IL-6 and TNF-α in the acute phase of schizophrenia and showed that treatment with antipsychotics decreased IL-6 but not TNF-α [95]. The above-mentioned meta-analysis showed increased levels of CIRS products including TGF-β during the acute episode of psychosis, which normalized with treatment [35] and increased sIL-2R levels as a possible trait marker of schizophrenia [35].

As in FEP, Borovcanin et al. (2012) reported decreased levels of IL-17 (lowered autoimmune and anti-inflammatory potential) coupled with increased levels of two CIRS cytokines, namely IL-4 and TGF-β [99]. Another study examined T-cell subsets (CD3+, CD4+, CD8+) and NK-cells as well as the CD4+/CD8+ ratio in schizophrenia patients in an acute psychotic episode and reported signs of both IRS and immunosuppression. Thus, increased CD3+ and CD4+ cells and an elevated CD4+/CD8+ ratio were observed in schizophrenia, whereas NK-cells were decreased [124]. After treatment, all T-cell alterations returned to normal while in chronic cases the number of NK-cells remained low and the CD4+/CD8+ ratio remained high, supporting that signs of immune activation and suppression are present in the acute and chronic phases of illness.

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8. IRS and CIRS in chronic schizophrenia

In patients with chronic schizophrenia, there are many signs of IRS activation including increased levels of IL-6, sTNF-R1 and sTNF-R2, CCL-11 (eotaxin) and CCL-3 (MIP-1α), while the levels of immune-regulatory CIRS cytokines, namely IL-4 and IL-10, are decreased [33, 102, 125]. Nevertheless, some of those immune markers, namely increased sTNF-R1 and sTNF-R2, also indicate increased CIRS functions in that condition [33, 125]. Fu et al. (2016) found significant increased levels of IL-3 and additionally a significant association between IL-3 levels and the PANSS score in chronic schizophrenia patients, which contrasts with their findings in FEP patients [98]. These authors suggested that lowered IL-3 in FEP patients may indicate that signs of immunosuppression are associated with developing schizophrenia and that IL-3 may increase as the disease progresses perhaps related to medication treatment or other factors that occur during chronic illness. Xiu et al. (2012) reported that serum levels of IL-18, another pro-inflammatory cytokine, are significantly higher in patients with chronic schizophrenia than in FEP patients and healthy controls and they also reported a positive correlation between IL-18 and the PANSS general psychopathology subscore [126].

Interestingly, Boll et al. (2017) performed regression analysis with different biomarkers and found that the main predictors of chronic schizophrenia were increased levels of sTNF-R1 (5-fold higher) and CCL-11 (2-fold higher) [125]. This indicates that signs of immune activation (namely the TNF-pathway with increased sTNF-R1 as biomarker) and Th-2 activation (increased CCL-11) are the best predictors for chronic schizophrenia, while in fact increased sTNF-R1 levels are part of the CIRS. Therefore, in chronic schizophrenia, the CIRS may not be activated to an extent necessary to counter-regulate the overly activated IRS.

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9. IRS and CIRS in (ultra) treatment resistant SCZ

The first paper reporting an association between the IRS and treatment resistant schizophrenia (TRS) was published in 1998 [127]. These authors found that serum IL-6 is significantly higher in TRS as compared to controls and patients who responded to treatment. Interestingly, increased levels of IL-6 and sIL-6R were inversely associated with CC16, an endogenous anti-cytokine which may constitute a trait marker for schizophrenia [127].

Other signs of IRS activation in TRS are: increased levels of sIL-1RA, IL-2, IL-10, sTNF-R1, sTNF-R2, CXCL-8, CCL-3 and CCL-2 [33, 64, 66, 125, 128]. Interestingly, a significant association was found between A-2518G polymorphism (rs1024611) of the MCP-1 gene (*CCL2*) and TRS with resistant patients more frequently carrying the G-allele [129]. Since G-allele carriers produce significantly more MCP-1 than non-carriers [130], this polymorphism may underpin the increased levels of MCP-1 in TRS. All in all, these results indicate that TRS is characterized by: a) signs of IRS activation as indicated by increases of M1 and TH-1 cytokines and chemokines, which are released during an IRS response; and b) activation of CIRS functions as indicated by increased levels of sIL-1RA, IL-10, sTNF-R1 and sTNF-R2.

10. IRS and CIRS in schizophrenia with depressive symptoms.

Many patients (up to 61%) with schizophrenia suffer from burdensome depressive symptoms or comorbid clinical depression, which is often poorly recognized [16]. Furthermore, depression is a common and harmful dimension of schizophrenia, particularly in FEP [131, 132]. Both schizophrenia and major depression or bipolar depression share alterations in immune pathways including increased pro-inflammatory cytokines, with a M1 macrophagic and Th1 response and activation of the tryptophan catabolite (TRYCAT) pathway through IDO induction

[16]. The latter authors proposed a model whereby schizophrenia is immunologically primed for an increased expression of depressive symptoms via the adverse effects of (among other elements) Th-1 and M1 macrophagic activation and their consequences including activation of the TRYCAT pathway with an increased production of neurotoxioc TRYCATs, including kynurenine [16]. Nevertheless, there is a paucity of data on immune functions in patients with schizophrenia and a comorbid depressive phenotype or depressive symptoms.

Noto et al. (2015) found higher IL-4 and TNF-α levels in FEP patients who also showed depression when compared to those without depression [33], suggesting that depression in FEP is accompanied by M1 macrophagic and Th-2 activation. These results suggest that depression in FEP is a key component that may contribute to aberrations in specific cytokines in FEP. Moreover, FEP patients with depression may have a different gene expression pattern compared to those without depression, namely a decreased expression of the *NDEL1* gene and increased expression of *COMT* gene [108], further underscoring that FEP plus depression could represent a biologically different phenotype when compared to FEP without depression. Yee et al. (2017) observed that in FEP patients, there were significant associations between the severity of depressive symptoms and gene expression of acute phase proteins, including Hp, alpha-1 antitrypsin and alpha-2 macroglobulin [92]. Overall, these results show that FEP with co-occurring depression may be accompanied by a mixed profile with inflammatory signs along with Th2 and macrophagic M1 activation. As such, FEP with depression may be accompanied by signs of IRS activation (acute phase response) and possibly M1 activation and signs of CIRS activation, namely increased haptoglobin and alpha-1 antitrypsin levels (which have immunosuppressive effects) and Th-2 activation.

 doi:10.20944/preprints201809.0289.v1

Recently, Kanchanatawan et al. reported that an increased production of TRYCATs (as measured using IgA responses to TRYCATs) was significantly associated with the severity of depression and anxiety symptoms in schizophrenia and that mainly picolinic acid, but also xanthurenic acid, quinolinic acid and 3-OH-kynurenine, were important in predictors of affective symptoms in schizophrenia [133].

Moreover, the same authors reported that specific changes in IgM-mediated regulatory activities with lowered IgM responses to 3-OH-kynurenine are associated with these affective dimensions. These data indicate that affective symptoms in schizophrenia may be driven by IRS activation leading to TRYCAT pathway activation and by inference increased immune regulation via increased levels of TRYCATs.

11. IRS and CIRS in deficit SCZ

A subset of patients with schizophrenia present negative symptoms (including apathy, alogia, social inhibition, flat affect, monotonous speech, lack of interest and anhedonia) and cognitive deficits (including deficits in semantic and episodic memory and executive functions) over the course of their illness [134]. This phenotype, referred to as deficit schizophrenia, differs from non-deficit schizophrenia in several aspects including poorer social functioning, worse long-term prognosis and a specific neurocognitive profile [135]. Recently, it was shown, using machine learning techniques, that this phenotype of schizophrenia is a distinct nosological entity shaped and modeled by the above-mentioned cognitive deficits and neuro-immune aberrations, including increased CCL-11, CCL-3, IL-10 and IgA responses to TRYCATs as compared to non-deficit schizophrenia [71, 79]. Therefore, deficit schizophrenia is accompanied by an activated TRYCAT pathway and patients with deficit schizophrenia patients exhibit increased

IgA responses directed to xanthurenic acid, picolinic acid, and quinolinic acid and relatively lowered IgA responses to kynurenic acid and anthranilic acid when compared to patients with nondeficit schizophrenia [79]. As such, deficit schizophrenia is characterized by signs of immune activation (increased cytokines, chemokines and TRYCATs) and increased CIRS activity as indicated by increased IL-10 and sIL-1RA levels and immune-regulatory TRYCATs as well. Moreover, deficit schizophrenia is accompanied by significant decreases in IgM autoimmune responses directed to all TRYCATs [75]. Generally, IgM responses are self-regulatory and therefore lowered IgM responses to TRYCATs may indicate lowered regulation of the TRYCAT pathway and consequently an increased vulnerability to develop TRYCAT pathway activation upon immune challenge [75]. This indicates that deficit schizophrenia is characterized by a deficit in the CIRS leading to an increased vulnerability to peripheral immune challenges.

