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# OUTLINING THE ABSENCE: FROM INFLAMMATION TO A DISTINCT ENDOPHENOTYPE FOR THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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***Summary***

*The concept of schizophrenia as a mental condition is subject to deconstruction for a broader approach toward a systemic disorder by encompassing the links with inflammation. Beyond the salient psychotic symptoms of schizophrenia, the negative symptoms remain the silent cause of deterioration and the hallmark of a worse prognosis. Either as part of a unitary disorder or as a distinct subtype of schizophrenia, the negative symptoms seem to be associated with specific biological features. They might suggest a more transparent phenotype of the underlying pathological process. Therefore, recent lines of research indicate that peripheral immune alterations may be predictive early-phase biomarkers for targeting a specific subgroup of schizophrenia patients at risk of later developing enduring negative symptoms. In this paper, we review 1. The most influential theories of inflammation in schizophrenia, in conjunction with 2. The hitherto data linking immune alterations to negative symptoms. Thus, we propose a theoretical framework to delineate a model of inflammatory endophenotype for the negative symptoms of schizophrenia.*

***Keywords:*** *schizophrenia, negative symptoms, cytokines, interleukin*

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## INTRODUCTION

Under the diagnosis of schizophrenia, modern psychiatry encompasses a miscellaneous phenotype of cognitive and behavioral alterations affecting approximately 1% of the population worldwide (Meyer et al. 2011), which leads to one of the most important causes of disability in developed countries (Kirkpatrick et al. 2014). This heterogeneous phenotype is clinically compartmentalized into positive, negative, cognitive, disorganization, mood, and motor symptom dimensions (Tandon et al. 2009). A historical tendency has polarized these dimensions between positive and negative symptoms (NS). The latter represent an absence or a significant decline in behavior or conative functions (Tandon et al. 2009), considered as early since Kraepelin's dementia praecox description and associated with the deteriorative process in schizophrenia (Kirkpatrick et al. 2006). A century later, the NS are still the main predictor of a poor prognosis and remain a diagnostical and therapeutic conundrum. For instance, it is well documented that patients with significant NS suffer a "disproportionate amount of impairment" (Kirkpatrick et al. 2006), and their therapeutic approaches are constantly inefficacious. These multiple symptom dimensions may indicate distinct underlying mechanisms from which specific components might be biomarkers from cause to clinical expression (Tandon et al., 2009). Such indicators constitute an intermediate phenotype or endophenotype (Allen et al. 2009). One of the recently proposed models of schizophrenia transcends the usual psychosis-centered paradigm and approaches its global burden as a systemic disorder (Kirkpatrick et al. 2014) that includes subclinical inflammation (Howes & McCutcheon 2017). This disbalance towards inflammation may be a distinct endophenotype of SCZ (Miller et al. 2011). Furthermore, a growing tendency in the literature indicates particular associations of NS with immune perturbations. In this paper, we aimed to overview the hypothesis of a distinct inflammatory endophenotype for the NS of schizophrenia. The general immunological theory of schizophrenia and the concept of NS, along with its derivational constructs, were examined to identify the link between negative phenotype and immune alterations in existing literature.

## SCHIZOPHRENIA: A SYSTEMIC PRO-INFLAMMATORY CONDITION

A deconstructing model for schizophrenia as a systemic disorder was posited a decade ago (Kirkpatrick et al. 2014), which includes non-psychiatric conditions such as metabolic syndrome or immune dysfunctions as integrant parts. These "comorbid" syndromes may share common pathways and factors where immune changes are constantly involved. It was argued that this constancy might be artefactual, resulting from multiple confounders such as medication, smoking, or stress (Müller 2014, Rubesa et al. 2018). On the other hand, there is a growing

body of evidence that these immune alterations cluster into a distinct immunophenotype of schizophrenia (Miller & Goldsmith 2017). Numerous observations indicate an epidemiological overlap between schizophrenia and neuroinflammation-inducing conditions such as herpes simplex virus (Bolu et al. 2016) and Toxoplasma gondii infections or autoimmune disorders (Rubesa et al. 2018). Still, no specific bacterial or viral agent could be associated with schizophrenia, but the immune response in itself would involve a higher risk (Müller 2014). In concordance with these findings, some authors proposed the term "mild localized chronic encephalitis" to emphasize the inflammatory mechanisms underpinning some schizophrenia-like psychoses (Bechter 2019, Pandarakalam 2022). One of the most fruitful lines of evidence about the immune anomalies in schizophrenia is the consistently altered levels of proinflammatory molecules, such as cytokines in the blood and cerebrospinal fluid (Rubesa et al. 2018). In addition, altered levels of proinflammatory cytokines were also detected in the serum of individuals at high risk for psychosis (Goldsmith et al. 2019) or with affective disorders (Goldsmith et al. 2016). Therefore, an immune disbalance with inflammatory activation seems to transcend the diagnostic boundaries across the psychotic continuum. All these data converge to consider a distinct inflammatory endophenotype for at least a specific subset of patients diagnosed with schizophrenia (Miller & Goldsmith 2017).

