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The Impact of Inflammation on neurocognition and Risk for Psychosis: A Critical Review

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Abstract

Neurocognitive difficulties are highly prevalent among people with schizophrenia and have been linked to increased inflammation, as well as dysfunction and disability. Poor neurocognitive functioning has also been documented in individuals at clinical high risk for psychosis (CHR) and a burgeoning literature point to alterations in inflammation markers in this population. However, there is limited information regarding the putative link between inflammation and neurocognition in CHR individuals, and the potential role of inflammation in the development of cognitive difficulties and psychosis. As previous reports indicate that early treatment in schizophrenia is associated with better outcomes, there is an urgent need to identify neurobiological mechanisms underlying cognitive deterioration and psychosis in CHR individuals to provide them with care prior to significant cognitive and functional declines. To address this gap in the literature, we review and summarize the relevant literatures on inflammation and neurocognitive dysfunction in schizophrenia and CHR individuals, point to remaining gaps, and suggest directions for future research.

Graphical Abstract

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Keywords

Clinical High Risk; Prodrome; Inflammation; Neurocognition; Psychosis; Schizophrenia

The psychosis prodrome of schizophrenia is characterized by attenuated psychotic, negative, and neurocognitive symptoms that typically result in decreased social, academic and occupational functioning prior to the onset of frank psychosis[1]. While historically the clinical management of schizophrenia often began at the first psychotic episode, such interventions were typically preceded by months or years of functional decline[1]. However, a growing literature indicates that early interventions are associated with a better response to treatment and improved functional outcomes [2], Consequently, efforts have been made to identify individuals at clinical high risk (CHR) for psychosis to better understand the pathophysiology underlying the onset of psychosis and to develop early interventions in order to delay or prevent onset of full psychotic symptoms. The CHR label describes individuals who meet criteria for a psychosis risk syndrome and are at risk for converting to a schizophrenia spectrum disorder. Because schizophrenia severely limits the most productive years of an individual's life, the promise of early detection and intervention is highly promising. Several characteristics, including age, severity of attenuated positive symptoms, poor social functioning, substance use, family history of schizophrenia[3], neurocognitive status[4], emotion recognition[5], and low socioeconomic status[6] have been found to be predictors of conversion to psychosis. Yet, despite these known risks, a significant portion of the risk for psychosis remains unexplained, which creates a barrier for predicting which individuals would benefit most from close monitoring and early treatment[7].

In recent years, a burgeoning has suggested links between poor neurocognition and inflammation in individuals with schizophrenia. Building on this work, in this manuscript we will review the current literature on the putative interplay between inflammation and

neurocognition in CHR individuals and discuss what is currently known about: 1) cognitive deficits in the CHR individuals; 2) neurocognitive dysfunction in people with schizophrenia and their links to inflammation; 3) neurocognitive dysfunction in mood disorders given etiological similarity to psychotic disorders; 4) candidate cytokines implicated in neurocognitive dysfunction in CHR individuals; and 5) evidence from pharmacologic and behavioral anti-inflammatory interventions in schizophrenia and their impact neurocognitive dysfunction in schizophrenia and related disorders.

Neurocognitive Deficits in CHR Individuals

CHR individuals display impaired neurocognition across multiple domains including processing speed, attention, working memory, reasoning and problem solving, as well as visual and verbal learning, with the greatest impairments described in processing speed, attention and working memory[8]. Several studies have shown that deficits in neurocognition can help to differentiate CHR individuals who will transition to psychosis from healthy controls[9]. CHR individuals who later developed psychosis had significantly lower baseline verbal memory scores compared with those who did not develop psychosis[10], suggesting that changes in neurocognition may serve as predictors of transition risk [9]. A meta-analysis of studies using the MATRICS Consensus Cognitive Battery (MCCB)[11] have found that individuals who converted to psychosis performed significantly worse in working memory and visual learning tasks, but not in other domains compared to non-converters[12]. Other studies found links between verbal IQ, processing speed, verbal memory and working memory and increased risk of transition to psychosis[10, 13-15]. Deficits in neurocognition were also found to be correlated with increased risk of transition to a psychotic disorder in a non-psychiatric sample of 11-21 year-olds from a primary care pediatrics setting[9].