Since the negative symptom cluster is a key in the conceptualization of deficit schizophrenia, it is also important to assess the associations between negative symptoms and cognitive deficits and aberrations in neuro-immune pathways. Thus, highly significant associations between cognitive deficits, negative symptoms and especially eotaxin (but also IL-10, sIL-1RA and MIP1) levels and neurotoxic TRYCATs, including xanthurenic acid, picolinic acid and 3-OH-kynurenine, were found in schizophrenia [71, 72, 136]. The negative symptoms of schizophrenia were also significantly correlated with IL-2, sIL-2R, CCL-11 [33, 137, 138], IL-6 [139], and the sIL1-RA [62]. Xiu et al. (2014) found an inverse relationship between IL-10 levels and negative symptoms, as well as with the PANSS cognitive factor subscores [103]. On the other hand, serum IL-4 and IL-10 concentrations are correlated with negative symptoms in drug-naive FEP patients [140]. A recent study [141] reported that serum IL-6 and CXCL-8 are strongly associated with negative and positive symptoms. Apart from associations between eotaxin and TRYCATs with cognitive deficits, also levels of some chemokines (CXCL8 or CCL2) were associated with cognitive deficits in schizophrenia [142]. All in all, negative symptoms are strongly associated with signs of M1 macrophagic (IL-6, IL-1RA, CXCL8), Th-1 (IL-2 and sIL-2R, TRYCAT pathway activation), and Th-2 (IL-4, CCL-11) activity, whilst also increased CIRS products (sIL-2R, sIL-1RA, TRYCATs) are associated with negative symptoms.

12. Are macrophages and T helper cells polarized in schizophrenia?

One major question in schizophrenia research is whether the different phenotypes are accompanied by macrophage (M1 versus M2) or Th (Th-1 versus Th-2 versus Th-17) polarization. It is important to consider the effects of M1/M2 polarization as M1 is a key factor in host defense against (intracellular) bacterial and viral infections, whereas M2 plays a key role in tissue repair, matrix remodeling and homeostasis [37, 143]. Classical M1 activation is mainly driven by the Th-1 production of IFN-γ, LPS and GM-CSF, while the key stimuli to generate the M2 phenotype are derived from Th-2 activity via IL-4 and IL-13, and immune complexes, IL-10 and glucocorticoids [37, 143]. Nevertheless, it should be underscored that the M1 and M2 phenotype do not exclude each other and together may develop a mixed phenotype with a continuum between the two polarized extremes [37]. Likewise, Th polarization towards either Th1, Th-17 or Th2 subsets plays a critical role is host defense (Th-1 being associated with M1) and repair (Th-2 being related to M2), while prolonged Th-1 and Th-2 activation induces pathophysiological responses including chronic inflammatory and degenerative disorders (Th-1-related), autoimmune conditions (Th-17 related) and asthma and allergic disease (Th-2 related).

Previous reports concluded that schizophrenia patients may have an impaired production of Th-1 cytokines and an overactivation of the Th-2 system, leading to a dysfunction in Th1/Th2

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balance and thus Th-2 polarization and consequently TRYCAT pathway activation [144, 145]. Nevertheless, this theory is not compatible with the findings of this review that M1 macrophages and Th-1 subsets as well as the TRYCAT pathway (Th-1-related) are activated in different schizophrenia subtypes. However, since no studies measured transcription factors, cell activation markers or antigen presenting molecules that may better define the macrophage and Th subsets we are confined to interpret cytokine biosignatures. In this respect, already in the 1990ties, it was described that schizophrenia is accompanied by activation of M1 (IL-6, sIL-1RA), Th-1 (sIL-2R) and Treg (IL-10) cytokines/receptors [22, 56, 146, 147]. As reviewed in previous sections, FEP is also accompanied by increased IL-1β, IL-6, TNF-α, sIL-2R and IL-10 levels indicating M1 and Th-2/Treg activation [29, 106].

Table 2 provides a summary of immune subsets in schizophrenia phenotypes as reviewed in this paper. As can be seen in Table 2, activation of M1, Th-1, Th-2 and Treg subsets is detected in the schizophrenia and its phenotypes and without a specific statistical approach it is challenging to conclude whether there is any polarization and which polarization type would prevail. Recently, a new statistical method was published to compute the ratio between various cytokines produced by Th-1 versus Th-2 cells and between M1 + Th-1 versus Th-2 + Treg by computing z unit weighted composite scores [32, 148].

Table 2. Summary on the IRS (immune-inflammatory response system) and CIRS (compensatory immune-regulatory reflex system) functions and findings in schizophrenia phenotypes.

Schizophrenia phenotype	Key findings	IRS functions	CIRS functions
Schizophrenia	8Acute phase (AP) response	-	8 Regulation by AP proteins
	8 IL-1, sIL-1RA, TNF, IL-6	8 M1, Pro-inflammatory effects	9 IL-1 signaling
	8 sTNFR1 and sTNFR2	-	9 TNF signaling
	8 IL-2, sIL-2R, IFN-γ, IL-12	8 Th-1	9 IL-2 signaling
	8 CCL-11, CCL-2, CCL-3 and CXCL-8	8 Chemotaxis	-

	8 TGF-β1 and IL-10	-	8 Treg regulation
	8 TRYCATs	-	9 T cell mediated immunity
First episode psychosis	8 Nuclear factor-κB	8 Pro-inflammatory mediator	-
	8 IL-1, IL-6 TNF sIL-1RA	8M1	9 IL-1 signaling
	8 sTNFR1 and sTNFR2		9 TNF signaling
	8 IFN-γ, IL-2, sIL-2R, IL-12	8Th-1	9 IL-2 signaling
	8 IL-15, IL-18	8 Pro-inflammatory	-
	8 IL-4, IL-13	-	8 Th-2 regulation
	8 IL-10 and TGF-β1	-	8 Treg regulation
	8 CXCL-8	8 Chemotaxis	-
Acute episodes	8 IL-1β, IL-6, TNF-α	8 M1, Pro-inflammatory effects	-
	8 IFN-γ, sIL-2R	8 Th-1	-
	8 IL-4	-	8 Th-2 regulation
	8 TGF-β1	-	8 Treg regulation
Chronic schizophrenia	8 IL-6	8 M1, Pro-inflammatory effects	-
	8 sTNF-R1 and sTNF-R2	-	9 TNF signaling
	8 IL-3 and IL-18	8 Pro-inflammatory	-
	9 IL-4	9 Th-2 regulation	-
	9 IL-10	9 Treg regulation	-
	8 CCL-11, CCL-3	8 Chemotaxis	-
Treatment resistant schizophrenia	8 IL-6, sIL-6R, sIL-1RA	8 IL-6 trans-signaling	-
	8 sTNFR1 and sTNFR2		9 TNF signaling
	8 IL-2	8 Th-1	-
	8 IL-10	-	8 Treg regulation
	8 CXCL-8, CCL-2, CCL-3	8 Chemotaxis	-

Comorbid depression	8 Haptoglobin, alpha-1 antitrypsin and alpha-2 macroglobulin	-	8 Regulation by AP proteins
	8 TNF-α	8 M1	
	8 TRYCATs	8 Th-1	8 Regulation
	8 IL-4	-	8 Th-2 regulation
Deficit schizophrenia	8 sIL-1RA	Indicates Th-1	9 IL-1 signaling
	8 TRYCAT pathway activation	Indicates Th-1	8 Regulation by TRYCATs
	9 IgM responses to TRYCATs	9 immune-regulation	-
	8 CCL-11	Indicates Th-2	-
	8 IL-10	-	8 Treg regulation
	8 CCL-11, CCL-3	8 Chemotaxis	-

Unfortunately, none of the papers described above has computed such ratios and hence no firm conclusions can be drawn. Recently, Noto et al. [141] published a paper that used z unit weighted composite scores computed on a wider array of cytokines that are predominantly produced by distinct subsets. This study reported that the most significant cytokines separating FEP from controls were granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6 and IL-12, representing M1 and Th-1 activation, and IL-4, IL-13, IL-5 and IL-10, representing Th-2 and Treg activation. **Figure 1** presents part of the results of that study focusing on M1, Th-1, Th-17, Th-2 and Treg and the ratios Th-1 / Th-2, and M1 + Th-1 + Th-17 / Th-2 + Treg. Therefore, the results suggest that M1, Th-1, Th-17, Th-2 and Treg may be functionally more active in FEP patients than in controls, whilst there were no significant differences in Th-1 / Th-2 ratio and M1 + Th-1 + Th-17 / Th-2 + Treg ratios between both groups. Moreover, all immune subsets were highly correlated with each other, namely all $r > 0.900$ ($p< 0.001$, $n=53$), while also M1 + Th-1 + Th-17 and Th-2 + Treg were strongly correlated ($r=0.955$. $p<0.001$, $n=53$). Thus, these results indicate that FEP is accompanied by a more generalized immune activation with interrelated increases in M1, Th-1, Th-2, Th-17 and Treg responses.

In fact, the cytokine biosignature in schizophrenia and FEP showing increased levels of TNF-α, IL-12, IL-4, IL-10 and IL-8 suggests that monocytes, macrophages and dendritic cells (DSs) are induced by infectious (bacterial or viral) agents (although complement factors cannot be ruled out). Moreover, the strong induction of M1 cytokines, including GM-CS and IL-6, and the lack of an IL-2 response in FEP suggests that a bacterial component could be the trigger [149] and that macrophages and DCs subsequently activate Th-1 cells followed by an immune-regulatory response involving Th-2 and Treg cells [149, 150].