## CYTOKINES: THE SALIENT SIGNATURE OF A PRO--INFLAMMATORY MILIEU IN SCHIZOPHRENIA

Mounting but disparate evidence indicates that schizophrenia is associated with perturbations of cytokine levels outside the brain (Rubesa et al. 2018). In a meta-analysis of blood cytokine alterations in psychiatric patients (Goldsmith et al. 2016), the results indicate that there are altered levels of various cytokines in individuals with schizophrenia. Specifically, both IL-6 and TNF-α are consistently elevated in both acutely relapsed and chronic patients, as compared to controls. Additionally, a meta-analysis suggests that cytokine levels may differ based on clinical status, with specific cytokines acting as either state or trait markers of the disease (Miller et al. 2011). Studies conducted on first-episode psychosis patients (FEP) indicate already modified levels of inflammatory cytokines (Dunleavy et al. 2022, Kubistova et al. 2012). These data suggest that the altered cytokine pattern is unlikely to be caused by medication effects alone. Otherwise, some authors argue that immune response dysregulation develops gradually with disease progression or appears as a long-term effect of the antipsychotics.(Frydecka et al. 2018). It is possible that the numerous findings related to altered cytokines profile and schizophrenia do not indicate the primary pathological process. After applying Bradford Hill's causality criteria, Manu et al. concluded that this association lacks a biological gradient, coherence, and specificity. Instead, they suggest an epiphenomenal explanation for this pro-inflammatory pattern, possibly related to other factors such as psychological stress or obesity (Manu et al. 2014). In summary, there is a divergence in the literature concerning the serum inflammatory cytokines in schizophrenia patients. One explanation for this limitation might come from the heterogeneous presentation of schizophrenia, currently diagnosed as a unitary disorder (see Table Nr.1). Therefore, most studies on schizophrenia have incorporated it within the diagnostic criteria, whereas breaking down the diagnosis into subtypes could reveal more specific connections with the underlying inflammatory processes.

## THE NEGATIVE SYMPTOMS AND DERIVATIONAL CONSTRUCTS

The negative features of schizophrenia have been described in connection with a deterioration process for over a century, as Kraepelin's "avolitional syndrome" stands at the foundation of the concept. Later, Crow classified schizophrenia into two main types. Type I is defined by positive symptoms and is responsive to antidopaminergic treatment. Type II is characterized by negative symptoms, poor response to antipsychotics, cognitive impairment, and neuroanatomic abnormalities (Marder & Galderisi 2017). This dialectical view became more evident with Carpenter's concept of deficit schizophrenia, defined by primary negative symptoms (Buchanan 2007). The most recent conceptualization of negative symptomatology describes five constructs organized around a two-factor structure: diminished expression and amotivated behavior (Kirkpatrick et al. 2011, Marder & Galderisi 2017). Regardless of the name, they represent a phenotype of an absence in one's mental and behavioral repertoire.

To isolate those NS presentations most relevant to clinical attention, two main concepts are used in research: persistent negative symptoms (PNS) and deficit schizophrenia (defSCZ) (Buchanan 2007). The PNS refer to long-standing negative symptoms, primary or secondary for at least six months, but unresponsive to the usual treatment (Buchanan 2007). On the other hand, defSCZ

**Table 1:** Schizophrenia as unitary disorder and cytokine level alterations

| Authors | Study design | Patients n | Controls n | Objective | Biomarkers included in the studies | Main Findings |
|---|---|---|---|---|---|---|
| (Frydecka et al. 2018) | Cross-sectional study<br>Case-control | 39 FEP[1]<br>39 MES[2] | 39 HCs[3] | To profile the level of several cytokines in patients compared to controls<br>The relationship between cytokine profile and the manifestation of psychosis | IL-1RA[4], IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IFN-γ[5], eotaxin-1, IP-10[6], FGF-2[7], G-CSF[8], GM-CSF[9], MCP-1[10], MIP-1α[11], TNF-α, VEGF-A[12], PDGF-BB[13], RANTES[14] | • No significant differences in the levels of inflammatory markers between FES patients and controls<br>• MES patients had significantly higher levels of IL-1RA, IL-6, IL- 7, IL-8, IL-9, IL-10, IL-13, eotaxin-1, GM-CSF, MCP-1, PDGF-BB, MIP- 1α, MIP-1β, IFN-γ, VEGF-A and RANTES |
| | Meta-analysis | 19 studies | | | MCP-1 (CCL2[15]), MIP-1α (CCL3[16]), MIP-1β (CCL4[17]), eotaxin-1 (CCL11[18]), fractalkine (CX3CL1[19]), IL-8 (CXCL8[20]) and IP-10 (CXCL10[21]) | • The majority of cytokine alterations are present only in MES patients.<br>• Only elevated MCP-1 (CCL2) levels appear in both groups of patients (FEP and MES patients) |
| (Feng et al. 2020) | Longitudinal study | 960 SCZ[22] | | Longitudinal changes in inflammatory markers in SCZ patients over 12 months under antipsychotic treatment<br>To see whether there is a relationship between baseline cytokine levels and PANSS[23] scores | White blood cells, CRP, IL- 6, adipokines (adiponectin and leptin), VCAM-1[24], ICAM-1[25], and E-Selectin | • A significant decrease of multiple cytokine levels between baseline and three months<br>• Higher IL-6 levels are associated with a more significant decrease in total PANSS scores, driven by changes in negative and general scores.<br>• Only the decrease in IL-6 levels was significantly associated with decreased PANSS scores for patients treated with ziprasidone. |
| (Goldsmith et al. 2016) | Meta-analysis | 68 studies for AR[26] patients (40 FEP and SCZ)<br>46 studies for chronic patients (18 SCZ) | | Cytokines levels across SCZ, BD,[27] and MDD[28]<br>Comparing and contrasting blood cytokines between acutely ill and chronically ill patients<br>The effects of treatment of the acute episode on cytokine levels | IFN-γ, IL-1β, IL-1RA, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, sIL-2R, sIL-6R, TGF-β, TNF-α, sTNF-R1 | • IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-10, sIL-2R, TGF-β and TNF-α levels were significantly increased and IL-4 levels significantly decreased in FEP versus HCs<br>• Levels of IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-12, sIL-2R, TGF-β, and TNF-α were all significantly increased, and the levels of IL-4 and IL-10 were significantly decreased in AR patients with chronic SCZ versus HCs<br>• In chronically ill patients,the levels of IL-1β, IL-6, sIL-2R and TNF-α were significantly increased, and IFN-γ levels significantly decreased versus HCs |