13. Is IRS or CIRS the prevailing phenotype in schizophrenia?

Another relevant question is whether the distinct schizophrenia phenotypes are associated with an predominantly activated IRS or otherwise with a predominant CIRS immune phenotype. In the 1990ties, Maes et al. described that schizophrenia is accompanied by IRS activation with activated M1 (IL-6, sIL-1RA), Th-1 (sIL-2R) and Treg (IL-10) phenotypes [21, 22, 56, 146]. Table 2 summarizes the findings of the present review and shows the evidence that all schizophrenia phenotypes are characterized by signs of both IRS and CIRS activation. Table 2 shows that both systems appear to co-exist in all schizophrenia phenotypes and that the IRS may be the prevailing phenotype in chronic schizophrenia. However, it is worth noting that no studies have provided a direct proof as to whether IRS is the predominant phenotype as no previous reports have used the adequate statistical method described by Maes and Carvalho (2018) to compute the IRS / CIRS ratio. Using this novel method, Noto et al. [141] computed the IRS / CIRS ratio as the ratio of the sum of the z values of all IRS cytokines (IL-6, TNF-α, IL-17, GM-CSF, IFN-(, IL-12 and IL-2) on the sum of the z values of the CIRS cytokines (IL-4, IL-5, IL-13, IL-10, sIL-1RA, sIL-2R, sTNF-R1, sTNF-R2). Figure 2 shows that the IRS ($p=0.0021$) and CIRS ($p=0.007$) indices as well as the IRS / CIRS ratio ($p=0.0031$) were significantly greater in FEP patients than in controls. Moreover, the IRS and CIRS indices were significantly and positively correlated ($r=0.639$, $p<0.001$, $n=53$), indicating that FEP is characterized by a more generalized activation of the immune system with a co-activation of the IRS and CIRS and a more dominant IRS. Nevertheless, table 2 shows that also in chronic schizophrenia, TRS and deficit schizophrenia the IRS and CIRS are activated, indicating that there is a new equilibrium between both components.

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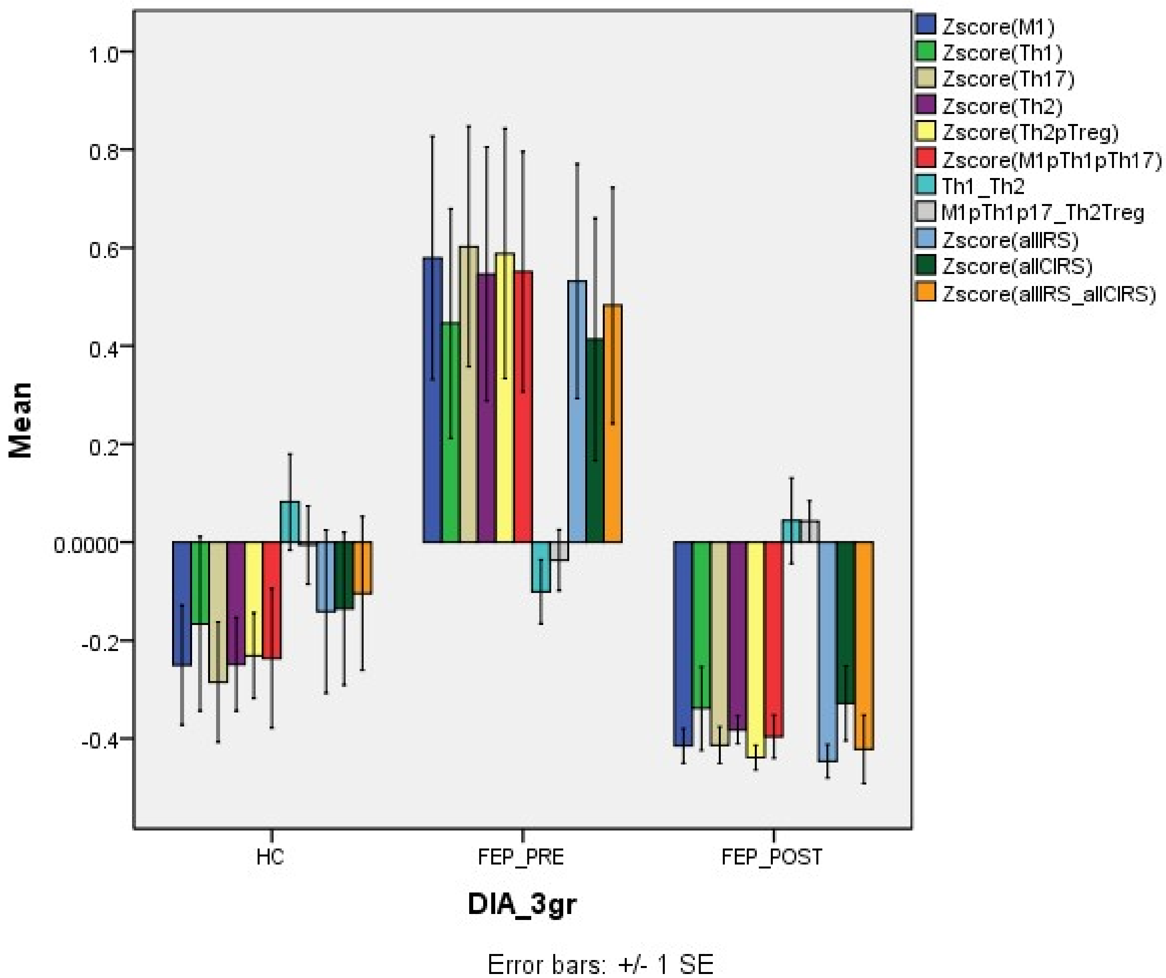

Figure 2. Measurements of macrophagic M1, T helper (Th)-1, Th-17, Th-2, T regulatory (Treg) phenotypes in healthy controls (HC), patients with first episode psychosis before treatment (FEP_PRE) and after treatment with antipsychotics (FEP_POST). Also shown are key ratios including the Th-1 / Th-2 (Th1_Th2) and M1 + Th1 + Th17 / Th2 + Treg (M1Th1Th17_Th2Treg) ratios, as well as indices of overall IRS activity (allIRS) and overall CIRS activity (allCIRS) and their ratio (allIRS_allCIRS). All values are shown as z scores (141).

The same study also reported that CIRS components such as sIL-1RA, sIL-2R, sTNF-R1 and sTNF-R2 are not increased in FEP [141]. The stronger activation of M1 and Th-1 subsets in schizophrenia and the lack of a significant increase in those CIRS receptors may explain the

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relatively stronger IRS response in FEP. All in all, these results show that while there is no significant imbalance between Th-1 and Th-2 cells and between M1 + Th-1 and Th-2 + Treg subsets in schizophrenia, this disorder may be accompanied by an overactive IRS that is not sufficiently counterbalanced by a less dominant CIRS.

Noto et al. [141] also reported that subchronic treatment with risperidone for some weeks may suppress M1, Th-1, Th-2 and Treg cytokines simultaneously (see Figure 2) and that the improvements in symptom profiles (negative symptoms, psychosis, excitation, and affective symptoms) from baseline to some weeks later are strongly predicted by increased plasma sTNF-RIs and IL-10 concentrations at baseline [141]. These findings suggest that the CIRS contributes to partial recovery from the acute phase of illness in FEP and that a deficit is the CIRS at baseline may negatively affect the clinical outcome.

14. Contributions of IRS as well as CIRS to pathophysiology

The current review shows that schizophrenia patients appear to be exposed to many adverse effects of M1 and Th-1 cytokines on neuronal circuitry including oxidative and nitrosative damage to neurons, changes in neuroplasticity, neurogenesis, neuronal signaling and apoptosis, which are denoted as neuroprogression [110, 151, 152]. Systemic immune-inflammation can cross the blood-brain barrier, driving changes in central inflammatory processes, especially those of astrocytes and microglia [151, 152]. Activated microglia and their release of M1 and Th-1 cytokines have been proposed to contribute to the progressive loss of brain tissue in schizophrenia [153] as shown in longitudinal MRI studies [152, 154]. Th-17 cytokines including IL-17 exert additional neurotoxic properties in the brain [155, 156].

In addition, increased plasma levels of IL-6 downregulate the expression of *AKT-1* and *DROSHA* genes thereby possibly affecting the microRNA machinery and many cellular

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functions [108]. Also, IRS-related chemokines including CXCL-8 contribute to neuroprogressive processes by facilitating migration of leukocytes through the blood brain barrier and sustaining neuroinflammation in the brain thus leading to neurotoxicity [157, 158]. Activated Th-1 and M1 subsets stimulate IDO and kynurenine 3-monooxygenase [159] to produce more cytotoxic, excitotoxic, and neurotoxic TRYCATs including picolinic acid, xanthurenic acid and quinolinic acid [71], thereby causing cognitive impairments including in episodic and semantic memory [136].

Moreover, products of Th-2 cytokines including IL-4, which are frequently described as cytokines with immune-regulatory effects, in fact may present with pro-inflammatory effects. For example, IL-4 may elevate IFN-γ production and activate M1 macrophages [160], while IL-4 and IL-13 have neurotoxic effects through oxidative stress pathways [161]. CCL-11, a product of Th-2 cells may be one of the most important factors leading to neurocognitive deficits (including episodic and sematic memory and executive functions), formal thought disorders and symptom dimensions for example by directly affecting hippocampal neurogenesis [71]. Microglia also produces IL-5 which in turn plays a role in neuroinflammation by increasing the activation and proliferation of microglia cells [162].

All in all, it appears that FEP is characterized by a peripheral IRS (M1, Th-1 and Th-17, chemokines), which is possibly caused by infectious agents, and which may induce Th-2 and Treg responses and therefore an increased negative feedback on the activated immune-inflammatory pathways. Moreover, products of the CIRS (e.g. IL-4 and IL-13 and noxious TRYCATs) and other Th-2-related cytokines/chemokines (e.g. CCL-11 and IL-5) have profound adverse effects on brain neuronal functioning and thus neuroprogressive pathways thereby

 doi:10.20944/preprints201809.0289.v1

causing different symptom dimensions and neurocognitive and memory deficits and the deficit phenotype [163].

Moreover, deficits in the CIRS as observed in schizophrenia may attenuate the regulatory feedback on the primary IRS, thereby priming the immune system to greater M1, Th1 and TH-2 responses following infections or other injuries. As reviewed here, attenuated CIRS functions comprise lowered plasma uteroglobin levels in schizophrenia [58], relatively lower levels of sIL-1RA, sIL-2R, sTNF-R1 and sTNF-R2 as compared with the increased levels of M1, Th-1 and Th-2 cytokines [141], and lowered levels of IgM-mediated autoimmune responses to TRYCATs [75].

15. Conclusions and outlook.

Figure 3 shows a summary of the findings of this study. Thus, an infection or other immune triggers could induce macrophagic M1 activation, which in turn activates T helper (Th)-1 subsets, which consequently activate the tryptophan catabolite (TRYCAT) pathway, Th-2 and T regulatory (Treg) subsets, acute phase protein (APP) production and thus the compensatory immune-regulatory reflex system (CIRS), which regulates the primary IRS response. Deficits in the CIRS (including lowered natural IgM-mediated immune regulation, lowered uteroglobulin, lowered IL-2 and TNF-α receptor levels) are accompanied by an exaggerated IRS response. Even after resolution of the acute episode, both the IRS and CIRS remain overactive, suggesting a new homeostatic setpoint between both components. The progression of schizophrenia, namely from the premorbid phase and first episode psychosis (FEP) through the debilitating stages of treatment resistant and chronic schizophrenia (TRS) and deficit schizophrenia, is accompanied by activation of both IRS and CIRS components. FEP is accompanied by an increased IRS /

doi:10.20944/preprints201809.0289.v1

CIRS ratio indicating a stronger immune-inflammatory process. The products of IRS and CIRS, including Th-1 (IL-1β, IL-6, TNF-α, GM-CSF, TRYCATs) and Th-2 (IL-4, IL-5, CCL-11) subsets as well as chemokines (CXCL-8) exert neurotoxic and neuroprogressive effects thereby inducing the symptom clusters of schizophrenia as well as cognitive deficits.

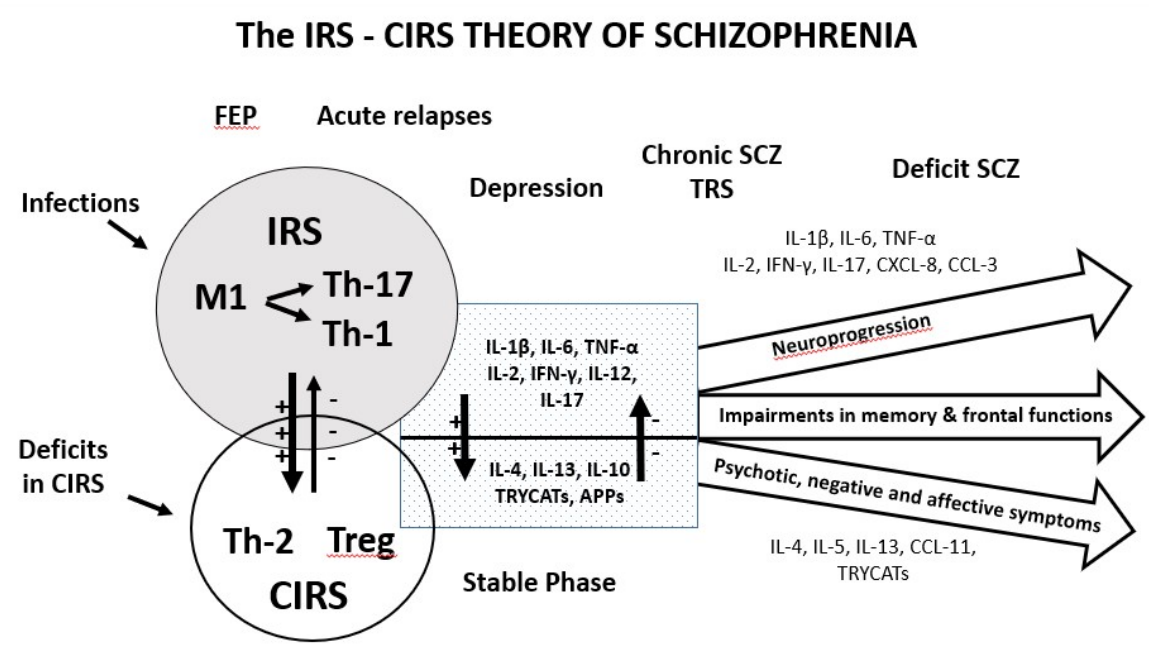

Figure 3. The immune-inflammatory responses system (IRS) and compensatory immune-regulatory reflex system (CIRS) theory of schizophrenia. Infections (and other injuries) may induce IRS activation via induction of macrophagic M1 and T helper (Th)-1 phenotypes, followed by activation of Th-17 and Th-2 and T regulatory (Treg) subsets. Deficits in the CIRS may increase the vulnerability to develop strong IRS responses following immune injuries. First episode psychosis (FEP), acute relapses, depressive symptoms dimensions, schronic schizophrenia (SCZ), treatment resistant schizophrenia and deficit schizophrenia are all accompanied by increments in IRS and CIRS. Even stable phase schizophrenia is accompanied by increased levels of IRS cytokines and CIRS products, including regulatory cytokines, acute phase proteins (APPs) and

tryptophan catabolites (TRYCATs). Products of M1, Th1, Th-17 and Th-2 cells may exert neurotoxic effects thereby causing neuroprogression with impairments in memory and frontal functions and the symptoms of schizophrenia as well. .

Acknowledgements

This study was funded by Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University, grant number RA61/016 and Chulalongkorn University; Government Budget; and by the Asahi Glass Foundation, Chulalongkorn University Centenary Academic Development Project and Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University, grant number RA60/042.

Conflict of interest

The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

Author's contributions

All the contributing authors have participated in the manuscript. CR and MM designed the study. All authors contributed to interpretation of the data and writing of the manuscript. All authors approved the final version of the manuscript.

References

1. GBD 2015 DALYs, HALE Collaborators: Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016, 388(10053):1603-1658.
2. Jaaskelainen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, Veijola J, Miettunen J: A systematic review and meta-analysis of recovery in schizophrenia. Schizophrenia bulletin 2013, 39:1296-1306.
3. Zhu Y, Li C, Huhn M, Rothe P, Krause M, Bighelli I, Schneider-Thoma J, Leucht S: How well do patients with a first episode of schizophrenia respond to antipsychotics: A systematic review and meta-analysis. Eur Neuropsychopharmacol 2017, 27(9):835-844.
4. Buchanan RW, Carpenter WT: Kaplan & Sadock′s Comprehensive Textbook of Psychiatry, 8th edn. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
5. Sham PC, Maclean CJ, Kendler KS: A typological model of schizophrenia based on age at onset, sex and familial morbidity. Acta psychiatrica Scandinavica 1994, 89:135-141.
6. Aleman A, Kahn RS, Selten JP: Sex differences in the risk of schizophrenia: evidence from meta-analysis. Archives of general psychiatry 2003, 60:565-571.
7. Gottesman II, Wolfgram DL: Schizophrenia Genesis: The Origins of Madness. New York, NY: Freeman; 1991.
8. Ingraham LJ, Kety SS: Adoption studies of schizophrenia. Am J Med Genet 2000, 97:18-22.
9. Sullivan PF, Kendler KS, Neale MC: Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Archives of general psychiatry 2003, 60:1187-1192.

10. Jia P, Wang L, Meltzer HY, Zhao Z: Common variants conferring risk of schizophrenia: a pathway analysis of GWAS data. Schizophrenia research 2010, 122:38-42.
11. McAllister AK: Major histocompatibility complex I in brain development and schizophrenia. Biological psychiatry 2014, 75:262-268.
12. Schmitt A, Leonardi-Essmann F, Durrenberger PF, Parlapani E, Schneider-Axmann T, Spanagel R, Arzberger T, Kretzschmar H, Herrera-Marschitz M, Gruber O et al: Regulation of immune-modulatory genes in left superior temporal cortex of schizophrenia patients: a genome-wide microarray study. World J Biol Psychiatry 2011, 12:201-215.
13. Cannon M, Jones PB, Murray RM: Obstetric complications and schizophrenia: Historical and meta-analytic review. American Journal of Psychiatry 2002, 159:1080–1092.
14. Cattane N, Richetto J, Cattaneo A: Prenatal exposure to environmental insults and enhanced risk of developing Schizophrenia and Autism Spectrum Disorder: focus on biological pathways and epigenetic mechanisms. Neuroscience and biobehavioral reviews 2018.
15. Clair DS, Xu M, Wang P, Yu Y, Fang Y, Zhang F, He L: Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959–1961. JAMA 2005, 294 557-562.
16. Anderson G, Maes M: Schizophrenia: linking prenatal infection to cytokines, the tryptophan catabolite (TRYCAT) pathway, NMDA receptor hypofunction, neurodevelopment and neuroprogression. Progress in neuro-psychopharmacology & biological psychiatry 2013, 42:5-19.