| Authors | Study design | Patients n | Controls n | Objective | Biomarkers included in the studies | Main Findings |
|---|---|---|---|---|---|---|
| (Miller et al. 2011) | Meta-analysis | 40 studies (FEP and SCZ) | | The relationship of blood and CSF[29] cytokines with the clinical status | IL-6, IL-12, TNF-α, IL-1β, IL-8, TGF-β[30], IL-1RA, IFN-γ, sIL-2R, IL-2, IL-10 | • In FEP : IL-1B, IL-6, IL-12, IFN-γ, TNF-a, TGF-B, SIL-2R increased versus HCs<br>• In AR: IL-10 decreased, and IL-6, IL-8, TNF-a, IFN-g, TGF-B, IL-1RA increased versus HCs<br>• IL-1β, IL-6, TGF-β=state markers IL-12, IFN-γ, TNF-α, and sIL-2R=trait markers<br>• There is no difference in IL-6 levels between stable medicated outpatients and control subjects. |
| (Pardo-de--Santayana et al. 2021) | Longitudinal study | 75 FEP | | The relationship between the active post-psychotic phase and the levels of blood cytokines over three years under antipsychotic treatment | ITAC[31], GM-CSF, Fractalkine, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17a, IL-21, IL-23, MIP-1α, MIP-1β[32], MIP-3α[33] and TNF-α | • The percentage of variation of the serum levels of MIP-3α during the first three months of antipsychotic treatment predicts the initial time to remission of psychosis in FEP patients |
| (Dimitrov et al. 2013) | Cross-sectional study | 47 SCZ | 20 | The relationship between the blood cytokine levels and the presentation of psychotic symptoms | | • Significantly increased levels of GRO[34], MCP-1, MDC[35], and sCD40L[36], and significantly decreased levels of IFN-γ, IL-2, IL-12p70, and IL-17, in SCZ patients compared to HCs<br>• Positive correlations between levels of cytokines and the PANSS scores in SCZ for G-CSF, IL-1β, IL1ra, IL-3, IL-6, IL-9, IL-10, sCD40L and TNF-β |
| (Lee et al. 2017) | Cross-sectional study Case-control | 95 SCZ | 95 | Comparing the levels of blood cytokines in SCZ and HCs | TNF-α, IL-6, IFN-γ | • Individuals with SCZ had higher levels of TNF-α and IL-6 but not IFN-γ than HCs |
| (Dunleavy et al. 2022) | Meta-analysis | Ten studies (FEP) | | Overview of cytokine alterations in antipsychotic naïve FEP patients relationship between cytokine levels and negative symptoms in FEP | TNF-α, IFN- γ, IL- 1β, IL- 2, IL-6, IL- 8, IL- 12, IL- 17, IL- 4 and IL- 10 | • IFN- γ, IL- 6, IL- 12, and IL- 17 are significantly increased in medication-naïve FEP |
| (Kubistova et al. 2012) | Case-control | 25 FEP | 25 | Comparing the levels of blood cytokines in FEP and HCs | TNF-α, IL- 6, IL- 8, IL- 10 | • Higher levels of IL-6 and TNF-α in FEP compared to HCs |

[1] First-episode psychosis; [2] Multi-Episode Schizophrenia; [3] Healthy controls; [4] Interleukin-1 receptor antagonist; [5] Interferon-gamma; [6] nterferon-gamma-inducible protein 10; [7] Fibroblast Growth Factor 2; [8] Granulocyte colony-stimulating factor; [9] Granulocyte-Macrophage colony-stimulating factor; [10] Monocyte Chemoattractant Protein-1; [11] Macrophage Inflammatory Protein-1 Alpha; [12] Vascular endothelial growth factor A; [13] Platelet-Derived Growth Factor BB; [14] Regulated on Activation, Normal T Cell Expressed and Secreted; [15] C-C motif chemokine ligand 2; [16] C-C motif chemokine ligand ; [17] C-C motif chemokine ligand 4; [18] C-C motif chemokine ligand 11; [19] C-X3-C motif chemokine ligand 1; [20] C-X3-C motif chemokine ligand 8; [21] C-X3-C motif chemokine ligand 10; [22] Schizophrenia; [23] Positive and Negative Symptoms Scale; [24] Vascular cell adhesion molecule 1; [25] Intercellular adhesion molecule 1; [26] Acutely Relapsed; [27] Bipolar disorder; [28] Major Depressive Disorder; [29] Cerebrospinal fluid; [30] Transforming Growth Factor beta; [31] Interferon inducible T-Cell Alpha Chemoattractant; [32] Macrophage Inflammatory Protein-1 Beta; [33] Macrophage Inflammatory Protein-3 Alpha; [34] Growth-regulated oncogene; [35] Macrophage-derived chemokine; [36] Soluble CD40 ligand

represents a cluster of distinct features, strictly limited to enduring primary NS, present for at least 12 months (Buchanan 2007). The prevalence of defSCZ is up to 20-30% in the clinical samples, and as the PNS refer to a broader concept, their prevalence is expected to be higher (Buchanan 2007). There is a growing body of findings suggesting that this subtype of schizophrenia may represent a categorical distinct entity inside the larger schizophrenia nosology (Kirkpatrick et al. 2001).

## MARKERS OF INFLAMMATION AND NEGATIVE SYMPTOMS

Multiple sources indicate that NS may be accompanied by a distinct immunological signature (Liemburg et al. 2018). We grouped these findings into two types of study designs: 1. non-comparative studies involving schizophrenia or FEP samples, where the NS scores were correlated to the levels of the inflammatory markers, and 2. comparative studies of defSCZ patients versus nondeficit patients and control (see Table Nr.2).