17. Brown AS: Prenatal infection as a risk factor for schizophrenia. Schizophrenia bulletin 2006, 32:200-202.

18. Torrey EF, Yolken RH: Toxoplasma gondii and schizophrenia. Emerg Infect Dis 2003, 9:1375-1380.

19. Heath RG, Krupp IM: Schizophrenia as an immunologic disorder. I. Demonstration of antibrain globulins by fluorescent antibody techniques. Archives of general psychiatry 1967, 16(1):1-9.

20. Smith RS, Maes M: The macrophage-T-lymphocyte theory of schizophrenia: additional evidence. Medical hypotheses 1995, 45(2):135-141.

21. Maes M, Delange J, Ranjan R, Meltzer HY, Desnyder R, Cooremans W, Scharpe S: Acute phase proteins in schizophrenia, mania and major depression: modulation by psychotropic drugs. Psychiatry research 1997, 66:1-11.

22. Maes M, Meltzer HY, Bosmans E: Immune-inflammatory markers in schizophrenia: comparison to normal controls and effects of clozapine. Acta psychiatrica Scandinavica 1994, 89(5):346-351.

23. Goldsmith DR, Rapaport MH, Miller BJ: A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Molecular psychiatry 2016, 21(12):1696-1709.

24. van Kesteren CF, Gremmels H, de Witte LD, Hol EM, Van Gool AR, Falkai PG, Kahn RS, Sommer IE: Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Translational psychiatry 2017, 7(3):e1075.

25. Orlovska-Waast S, Kohler-Forsberg O, Brix SW, Nordentoft M, Kondziella D, Krogh J, Benros ME: Cerebrospinal fluid markers of inflammation and infections in schizophrenia

and affective disorders: a systematic review and meta-analysis. Molecular psychiatry 2018.

26. Wang AK, Miller BJ: Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons Between Schizophrenia, Bipolar Disorder, and Depression. Schizophrenia bulletin 2018, 44(1):75-83.

27. Sanders AR, Drigalenko EI, Duan J, Moy W, Freda J, Goring HHH, Gejman PV: Transcriptome sequencing study implicates immune-related genes differentially expressed in schizophrenia: new data and a meta-analysis. Translational psychiatry 2017, 7(4):e1093.

28. Pouget JG: The Emerging Immunogenetic Architecture of Schizophrenia. Schizophrenia bulletin 2018, 44(5):993-1004.

29. Noto C, Ota VK, Gouvea ES, Rizzo LB, Spindola LM, Honda PH, Cordeiro Q, Belangero SI, Bressan RA, Gadelha A et al: Effects of risperidone on cytokine profile in drug-naïve first-episode psychosis. Int J Neuropsychopharmacol 2014, 18(4).

30. Gadelha A, Yonamine CM, Nering M, Rizzo LB, Noto C, Cogo-Moreira H, Teixeira AL, Bressan R, Maes M, Brietzke E et al: Angiotensin converting enzyme activity is positively associated with IL-17a levels in patients with schizophrenia. Psychiatry research 2015, 229(3):702-707.

31. Li H, Zhang Q, Li N, Wang F, Xiang H, Zhang Z, Su Y, Huang Y, Zhang S, Zhao G et al: Plasma levels of Th17-related cytokines and complement C3 correlated with aggressive behavior in patients with schizophrenia. Psychiatry research 2016, 246:700-706.

32. Maes M, Carvalho AF: The Compensatory Immune-Regulatory Reflex System (CIRS) in Depression and Bipolar Disorder. Molecular neurobiology 2018.

33. Noto C, Ota VK, Santoro ML, Ortiz BB, Rizzo LB, Higuchi CH, Cordeiro Q, Belangero SI, Bressan RA, Gadelha A et al: Effects of depression on the cytokine profile in drug naïve first-episode psychosis. Schizophrenia research 2015, 164(1-3):53-58.

34. Kim YK, Myint AM, Lee BH, Han CS, Lee HJ, Kim DJ, Leonard BE: Th1, Th2 and Th3 cytokine alteration in schizophrenia. Progress in neuro-psychopharmacology & biological psychiatry 2004, 28(7):1129-1134.

35. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B: Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biological psychiatry 2011, 70(7):663-671.

36. Maes M, Song C, Yirmiya R: Targeting IL-1 in depression. Expert Opin Ther Targets 2012, 16(11):1097-1112.

37. Martinez FO, Gordon S: The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000prime reports 2014, 6:13.

38. Maes M, Anderson G, Kubera M, Berk M: Targeting classical IL-6 signalling or IL-6 trans-signalling in depression? Expert Opin Ther Targets 2014, 18(5):495-512.

39. Idriss HT, Naismith JH: TNF alpha and the TNF receptor superfamily: structure-function relationship(s). Microscopy research and technique 2000, 50(3):184-195.

40. Bouma MG, Buurman WA: Assay of soluble tumor necrosis factor receptors. Methods in molecular medicine 2000, 36:91-100.

41. Huang ZS, Chiang BL, Hsu KL: Serum level of soluble tumor necrosis factor receptor II (sTNF-R75) is apparently an index of overall monocyte-related infectious and

inflammatory activity. The American journal of the medical sciences 2000, 320(3):183-187.

42. Arandjelovic S, Dragojlovic N, Li X, Myers RR, Campana WM, Gonias SL: A derivative of the plasma protease inhibitor alpha(2)-macroglobulin regulates the response to peripheral nerve injury. Journal of neurochemistry 2007, 103(2):694-705.

43. Chen X, Kong X, Zhang Z, Chen W, Chen J, Li H, Cao W, Ge Y, Fang S: Alpha-2-macroglobulin as a radioprotective agent: a review. Chinese journal of cancer research = Chung-kuo yen cheng yen chiu 2014, 26(5):611-621.

44. Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T, Cairns M, Weickert CS: Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. Molecular psychiatry 2013, 18:206-214.

45. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E: Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biological psychiatry 2008, 63:801-808.

46. Anderson G, Berk M, Dodd S, Bechter K, Altamura AC, Dell'osso B, Kanba S, Monji A, Fatemi SH, Buckley P et al: Immuno-inflammatory, oxidative and nitrosative stress, and neuroprogressive pathways in the etiology, course and treatment of schizophrenia. Progress in neuro-psychopharmacology & biological psychiatry 2013, 42:1-4.

47. Meyer U: Developmental neuroinflammation and schizophrenia. Progress in neuro-psychopharmacology & biological psychiatry 2013, 42:20-34.

48. Maes M, Delanghe J, Bocchio Chiavetto L, Bignotti S, Tura GB, Pioli R, Zanardini R, Altamura CA: Haptoglobin polymorphism and schizophrenia: genetic variation on chromosome 16. Psychiatry research 2001, 104(1):1-9.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 17 September 2018 doi:10.20944/preprints201809.0289.v1

49. Delanghe J, Langlois M, Duprez D, De Buyzere M, Clement D: Haptoglobin polymorphism and peripheral arterial occlusive disease. Atherosclerosis 1999, 145(2):287-292.

50. Guetta J, Strauss M, Levy NS, Fahoum L, Levy AP: Haptoglobin genotype modulates the balance of Th1/Th2 cytokines produced by macrophages exposed to free hemoglobin. Atherosclerosis 2007, 191(1):48-53.

51. Dalan R, Liew H, Goh LL, Gao X, Chew DE, Boehm BO, Leow MK: The haptoglobin 2-2 genotype is associated with inflammation and carotid artery intima-media thickness. Diabetes & vascular disease research 2016, 13(5):373-376.

52. Quaye IK: Haptoglobin, inflammation and disease. Transactions of the Royal Society of Tropical Medicine and Hygiene 2008, 102(8):735-742.

53. Licinio J, Seibyl JP, Altemus M, Charney DS, Krystal JH: Elevated CSF levels of interleukin-2 in neuroleptic-free schizophrenic patients. The American journal of psychiatry 1993, 150(9):1408-1410.

54. Ganguli R, Yang Z, Shurin G, Chengappa KN, Brar JS, Gubbi AV, Rabin BS: Serum interleukin-6 concentration in schizophrenia: elevation associated with duration of illness. Psychiatry research 1994, 51(1):1-10.

55. Katila H, Appelberg B, Hurme M, Rimon R: Plasma levels of interleukin-1 beta and interleukin-6 in schizophrenia, other psychoses, and affective disorders. Schizophrenia research 1994, 12(1):29-34.

56. Maes M, Meltzer HY, Buckley P, Bosmans E: Plasma-soluble interleukin-2 and transferrin receptor in schizophrenia and major depression. European archives of psychiatry and clinical neuroscience 1995, 244(6):325-329.

57. Sirota P, Schild K, Elizur A, Djaldetti M, Fishman P: Increased interleukin-1 and interleukin-3 like activity in schizophrenic patients. Progress in neuro-psychopharmacology & biological psychiatry 1995, 19(1):75-83.

58. Maes M, Bosmans E, Ranjan R, Vandoolaeghe E, Meltzer HY, De Ley M, Berghmans R, Stans G, Desnyder R: Lower plasma CC16, a natural anti-inflammatory protein, and increased plasma interleukin-1 receptor antagonist in schizophrenia: effects of antipsychotic drugs. Schizophrenia research 1996, 21(1):39-50.