**Interleukin-6 (IL-6)** represents one of the most consistently associated pro-inflammatory cytokines with NS (Al-Hakeim et al. 2021, Dahan et al. 2018, Dai et al. 2020, Enache et al. 2021, Feng et al. 2020, Garcia-Rizo et al. 2012, Goldsmith et al. 2018, 2019, Stojanovic et al. 2014). High levels of IL-6 were found to indicate NS-tendency in the case of high-risk subjects for psychosis (Goldsmith et al. 2019, Stojanovic et al. 2014) or in the FEP (Garcia-Rizo et al. 2012, Stojanovic et al. 2014), which indicates that the prodromal syndrome might be characterized by a "refined" inflammatory-deficit status. In some studies that operated with the deficit schizophrenia concept, IL-6 levels mark the distinction line between deficit and nondeficit samples, with higher levels in the deficit group (Goldsmith et al. 2018). In a more recent study, IL-6 levels were strongly correlated with the negative features when PANSS scores were compared with different cytokines (Dahan et al. 2018).

Another biomarker that is believed to be associated with NS is **tumor necrosis factor-alpha** (TNF-α). (Enache et al. 2021, Goldsmith et al. 2018, Roomruangwong et al. 2020). As with IL-6, in a study comparing deficit versus nondeficit schizophrenia patients, TNF-α plasma levels were found to be significantly elevated in the deficit group, where they were specifically associated with increased blunted affect, alogia, and total NS scores (Goldsmith et al. 2018). In addition, higher baseline levels of TNF-α may also predict increments in NS scores for the clinical high-risk individuals on follow-ups (Goldsmith et al. 2019). Besides the cytokine serum levels, the

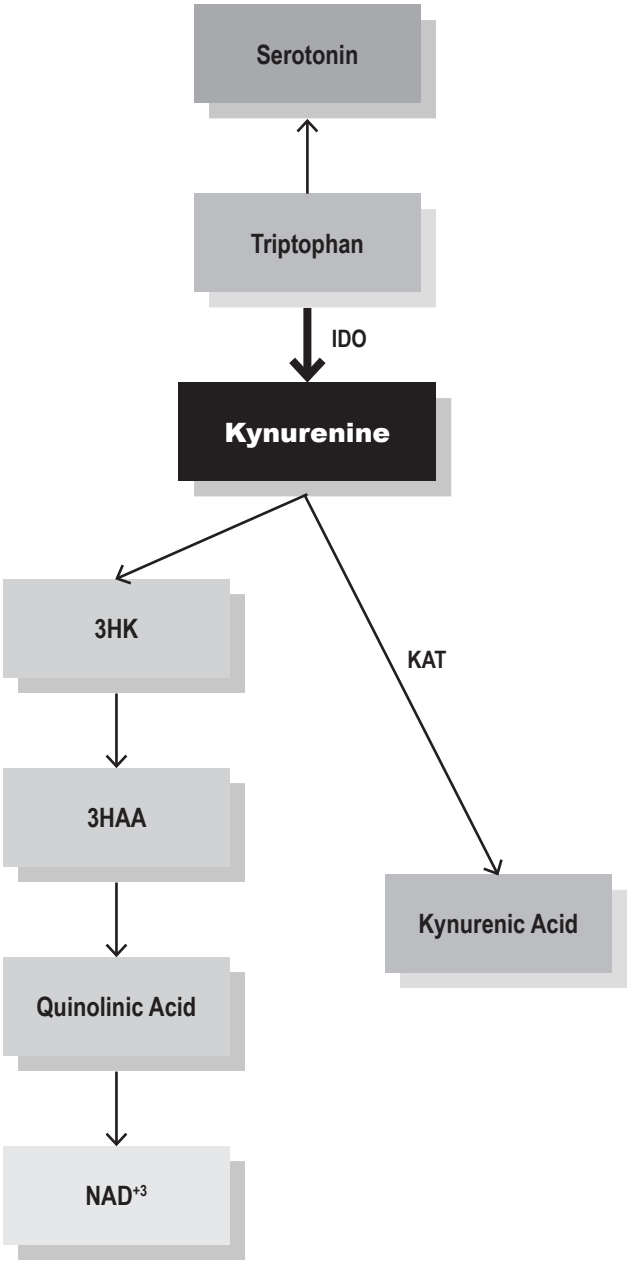


**Fig. 1 Kynurenine pathway:** It was observed that the KPs occur in different tissues, including the immune system and the brain, where the IDO enzyme catalyzes the conversion of TRP to KYN (Savitz 2020). Two main branches emerge from this latter path whose activity is usually negligible under physiological conditions (Savitz 2020): on one branch, KYN is converted to QA, and finally, to NAD+3, and on the other branch, the rest of KYN is transformed into KA (Dantzer et al. 2008, Savitz 2020).

KP= kynurenic pathways; IDO= indoleamine 2,3-dioxygenase; TRP=Triptophan; KYN=Kynurenine; KAT=kynurenine aminotransferase; 3HK=3-hidroxykynurenine; 3HAA=3 hydroxyanthranilic acid; NAD+3=nicotine amide dinucleotide; QA= quinolinic acid; KA= kynurenic acid.