59. Fan X, Goff DC, Henderson DC: Inflammation and schizophrenia. Expert review of neurotherapeutics 2007, 7(7):789-796.

60. Coelho FM, Reis HJ, Nicolato R, Romano-Silva MA, Teixeira MM, Bauer ME, Teixeira AL: Increased serum levels of inflammatory markers in chronic institutionalized patients with schizophrenia. Neuroimmunomodulation 2008, 15:140-144.

61. Hope S, Melle I, Aukrust P, Steen NE, Birkenaes AB, Lorentzen S, Agartz I, Ueland T, Andreassen OA: Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor Bipolar Disord 2009, 11:726-734.

62. Hope S, Ueland T, Steen NE, Dieset I, Lorentzen S, Berg AO, Agartz I, Aukrust P, Andreassen OA: Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. Schizophrenia research 2013, 145(1-3):36-42.

63. Noto C, Gadelha A, Belangero SI, Spindola LM, Rocha NP, de Miranda AS, Teixeira AL, Cardoso Smith MA, de Jesus Mari J, Bressan RA et al: Circulating levels of sTNFR1

as a marker of severe clinical course in schizophrenia. Journal of psychiatric research 2013, 47(4):467-471.

64. Maes M, Bocchio Chiavetto L, Bignotti S, Battisa Tura GJ, Pioli R, Boin F, Kenis G, Bosmans E, de Jongh R, Altamura CA: Increased serum interleukin-8 and interleukin-10 in schizophrenic patients resistant to treatment with neuroleptics and the stimulatory effects of clozapine on serum leukemia inhibitory factor receptor. Schizophrenia research 2002, 54(3):281-291.

65. Zhang XY, Zhou DF, Zhang PY, Wu GY, Cao LY, Shen YC: Elevated interleukin-2, interleukin-6 and interleukin-8 serum levels in neuroleptic-free schizophrenia: association with psychopathology. Schizophrenia research 2002, 57(2–3):247–258.

66. Zhang XY, Zhou DF, Cao LY, Zhang PY, Wu GY, Shen YC: Changes in serum interleukin-2, -6, and -8 levels before and during treatment with risperidone and haloperidol: relationship to outcome in schizophrenia. The Journal of clinical psychiatry 2004, 65(7):940-947.

67. Teixeira AL, Reis HJ, Nicolato R, Brito-Melo G, Correa H, Teixeira MM, Romano-Silva MA: Increased serum levels of CCL11/eotaxin in schizophrenia. Prog Neuro-Psychopharmacol Biol Psychiatry 2008, 32:710-714.

68. Beumer W, Drexhage RC, De Wit H, Versnel MA, Drexhage HA, Cohen D: Increased level of serum cytokines, chemokines and adipokines in patients with schizophrenia is associated with disease and metabolic syndrome. Psychoneuroendocrinology 2012, 37(12):1901–1911.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 17 September 2018 doi:10.20944/preprints201809.0289.v1

69. Reale M, Patruno A, De Lutiis MA, Pesce M, Felaco M, Di Giannantonio M, Di Nicola M, Grilli A: Dysregulation of chemo-cytokine production in schizophrenic patients versus healthy controls. BMC Neurosci 2011, 12:13.

70. Stuart MJ, Baune BT: Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. Neuroscience and biobehavioral reviews 2014, 42:93–115.

71. Sirivichayakul S, Kanchanatawan B, Thika S, Carvalho AF, Maes M: Eotaxin, an Endogenous Cognitive Deteriorating Chemokine (ECDC), Is a Major Contributor to Cognitive Decline in Normal People and to Executive, Memory, and Sustained Attention Deficits, Formal Thought Disorders, and Psychopathology in Schizophrenia Patients. Neurotoxicity research 2018.

72. Sirivichayakul S, Kanchanatwan B, Thika S, Carvalho A, Maes M: A new schizophrenia model: immune activation is associated with induction of the tryptophan catabolite pathway and increased eotaxin levels which together determine memory impairments and schizophrenia symptom dimensions. bioRxiv 2018 (preprint):393173.

73. Carr MW, Roth SJ, Luther E, Rose SS, Springer TA: Monocyte chemoattractant protein 1 acts as a T-lymphocyte chemoattractant. Proceedings of the National Academy of Sciences of the United States of America 1994, 91(9):3652-3656.

74. Plitman E, Iwata Y, Caravaggio F, Nakajima S, Chung JK, Gerretsen P, Kim J, Takeuchi H, Chakravarty MM, Remington G et al: Kynurenic Acid in Schizophrenia: A Systematic Review and Meta-analysis. Schizophrenia bulletin 2017, 43(4):764-777.

75. Kanchanatawan B, Sirivichayakul S, Ruxrungtham K, Carvalho AF, Geffard M, Anderson G, Maes M: Deficit Schizophrenia Is Characterized by Defects in IgM-

Mediated Responses to Tryptophan Catabolites (TRYCATs): a Paradigm Shift Towards Defects in Natural Self-Regulatory Immune Responses Coupled with Mucosa-Derived TRYCAT Pathway Activation. Molecular neurobiology 2017, [Epub ahead of print].

76. Lee M, Jayathilake K, Dai J, Meltzer HY: Decreased plasma tryptophan and tryptophan/large neutral amino acid ratio in patients with neuroleptic-resistant schizophrenia: relationship to plasma cortisol concentration. Psychiatry research 2011, 185(3):328-333.

77. Barry S, Clarke G, Scully P, Dinan TG: Kynurenine pathway in psychosis: evidence of increased tryptophan degradation. Journal of psychopharmacology (Oxford, England) 2009, 23(3):287-294.

78. Linderholm KR, Skogh E, Olsson SK, Dahl ML, Holtze M, Engberg G, Samuelsson M, Erhardt S: Increased levels of kynurenine and kynurenic acid in the CSF of patients with schizophrenia. Schizophrenia bulletin 2012, 38(3):426-432.

79. Kanchanatawan B, Sirivichayakul S, Ruxrungtham K, Carvalho AF, Geffard M, Ormstad H, Anderson G, Maes M: Deficit, but Not Nondeficit, Schizophrenia Is Characterized by Mucosa-Associated Activation of the Tryptophan Catabolite (TRYCAT) Pathway with Highly Specific Increases in IgA Responses Directed to Picolinic, Xanthurenic, and Quinolinic Acid. Molecular neurobiology 2017, Feb 8 [Epub ahead of print].

80. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R: The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Progress in neuro-psychopharmacology & biological psychiatry 2011, 35(3):702-721.

81. Lee GK, Park HJ, Macleod M, Chandler P, Munn DH, Mellor AL: Tryptophan deprivation sensitizes activated T cells to apoptosis prior to cell division. Immunology 2002, 107(4):452-460.

82. Maes M, Mihaylova I, Ruyter MD, Kubera M, Bosmans E: The immune effects of TRYCATs (tryptophan catabolites along the IDO pathway): relevance for depression - and other conditions characterized by tryptophan depletion induced by inflammation. Neuro endocrinology letters 2007, 28(6):826-831.

83. Khoury R, Nasrallah HA: Inflammatory biomarkers in individuals at clinical high risk for psychosis (CHR-P): State or trait? Schizophrenia research 2018.

84. Zeni-Graiff M, Rizzo LB, Mansur RB, Maurya PK, Sethi S, Cunha GR, Asevedo E, Pan P, Zugman A, Yamagata AS et al: Peripheral immuno-inflammatory abnormalities in ultra-high risk of developing psychosis. Schizophrenia research 2016, 176(2-3):191-195.

85. Stojanovic A, Martorell L, Montalvo I, Ortega L, Monseny R, Vilella E, Labad J: Increased serum interleukin-6 levels in early stages of psychosis: associations with at-risk mental states and the severity of psychotic symptoms. Psychoneuroendocrinology 2014, 41:23-32.

86. Kappelmann N, Khandaker GM, Dal H, Stochl J, Kosidou K, Jones PB, Dalman C, Karlsson H: Systemic inflammation and intelligence in early adulthood and subsequent risk of schizophrenia and other non-affective psychoses: a longitudinal cohort and co-relative study. Psychological medicine 2018:1-8.

87. Sanger TM, Lieberman JA, Tohen M, Grundy S, Beasley CJ, Tollefson GD: Olanzapine versus haloperidol treatment in first-episode psychosis. The American journal of psychiatry 1999, 156(1):79-87.

88. McCleery A, Ventura J, Kern RS, Subotnik KL, Gretchen-Doorly D, Green MF, Hellemann GS, Nuechterlein KH: Cognitive functioning in first-episode schizophrenia: MATRICS Consensus Cognitive Battery (MCCB) Profile of Impairment. Schizophrenia research 2014, 157(1-3):33-39.

89. Li T, Wang Q, Zhang J, Rolls ET, Yang W, Palaniyappan L, Zhang L, Cheng W, Yao Y, Liu Z et al: Brain-Wide Analysis of Functional Connectivity in First-Episode and Chronic Stages of Schizophrenia. Schizophrenia bulletin 2017, 43(2):436-448.

90. Torres US, Duran FL, Schaufelberger MS, Crippa JA, Louzã MR, Sallet PC, Kanegusuku CY, Elkis H, Gattaz WF, Bassitt DP et al: Patterns of regional gray matter loss at different stages of schizophrenia: A multisite, cross-sectional VBM study in first-episode and chronic illness. Neuroimage Clin 2016, 12:1-15.