**Table 2:** The negative symptoms of schizophrenia and the peripheral immune alterations

| Authors | Study design | | Findings related to NS1 |
|---|---|---|---|
| | Deficit vs nondeficit sample | Correlation between NS and biomarkers in SCZ sample | |
| (Garcia-Rizo et al. 2012) | Compare inflammatory markers between drug-naive affective and nonaffective psychoses. | | Increased IL-6 and CRP levels in the deficit sample compared to the non-deficit sample |
| (Goldsmith et al. 2019) | | Evaluation of inflammatory markers in individuals at CHR[2] | IL-6 and TNF-a predict NS in CHR individuals |
| (Goldsmith et al. 2018) | Compare inflammatory markers among deficit SCZ[3], nondeficit SCZ, and HCs[4] | | Increased TNF-α and IL-6 levels in patients with deficit schizophrenia<br>compared to non-deficit and HCs |
| (Feng et al. 2020) | | Longitudinal evaluation of inflammatory markers in SCZ patients | IL-6 may be a reliable prognostic biomarker for the NS |
| (Dahan et al. 2018) | | Association of serum cytokine levels with the degree of psychotic manifestation in SCZ patients | IL-6 correlates explicitly with the NS |
| (Enache et al. 2021) | | Association of blood cytokines and complement markers with the presence of antipsychotic non-response and symptom severity in patients with psychosis | IL-8, TNF-α, and IL-10 positively correlated with NS severity |
| (Stojanovic et al. 2014) | | Evaluation of inflammatory markers in ARMS[5] subjects, PD[6], and HCs | IL-6 is positively correlated with the severity of NS severity in both ARMS and PD patients |
| (Roomruangwong et al. 2020) | Evaluation of IRS[7] and CIRS[8] roles in the different SCZ phenotypes: FEP[9], AR[10], MES[11], TRS[12], comorbid depression, and deficit SCZ | | Impairments in the CIRS are associated with deficit SCZ. |
| (Turhan et al. 2016) | | Evaluation of TNF-α, sTNF-αRI[13], and sTNF-αRII[14] levels in patients with SCZ and HCs and their relationship with the symptoms of SCZ | sTNF-α I and sTNF-α II levels negatively correlated with NS |
| (Chen et al. 2021) | | Evaluation of risperidone treatment effect on IGF-1[15] and IL-17 levels in drug naïve FEP | IGF-1 levels at the baseline negatively correlated with the reduction in NS score |
| (Maes et al. 2019) | Compare the IgA/IgM antibodies responses to Gram-negative bacteria between deficit and nondeficit SCZ. | | Increased IgA antibody responses to Gram-Negative Bacteria and Lower IgM responses to OSEs[16] in deficit SCZ compared to nondeficit and HCs |
| (Maes et al. 2020) | Examine whether IL-6, TNF-a, and Il-4 predict deficit SCZ | | IL-6 and TNF-a levels increased in deficit SCZ compared to nondeficit and HCs<br>TNF-a levels predict NS. |
| (Kanchanatawan et al. 2018) | Compare the IgM antibodies responses to TRYCATs[17] between deficit and nondeficit SCZ. | | Lower IgM responses to TRYCAT in deficit SCZ compared to nondeficit and HCs |
| (Dai et al. 2020) | Compare the serum protein factor levels between positive and negative symptoms of SCZ. | | Increased IL-6 and IL-1β in SCZ patients characterized by NS |
| (Dunleavy et al. 2022) | | Meta-analysis and systematic review of cytokine perturbations in antipsychotic-naïve FEP populations and assess the relationship between inflammatory biomarkers and NS severity | Moderate positive correlations between<br>IL- 1β, IL- 2, IL- 6 and TNF- α and NS<br>Strong positive correlation between IL-4 and NS |

[1] Negative Symptoms; [2] Clinically high-risk for psychosis; [3] Schizophrenia; [4] Healthy controls; [5] At-risk mental state; [6] Psychotic disorder; [7] Immune-Inflammatory Response System; [8] Compensatory Immune-Regulatory Reflex System; [9] First-episode psychosis; [10] Acutely relapsed; [11] Multi-episode Schizophrenia; [12] Treatment-resistant schizophrenia ; [13] Soluble Tumor Necrosis Factor Alpha Receptor I; [14] Soluble Tumor Necrosis Factor Alpha Receptor II; [15] Insulin Growth Factor; [16] oxidative specific epitopes; [17] tryptophan catabolites

soluble TNF-α receptor (sTNF-αR) levels were also lower in schizophrenia patients versus healthy controls, while inversely correlated with the negative symptomatology (Turhan et al. 2016). Intriguingly, soluble TNF-αRII is considered neuroprotective and might play a role in a broader mechanism that regulates the inflammatory systemic response (Roomruangwong et al. 2020).

Even if to a lesser extent, some evidence shows that other cytokine levels are modified along with the severity of the negative traits such as **interleukin-1 beta** (Dai et al. 2020; Fillman et al. 2016), **insulin-like growth factor (IGF-1)** (Chen et al. 2021), **interleukin-2 (IL-2)** (Asevedo et al. 2014), **interleukin-10 (IL-10)** or **interleukin-4 (IL-4)** in various schizophrenia samples (Maes et al. 2020).

## THE IMMUNOLOGICAL THEORY OF SCHIZOPHRENIA

Three levels of explanation for the role of immune dysfunction in the pathogenesis of schizophrenia as a unitary disorder have been considered: 1. On the ontogenetic level, **the vulnerability/diathesis-stress model**; 2. On a cell level, **the activation of microglia**; and 3. On the biochemical level, **the altered kynurenine pathway**.

**The vulnerability-stress model**: A contribution of the immune anomalies to the origination and development of schizophrenia was first posited several decades ago through the vulnerability-stress model (Zubin & Spring 1977). This view emphasizes the role of physical and mental insults in triggering psychosis where there is genetic susceptibility (Müller et al. 2015).

First, it was observed that most of the polymorphisms associated with schizophrenia involve variation in the Major Histocompatibility Complex (MHC) locus (Birnbaum & Weinberger 2020, Sekar et al. 2016). This association created the premise to infer that at least some of the genes responsible for schizophrenia may be variants of the immunome (Rubesa et al. 2018). In humans, the MHC region, localized on chromosome 6, contains multiple genes active in encoding immune functions (Meyer et al. 2011), from which the complement component 4 (C4) locus variation was found to be the strongest signal associated with schizophrenia (Sekar et al. 2016). Furthermore, elevated complement activity might promote excessive microglia-mediated pruning (Sekar et al. 2016), a cardinal neurodevelopmental process considered to be involved in schizophrenia. This common diathesis for schizophrenia and immune disbalance was also suggested by some recent meta-analyses concluding that specific polymorphisms of the IL1B, IL6, and sIL6R genes (Hudson & Miller 2018) or lower production of IL-10 genotypes (Gao et al. 2014) might be associated with a higher risk for schizophrenia.

Second, the stress factor affects such a diathesis in critical periods of ontogeny (Howes & McCutcheon 2017). These stressors may consist of perinatal insults such as fetal exposure to an inflammatory environment (Birnbaum & Weinberger 2020). A growing body of evidence indicates that an induced maternal immune activation by mediators, including viral or bacterial infections, increases the risk for schizophrenia-like behavior in offspring (Birnbaum & Weinberger 2020, Meyer et al. 2011). Thus, rodent models of induced maternal inflammation by administering lipopolysaccharide (LPS) simulating bacterial infection, along with parallel evidence of alterations in maternal cytokines during pregnancy in humans, are associated with a higher risk for schizophrenia phenotype (Miller & Goldsmith 2017). Later exposure to various stressors during the peri-pubertal period may lead to a **priming state**, consisting of an exaggerated inflammatory response to a repetitive stimulus, leading to CNS consequences (Howes & McCutcheon 2017).

**Central inflammation:** The pro-inflammatory cytokines exert pleiotropic activities in the CNS varying from altering the fetal neuroanatomy (Ellman et al. 2010) to enhancing either neurotoxicity or neuroprotection, all these effects being mainly modulated by microglia (Na et al. 2014). Microglia represent the resident immune cells of the CNS, reacting to different environmental triggers as explained in the **vulnerability-stress model** (Howes & McCutcheon 2017, Rubesa et al. 2018). Multiple centripetal pathways activate microglia (Rubesa et al. 2018) to oscillate between two states (Howes & McCutcheon 2017): 1. M1 is activated by peripheral cytokines, which trigger inflammation by releasing a wide range of cytokines and neurotoxic factors, such as IL-6, TNF-α, IL-1β, and glutamate. M2, on the other hand, has anti-inflammatory properties. In schizophrenia, the M1 pathway is dominant, leading to excessive inflammatory response, synaptic loss, and, ultimately, extensive pruning (Howes & McCutcheon 2017). This proinflammatory orientation of microglial activity could represent the expression of the priming achieved earlier in life (Howes & McCutcheon 2017). This cellular shift to a higher inflammatory cytokine expression will also be translated into neurochemical pathway alterations.

**The kynurenine pathway:** Kynurenine (KYN) is a downstream product of the tryptophan (TRP) metabolism ( shown in Fig. 1). It was hypothesized that M1-released cytokines might stimulate the indoleamine 2,3-dioxygenase (IDO) (Y. Zhang et al. 2021) and turn the balance towards the conversion to kynurenine and its final

metabolites (Dantzer et al. 2008): 1. the QA, an NMDA receptor agonist leading to excitotoxicity, and 2. The KA with NMDA receptor antagonism, considered to be neuroprotective (Dantzer et al. 2008, Savitz 2020). Moreover, KA is the only known endogenous NMDA receptor antagonist (Savitz 2020). It is not surprising that some authors have suggested that an excessive amount of KA may contribute to the development of schizophrenia (Schwarcz et al. 2012), in concordance with the NMDA receptor antagonism or hypofunction (Pandarakalam 2022, Rubesa et al. 2018). In support of this theory, rich evidence shows elevated levels of KYN and KA in the CNS of schizophrenia patients (Krause et al. 2013, Plitman et al. 2017), while increased QA levels were associated with depressogenic effects (Savitz 2020). Therefore, depression and negative symptoms may represent different facades of an underpinning pro-inflammatory shift.

## NEGATIVE SYMPTOMS AT THE EPICENTER OF INFLAMMATION IN SCHIZOPHRENIA: LINKS TO THE GENERAL IMMUNOLOGICAL THEORY

We propose a framework of several models to explain the links between NS and the general immunological theory of schizophrenia across a spectrum from broad to narrow: the sickness behavioral syndrome, a negative-like phenotype, experimentally produced by pro-inflammatory cytokines; brain blood barrier (BBB) hyperpermeability, parallel with severe NS; activation of counterbalance mechanisms, and deficit schizophrenia as a discrete entity beyond the gradient cumulative changes.

### The sickness behavioral syndrome: a transdiagnosis model for the NS

IL-6, IL-1β, and TNF-α administration can generate an experimental condition known as sickness behavioral syndrome (Dantzer et al. 2008). The sickness behavior, which consists of decreased motor activity, social withdrawal, increased slow-wave sleep, and altered cognition, has been described in depression (Dantzer et al. 2008). Even if not validated within schizophrenia syndrome, this animal model approximates the NS, suggesting similar mechanisms underpinning both depression and SCZ. Otherwise, NS seem to be transdiagnostic, as they were also reported in other psychiatric conditions, while their endurance might be the hallmark of schizophrenia (Möller 2016).

### Brain-blood-barrier permeability and neuroinflammation:

NS may be a more transparent phenotype for the peripheral inflammation observed in schizophrenia, as they may also evoke a "transparentization" of the CNS barriers. S100 calcium binding protein (S100B) could be at the nexus of this intricate relationship (X. Y. Zhang et al. 2010). S100B is a protein with cytokine-like activities involved in neuroinflammation. It is found in elevated levels in the sera of schizophrenia patients, for which it has been proposed as a possible biomarker (Wu et al. 2018). Furthermore, higher serum levels of S100B have been associated explicitly with deficit syndrome or correlated with the severity of NS (X. Y. Zhang et al. 2010). It has been previously reported that there is an increased permeability of the BBB in individuals with schizophrenia (Najjar et al. 2017). However, research on specific connections with the negative phenotype is lacking. A recent Chinese study highlighted a possible connection between elevated levels of S100B in patients with severe NS and some risk variants of aquaporin-4 (AQP4) (Wu et al. 2018). This protein acts as a water channel highly expressed in the astrocytes surrounding the capillaries of BBB (Wu et al. 2018). It has been found that specific alleles encoding AQP4 are associated with increased levels of S100B and higher PANSS negative scores (Wu et al. 2018), suggesting that persistent neuroinflammation doubled by severe NS might be linked with the alteration of BBB integrity (Wu et al. 2018). This finding should be confirmed with additional studies on biomarkers of BBB disruption in relation to specific NS constructs.