91. Gaebel W, Jänner M, Frommann N, Pietzcker A, Köpcke W, Linden M, Müller P, Müller-Spahn F, Tegeler J: First vs multiple episode schizophrenia: two-year outcome of intermittent and maintenance medication strategies. Schizophrenia research 2002, 53(1-2):145-159.

92. Yee JY, Nurjono M, Ng WY, Teo SR, Lee TS, Lee J: Peripheral blood gene expression of acute phase proteins in people with first episode psychosis. Brain, behavior, and immunity 2017, 65:337-341.

93. Garcia-Bueno B, Bioque M, Mac-Dowell KS, Barcones MF, Martinez-Cengotitabengoa M, Pina-Camacho L, Rodriguez-Jimenez R, Saiz PA, Castro C, Lafuente A et al: Pro-/Anti-inflammatory dysregulation in patients with first episode of psychosis: toward an integrative inflammatory hypothesis of schizophrenia. Schizophrenia bulletin 2014, 40:376-387.

94. Zhu Q, Li X, Hie G, Yuan X, Lü L, Song X: Analysis of the changes of serum high mobility group protein B1 and cytokines in first-episode schizophrenia patients. Zhonghua Yi Xue Za Zhi 2015, 95(47):3818-3822.

95. Kubistova A, Horacek J, Novak T: Increased interleukin-6 and tumor necrosis factor alpha in first episode schizophrenia patients versus healthy controls. Psychiatria Danubina 2012, 24 Suppl 1:S153-156.

96. de Witte L, Tomasik J, Schwarz E, Guest PC, Rahmoune H, Kahn RS, Bahn S: Cytokine alterations in first-episode schizophrenia patients before and after antipsychotic treatment. Schizophrenia research 2014, 154(1-3):23-29.

97. Zhang XY, Tang W, Xiu MH, Chen DC, Yang FD, Tan YL, Wang ZR, Zhang F, Liu J, Liu L et al: Interleukin 18 and cognitive impairment in first episode and drug naïve schizophrenia versus healthy controls. Brain, behavior, and immunity 2013, 32:105-111.

98. Fu YY, Zhang T, Xiu MH, Tang W, Han M, Yun LT, Chen DC, Chen S, Tan SP, Soares JC et al: Altered serum levels of interleukin-3 in first-episode drug-naive and chronic medicated schizophrenia. Schizophrenia research 2016, 176(2-3):196-200.

99. Borovcanin M, Jovanovic I, Radosavljevic G, Djukic Dejanovic S, Bankovic D, Arsenijevic N, Lukic ML: Elevated serum level of type-2 cytokine and low IL-17 in first episode psychosis and schizophrenia in relapse. Journal of psychiatric research 2012, 46(11):1421-1426.

100. Brinholi FF, Noto C, Maes M, Bonifácio KL, Brietzke E, Ota VK, Gadelha A, Cordeiro Q, Belangero SI, Bressan RA et al: Lowered paraoxonase 1 (PON1) activity is associated with increased cytokine levels in drug naïve first episode psychosis. Schizophrenia research 2015, 166(1-3):225-230.

101. Kaminska T, Wysocka A, Marmurowska-Michalowska H, Dubas-Slemp H, Kandefer-Szerszen M: Investigation of serum cytokine levels and cytokine production in whole blood cultures of paranoid schizophrenic patients. Arch Immunol Ther Exp (Warsz) 2001, 49(6):439-445.

102. Pedrini M, Massuda R, Fries GR, de Bittencourt Pasquali MA, Schnorr CE, Moreira JC, Teixeira AL, Lobato MI, Walz JC, Belmonte-de-Abreu PS et al: Similarities in serum oxidative stress markers and inflammatory cytokines in patients with overt schizophrenia at early and late stages of chronicity. Journal of psychiatric research 2012, 46(6):819-824.

103. Xiu MH, Yang GG, Tan YL, Chen DC, Tan SP, Wang ZR, Yang FD, Okusaga O, Soares JC, Zhang XY: Decreased interleukin-10 serum levels in first-episode drug-naïve schizophrenia: relationship to psychopathology. Schizophrenia research 2014, 156(1):9-14.

104. Howard M, O'Garra A: Biological properties of interleukin 10. Immunol Today 1992, 13(6):198-200.

105. Fraguas D, Diaz-Caneja CM, Ayora M, Hernandez-Alvarez F, Rodriguez-Quiroga A, Recio S, Leza JC, Arango C: Oxidative Stress and Inflammation in First-Episode Psychosis: A Systematic Review and Meta-analysis. Schizophrenia bulletin 2018.

106. Upthegrove R, Manzanares-Teson N, Barnes NM: Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. Schizophrenia research 2014, 155(1-3):101-108.

107. Di Nicola M, Cattaneo A, Hepgul N, Di Forti M, Aitchison KJ, Janiri L, Murray RM, Dazzan P, Pariante CM, Mondelli V: Serum and gene expression profile of cytokines in first-episode psychosis. Brain, behavior, and immunity 2013, 31:90-95.

108. Noto C, Ota VK, Santoro ML, Gouvea ES, Silva PN, Spindola LM, Cordeiro Q, Bressan RA, Gadelha A, Brietzke E et al: Depression, Cytokine, and Cytokine by Treatment Interactions Modulate Gene Expression in Antipsychotic Naïve First Episode Psychosis. Molecular neurobiology 2016, 53(8):5701-5709.

109. Nilsson LK, Nordin C, Jonsson EG, Engberg G, Linderholm KR, Erhardt S: Cerebrospinal fluid kynurenic acid in male and female controls - correlation with monoamine metabolites and influences of confounding factors. Journal of psychiatric research 2007, 41(1-2):144-151.

110. Davis J, Eyre H, Jacka FN, Dodd S, Dean O, McEwen S, Debnath M, McGrath J, Maes M, Amminger P et al: A review of vulnerability and risks for schizophrenia: Beyond the two hit hypothesis. Neuroscience and biobehavioral reviews 2016, 65:185-194.

111. Huang WJ, Liu ZC, Wei W, Wang GH, Wu JG, Zhu F: Human endogenous retroviral pol RNA and protein detected and identified in the blood of individuals with schizophrenia. Schizophrenia research 2006, 83(2–3):193-199.

112. Karlsson H, Bachmann S, Schroder J, McArthur J, Torrey EF, Yolken RH: Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. Proc Natl Acad Sci USA 2001, 98(8):4634-4639.

113. Karlsson H, Schroder J, Bachmann S, Bottmer C, Yolken RH: HERV-W-related RNA detected in plasma from individuals with recent-onset schizophrenia or schizoaffective disorder. Molecular psychiatry 2004, 9(1):12-13.

114. Yao Y, Schröder J, Nellåker C, Bottmer C, Bachmann S, Yolken RH, Karlsson H: Elevated levels of human endogenous retrovirus-W transcripts in blood cells from patients with first episode schizophrenia. Genes Brain Behav 2008, 7(1):103-112.

115. Dickerson F, Lillehoj E, Stallings C, Wiley M, Origoni A, Vaughan C, Khushalani S, Sabunciyan S, Yolken R: Antibodies to retroviruses in recent onset psychosis and multi-episode schizophrenia. Schizophrenia research 2012, 138(2-3):198-205.

116. Antony JM, Ellestad KK, Hammond R, Imaizumi K, Mallet F, Warren KG, Power C: The human endogenous retrovirus envelope glycoprotein, syncytin-1, regulates neuroinflammation and its receptor expression in multiple sclerosis: a role for endoplasmic reticulum chaperones in astrocytes. Journal of immunology (Baltimore, Md : 1950) 2007, 179(2):1210-1224.

117. Arias I, Sorlozano A, Villegas E, de Dios Luna J, McKenney K, Cervilla J, Gutierrez B, Gutierrez J: Infectious agents associated with schizophrenia: a meta-analysis. Schizophrenia research 2012, 136(1-3):128-136.

118. Krause D, Matz J, Weidinger E, Wagner J, Wildenauer A, Obermeier M, Riedel M, Müller N: The association of infectious agents and schizophrenia. World J Biol Psychiatry 2010, 11(5):739-743.

119. Perron H, Lang A: The human endogenous retrovirus link between genes and environment in multiple sclerosis and in multifactorial diseases associating neuroinflammation. Clin Rev Allergy Immunol 2010, 39(1):51-61.

120. Frank O, Jones-Brando L, Leib-Mosch C, Yolken R, Seifarth W: Altered transcriptional activity of human endogenous retroviruses in neuroepithelial cells after infection with Toxoplasma gondii. J Infect Dis 2006, 194(10):1447–1449.

121. Li F, Nellåker C, Sabunciyan S, Yolken RH, Jones-Brando L, Johansson AS, Owe-Larsson B, Karlsson H: Transcriptional derepression of the ERVWE1 locus following influenza A virus infection. J Virol 2014, 88(8):4328-4337.

122. Torrey EF, Bartko JJ, Yolken RH: Toxoplasma gondii and other risk factors for schizophrenia: an update. Schizophrenia bulletin 2012, 38(3):642–647.

123. Rolland A, Jouvin-Marche E, Viret C, Faure M, Perron H, Marche PN: The envelope protein of a human endogenous retrovirus-W family activates innate immunity through CD14/TLR4 and promotes Th1-like responses. Journal of immunology (Baltimore, Md : 1950) 2006, 176(12):7636–7644.

124. Sperner-Unterweger B, Whitworth A, Kemmler G, Hilbe W, Thaler J, Weiss G, Fleischhacker WW: T-cell subsets in schizophrenia: a comparison between drug-naive first episode patients and chronic schizophrenic patients. Schizophrenia research 1999, 38(1):61-70.