### The compensatory immune regulatory system and its disbalance

IL-10 exerts anti-inflammatory effects so that one would expect decreased levels in a pro-inflammatory climate. Findings are contradictory: some studies indicate increased levels of IL-10 in the sera of SCZ patients (Enache et al. 2021), while others show decreased IL-10 production (Gao et al. 2014; Xiu et al. 2014) in relation to the NS. Such a divergence might be explained through a continuum model of inflammation tendency in SCZ syndrome, where the negative features might reflect the failure of counterbalance mechanisms. In this model, the elevation of IL-10 levels could be interpreted through activating the **compensatory immune regulatory system (CIRS**). This mechanism counterbalances the overactive inflammatory responses (Roomruangwong et al. 2020). Other serum alterations such as modified levels of haptoglobin, soluble interleukin-2 receptor (sIL-2R), sIL-1R

antagonist, transforming growth factor (TGF)-β, sTNF-αRI, and sTNF-αRII could be considered as markers of CIRS in schizophrenia (Kanchanatawan, Sriswasdi, et al. 2018; Maes, Kanchanatawan, et al. 2019a, Roomruangwong et al. 2020). Decreased levels of anti-inflammatory factors such as IL-10 in a pro-inflammatory milieu might evoke the dysfunction of CIRS and suggest a specific subgroup of SCZ patients characterized by severe NS. Future studies involving CIRS markers and NS constructs are needed to test for the CIRS collapse hypothesis in the emergence of the negative phenotype.

### Deficit syndrome: the cut-off endpoint of inflammation continuum in schizophrenia

DefSCZ involves categorial distinct neuroimmune traits, accordingly to a series of recent studies conducted by Maes and his team (Kanchanatawan, Sriswasdi, et al. 2018; Maes, Kanchanatawan, et al. 2019a, Roomruangwong et al. 2020). These neuroimmune alterations include high IgA levels and low IgM responses to some of the tryptophan catabolites (TRYCATs) (Kanchanatawan, Sirivichayakul, et al. 2018). As described before, the TRYCATs are the final products of the KP that is catalyzed by IDO, a highly expressed enzyme in neuroinflammation, while the IgM antibodies are considered to be part of CIRS (Kanchanatawan, Sirivichayakul, et al. 2018; Maes, Kanchanatawan, et al. 2019a). Therefore, the lower levels of IgM suggest that CIRS may be under-responsive in defSCZ. In contrast, IgA overreaction pleads for mucosal bacterial transgressions, such as gut commensal bacteria (Maes, Kanchanatawan, et al. 2019b). Additionally, the defSCZ samples had increased IgA responses to five Gram-negative bacteria, which evokes a possible increased bacterial translocation into blood (Maes, Kanchanatawan, et al. 2019b). Hence, this IgA overreaction might be the echo of distant infectious assaults. Moreover, it is known that gut microbiota might alter the permeability of BBB (Braniste et al. 2014; Maes, Sirivichayakul, et al. 2019), as translocation of some Gram-negative bacteria represents a highly immunogenic process involving exposure to LPS (Banks 2006) with CNS damage. Another important finding concerns the higher levels of pro-inflammatory cytokines such as TNF-α and IL-6 in the deficit samples (Maes, Kanchanatawan, et al. 2019a). They might be fundamental mediators in the pathobiology of the NS through neuroinflammation and the activation of the IDO pathway, with a final increased production of neurotoxic TRYCATs (Kanchanatawan, Sirivichayakul, et al. 2018). An earlier study on TRYCATs responses to LPS inoculation and antipsychotics had revealed that higher levels of tryptophan were correlated with lower NS scores, suggesting that the kynurenine pathway might be (part of) the red line connecting neuroinflammation and the primary NS (Krause et al. 2013). In addition, impaired dopamine release might result from a mechanism linking the KYN pathway and ventral striatal circuits, particularly associated with the motivational deficit (Goldsmith & Rapaport 2020). Figure 2 displays a clear illustration of the neuro-immune processes mentioned earlier.

## CONCLUSION

Four fundamental questions arise during this paper: 1. What is schizophrenia? 2. What is the deficit of schizophrenia, and how do we identify it? 3. If identified, is there an objective biological basis for this deficit? 4. How to manage this deficit? The initial interrogation doesn't challenge the operational definition of schizophrenia but rather alludes to its extended trans-psychiatric implications: multiple sources support a convergence of metabolic and neurological modifications into one phenotype associated with constant subclinical inflammation. The deficit of schizophrenia reflects the evolution and prognosis of the diagnosed patient, as it is a synonym for their deterioration. While hallucinations and delusions are salient additions to one's mental activity, the main issue of this deficit is the slow fading away of the individual, which is reflected in the negative symptoms. Even if intuited in clinical practice, it is still challenging to identify and isolate the NS in the complicated clinical scenario of a psychotic patient. While in the symptoms of the mind, NS refer to an absence, in biological terms, they might translate into subclinical inflammation. Suppose the association between NS and a set of biomarkers will be emphasized as consistent by future studies. In that case, two possible formulations emerge: deficit schizophrenia as one of the two discrete types of the disease or NS as a more transparent phenotype of the underlying inflammatory process. Either way would open new perspectives for the last question about the management of this deficit: 1) identifying the high-risk patients to develop enduring NS by accessible serum biomarkers indicating such a phenotype; 2) prevention by therapeutic interventions from the FEP as such modified biomarkers would reflect a more advanced pathological process than the clinical picture, and 3) as long as more specific biochemical and immune mechanisms would be elucidated, some new agents might target this primary deficit of schizophrenia.