125. Boll KM, Noto C, Bonifácio KL, Bortolasci CC, Gadelha A, Bressan RA, Barbosa DS, Maes M, Moreira EG: Oxidative and nitrosative stress biomarkers in chronic schizophrenia. Psychiatry research 2017, 253:43-48.

126. Xiu MH, Chen DC, Wang D, Zhang K, Dong A, Tang W, Zhang F, Liu LJ, Liu JH, Liu HB et al: Elevated interleukin-18 serum levels in chronic schizophrenia: Association with psychopathology. Journal of psychiatric research 2012, 46(8):1093-1098.

127. Lin A, Kenis G, Bignotti S, Tura GJ, De Jong R, Bosmans E, Pioli R, Altamura C, Scharpé S, Maes M: The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6. Schizophrenia research 1998, 32(1):9-15.

128. Maes M, Bocchio Chiavetto L, Bignotti S, Battisa Tura G, Pioli R, Boin F, Kenis G, Bosmans E, de Jongh R, Lin A et al: Effects of atypical antipsychotics on the inflammatory response system in schizophrenic patients resistant to treatment with typical neuroleptics. Eur Neuropsychopharmacol 2000, 10(2):119-124.

129. Mundo E, Altamura AC, Vismara S, Zanardini R, Bignotti S, Randazzo R, Montresor C, Gennarelli M: MCP-1 gene (SCYA2) and schizophrenia: a case-control association study. Am J Med Genet B Neuropsychiatr Genet 2005, 132B(1):1-4.

130. Rovin BH, Lu L, Saxena R: A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. Biochem Biophys Res Commun 1999, 259(2):344–348.

131. Upthegrove R, Birchwood M, Ross K, Brunett K, McCollum R, Jones L: The evolution of depression and suicidality in first episode psychosis. Acta psychiatrica Scandinavica 2010, 122(3):211-218.

132. Sonmez N, Rossberg JI, Evensen J, Barder HE, Haahr U, Ten Velden Hegelstad W, Joa I, Johannessen JO, Langeveld H, Larsen TK et al: Depressive symptoms in first-episode psychosis: a 10-year follow-up study. Early intervention in psychiatry 2016, 10(3):227-233.

133. Kanchanatawan B, Thika S, Sirivichayakul S, Carvalho AF, Geffard M, Maes M: In Schizophrenia, Depression, Anxiety, and Physiosomatic Symptoms Are Strongly Related to Psychotic Symptoms and Excitation, Impairments in Episodic Memory, and Increased Production of Neurotoxic Tryptophan Catabolites: a Multivariate and Machine Learning Study. Neurotoxicity research 2018, 33(3):641-655.

134. Milev P, Ho BC, Arndt S, Andreasen NC: Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. The American journal of psychiatry 2005, 162(3):495-506.

135. Kirkpatrick B, Galderisi S: Deficit schizophrenia: an update. World psychiatry : official journal of the World Psychiatric Association (WPA) 2008, 7(3):143-147.

136. Kanchanatawan B, Hemrungrojn S, Thika S, Sirivichayakul S, Ruxrungtham K, Carvalho AF, Geffard M, Anderson G, Maes M: Changes in Tryptophan Catabolite (TRYCAT) Pathway Patterning Are Associated with Mild Impairments in Declarative Memory in Schizophrenia and Deficits in Semantic and Episodic Memory Coupled with Increased False-Memory Creation in Deficit Schizophrenia. Molecular neurobiology 2017, Sep 5 [Epub ahead of print].

137. Asevedo E, Rizzo LB, Gadelha A, Mansur RB, Ota VK, Berberian AA, Scarpato BS, Teixeira AL, Bressan RA, Brietzke E: Peripheral interleukin-2 level is associated with negative symptoms and cognitive performance in schizophrenia. Physiology & behavior 2014, 129:194-198.

138. Bresee C, Rapaport MH: Persistently increased serum soluble interleukin-2 receptors in continuously ill patients with schizophrenia. Int J Neuropsychopharmacol 2009, 12(6):861–865.

139. Kim YK, Kim L, Lee MS: Relationships between interleukins, neurotransmitters and psychopathology in drug-free male schizophrenics. Schizophrenia research 2000, 44(3):165–175.

140. Simsek S, Yildirim V, Cim A, Kaya S: Serum IL-4 and IL-10 Levels Correlate with the Symptoms of the Drug-Naive Adolescents with First Episode, Early Onset Schizophrenia. Journal of child and adolescent psychopharmacology 2016, 26(8):721-726.

141. Noto MN, Maes M, Nunes SO, Ota VK, Rossaneisf AC, Verri JW, Cordeiro Q, Belangero SI, Gadelha A, Bressan RA et al: Activation of the immune-inflammatory

response system and the compensatory immune-regulatory reflex system in antipsychotic naive first episode psychosis. 2018 (preprint).

142. Asevedo E, Gadelha A, Noto C, Mari RB, Zugman A, Belangero SIN, Berberian AA, Scarpato BS, Leclerc E, Teixeira AL et al: Impact of peripheral levels of chemokines, BDNF and oxidative markers on cognition in individuals with schizophrenia. Journal of psychiatric research 2013, 47:1376-1382.

143. Mantovani A, Sozzani S, Locati M, Schioppa T, Saccani A, Allavena P, Sica A: Infiltration of tumours by macrophages and dendritic cells: tumour-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Novartis Foundation symposium 2004, 256:137-145; discussion 146-138, 259-169.

144. Schwarz MJ, Muller N, Riedel M, Ackenheil M: The Th2-hypothesis of schizophrenia: a strategy to identify a subgroup of schizophrenia caused by immune mechanisms. Medical hypotheses 2001, 56(4):483-486.

145. Muller N, Krause D, Weidinger E, Schwarz M: [Immunological treatment options for schizophrenia]. Fortschritte der Neurologie-Psychiatrie 2014, 82(4):210-219.

146. Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY: Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. Journal of psychiatric research 1995, 29(2):141-152.

147. Maes M: Cytokines in schizophrenia. Biological psychiatry 1997, 42(4):308-309.

148. Guimaraes PM, Scavuzzi BM, Stadtlober NP, Franchi Santos L, Lozovoy MAB, Iriyoda TMV, Costa NT, Reiche EMV, Maes M, Dichi I et al: Cytokines in systemic lupus erythematosus: far beyond Th1/Th2 dualism lupus: cytokine profiles. Immunology and cell biology 2017, 95(9):824-831.

149. Yusa T, Tateda K, Ohara A, Miyazaki S: New possible biomarkers for diagnosis of infections and diagnostic distinction between bacterial and viral infections in children. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 2017, 23(2):96-100.

150. Degre M: Interferons and other cytokines in bacterial infections. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research 1996, 16(6):417-426.

151. Leonard B, Maes M: Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neuroscience and biobehavioral reviews 2012, 36(2):764-785.

152. Davis J, Moylan S, Harvey BH, Maes M, Berk M: Neuroprogression in schizophrenia: Pathways underpinning clinical staging and therapeutic corollaries. Aust N Z J Psychiatry 2014, 48(6):512–529.

153. Monji A, Kato T, Kanba S: Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. Psychiatry and clinical neurosciences 2009, 63(3):257-265.

154. Salisbury DF, Kuroki N, Kasai K, Shenton ME, McCarley RW: Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. Archives of general psychiatry 2007, 64(5):521-529.

155. Tzartos JS, Friese MA, Craner MJ, Palace J, Newcombe J, Esiri MM, Fugger L: Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. The American journal of pathology 2008, 172(1):146-155.

156. Senior K: Interleukin-17 and brain injury in stroke. Nature Reviews Neurology 2009, 5:524.

157. Willette AA, Coe CL, Birdsill AC, Bendlin BB, Colman RJ, Alexander AL, Allison DB, Weindruch RH, Johnson SC: Interleukin-8 and interleukin-10, brain volume and microstructure, and the influence of calorie restriction in old rhesus macaques. Age (Dordrecht, Netherlands) 2013, 35(6):2215-2227.

158. McLarnon JG: Chemokine Interleukin-8 (IL-8) in Alzheimer's and Other Neurodegenerative Diseases. J Alzheimers Dis Parkinsonism 2016, 6:273.

159. Connor TJ, Starr N, O'Sullivan JB, Harkin A: Induction of indolamine 2,3-dioxygenase and kynurenine 3-monooxygenase in rat brain following a systemic inflammatory challenge: a role for IFN-gamma? Neuroscience letters 2008, 441(1):29-34.

160. Gadani SP, Cronk JC, Norris GT, Kipnis J: IL-4 in the brain: a cytokine to remember. Journal of immunology (Baltimore, Md : 1950) 2012, 189(9):4213-4219.

161. Mori S, Maher P, Conti B: Neuroimmunology of the Interleukins 13 and 4. Brain sciences 2016, 6(2).

162. Liva SM, de Vellis J: IL-5 induces proliferation and activation of microglia via an unknown receptor. Neurochemical research 2001, 26(6):629-637.

163. Kanchanatawan B, Maes M: The effects of the tryptophan catabolite pathway on negative symptoms and deficit schizophrenia and partly mediated by executive impairments: results of partial least squares path modeling. CNS Neurol Disord Drug Targets 2018, Jul 2. pii: CNSNDDT-EPUB-91436.

 doi:10.20944/preprints201809.0289.v1