In conclusion, new studies are needed to build up this research trajectory on the inflammatory nature of negative symptoms so that a screening model for schizophrenia patients using some feasible biomarkers would be possible.

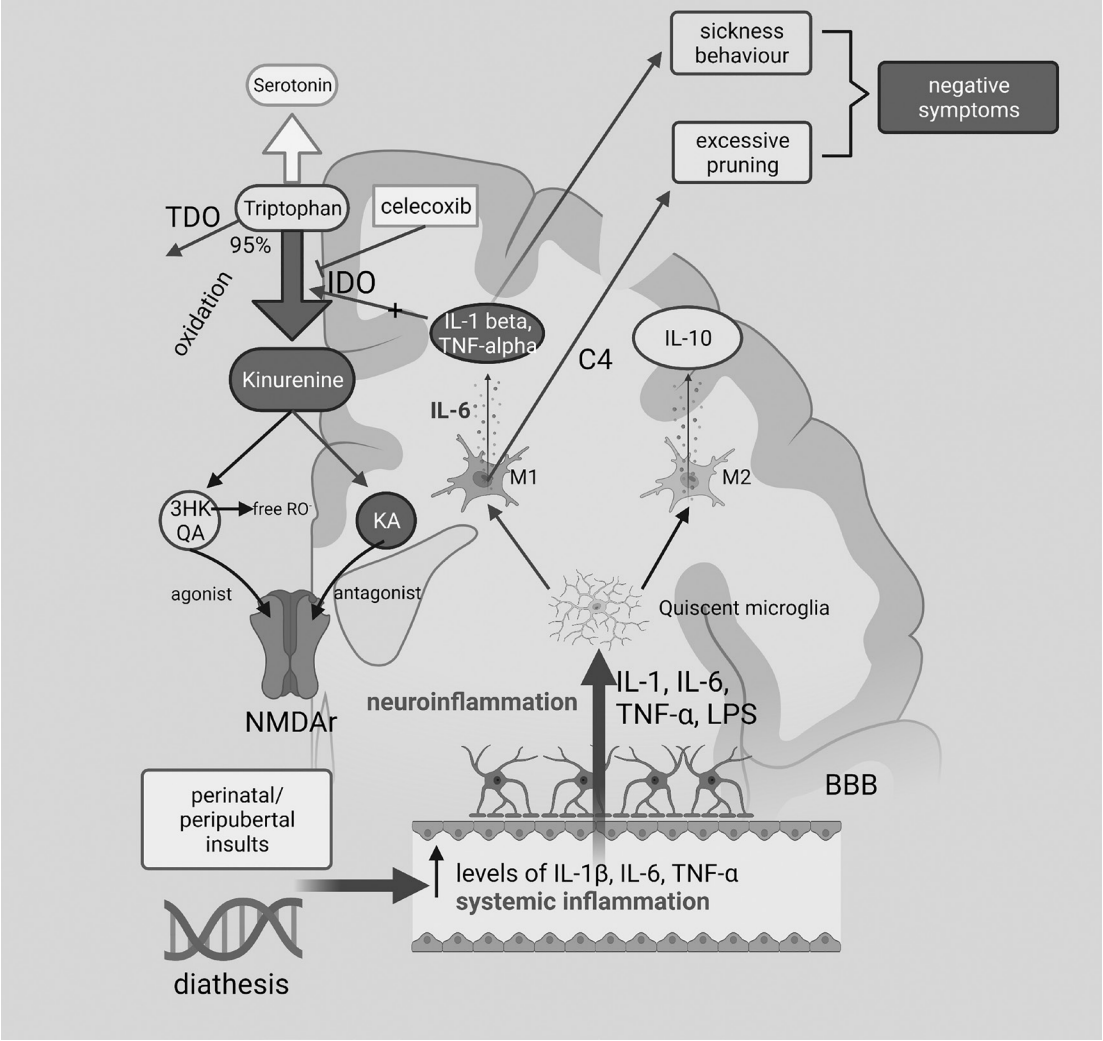


**Fig. 2** Neuroinflammation and the links to the negative symptoms of schizophrenia: Environmental stress factors such as infections during critical periods of ontogeny (perinatal/peripubertal stress) can promote an excessive systemic inflammatory response on a vulnerable genetic ground (diathesis). This systemic inflammation involves elevated levels of pro-inflammatory cytokines in the bloodstream that can cross the BBB through specific cytokine transporters. The integrity of BBB can also be altered by exposure to LPS generated by translocated bacteria. In the end, all these various assaults increase the permeability of BBB, which permits greater transgressions to CNS. Increased IgA levels echo this transgression, while decreased IgM levels suggest an under-responsive CIRS. The inflow of such an immunogenic wave into CNS would prime the quiescent microglia to M1 status, characterized by increased production of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α that characterize altogether the subclinical neuroinflammation associated with schizophrenia. Such a priming state might also be achieved by participating in an over-activated complement (C4), triggering M1 microglia to excessive pruning. This excessive loss of cortical synapses might contribute to the primary deficit in schizophrenia. Also, IL-1β and TNF-α induce the sickness behavior syndrome associated with a negative-like phenotype. The proinflammatory cytokines stimulate IDO, which converts tryptophan into kynurenine and, therefore, neuroinflammation catalyzes the shift toward the production of kynurenine and its final catabolites: 3HK, QA, and KA, considered to be neurotoxic. Moreover, KA exerts antagonistic effects on NMDAr and might play an essential role in the theory of defective NMDAr in schizophrenia.

BBB=brain-blood barrier; LPS= lipopolysaccharide; CNS=central nervous system; M1=pro-inflammatory; M2=anti-inflammatory; IDO=indoleamine 2,3-dioxygenase; 3HK=3-hydroxykynurenine; QA= quinolinic acid; KA= kynurenic acid; CIRS= compensatory immune system; NMDAr=NMDA receptor

***Ethical Considerations:*** Does this study include human subjects? NO

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