Consistent with these findings, neurocognitive deficits have been found to be associated with a reduction in gray and white matter over time in those who convert to psychosis[16]. Multiple neuroimaging studies have shown reductions in cortical and gray matter and a steeper rate of gray matter loss in the right superior frontal, middle frontal, medial orbitofrontal cortical regions[17], as well as superior temporal gyrus [18] in individuals who eventually convert to schizophrenia compared to non-converters. Interestingly, some studies show that white matter integrity dysregulation on imaging is correlated with increased weight in individuals with schizophrenia,[19] suggesting a possible interplay between cognitive changes and metabolic disorders in this group.

Neurocognitive Dysfunction in Schizophrenia: Links to Inflammation

Immune activation as measured by increased circulating cytokines has been found to be correlated with decreased cognitive function in individuals with schizophrenia and healthy controls[20], suggesting a role for inflammation in worsening neurocognitive dysfunction. In addition to changes in neurocognition, several studies have indicated that individuals with schizophrenia display alterations in inflammation markers and have proposed that inflammation may also contribute to both positive and negative symptoms in schizophrenia[21, 22]. Consistent with these findings, systemic inflammation causes microglia, brain macrophages, to release inflammatory cytokines, which bind to receptors on

neurons and activate signaling pathways which can lead to changes in mood, cognition and behavior[23].

A leading hypothesis about the origins of schizophrenia suggests it results from a dysfunction in parvalbumin interneurons (PVIs) via hypofunction of N-methyl-D-aspartate receptors (NMDARs). These networks are involved in cognitive processes such as working memory, which are disrupted in schizophrenia [24]. Increased inflammation in individuals with schizophrenia has been extensively described[25], though it was initially unclear whether it was related primary to the disorder or to lifestyle factors such as being sedentary and eating a nutrient-poor diet[26]. However, genome-wide association studies implicated regions of chromosome 6 spanning the Major Histocompatibility Complex (MHC), particularly component 4 (C4 gene), which is involved in opsonization of pathogens and synaptic pruning, in schizophrenia[27]. Polymorphisms in other pro-inflammatory cytokine genes, such as IL-6 receptor (IL-6R)[28] and IL-1 β [29] have also been linked to increased risk of schizophrenia, suggesting a shared origin between schizophrenia and immune system dysfunction that is independent of lifestyle factors. Additionally, our group have recently demonstrated that poor neurocognition and daily function were significantly and negatively associated with increased peripheral TNF- α and IL-12p70 in individuals with schizophrenia[30]. Related with these findings, reduced cortical grey matter and superior frontal gyrus in post-mortem brains from individuals with schizophrenia were also correlated with elevated IL-6 and IL-1 β [31].

Neurocognitive Dysfunction in Mood Disorders: Links to Inflammation

Changes in inflammation have been implicated in other psychiatric disorders such as major depressive disorder (MDD) and bipolar disorder, where aberrant macrophage, T cell activation, and altered cytokine levels have been described[32]. Also of interest, elevated TNF- α and changes in other cytokines have been correlated with increased affective symptoms, changes in brain morphology, and decreased cognition[20]. Increased inflammatory markers, in particular, have been found to be negatively associated with cognition, though there is significant heterogeneity among published articles regarding which cytokines are involved[20, 33, 34]. In one study, sTNF-R1, IL-1Ra and sCD40L have been implicated in decreased cognitive performance as measured by the Wechsler Abbreviated Scale of Intelligence (WASI)[20]. Likewise, a number of inflammation markers including IL-6, TNF- α , sIL-2R and IL-1RA have been found to be significantly elevated in MDD and bipolar disorder [34], though studies are inconclusive regarding their role in cognition.

Inflammation in Individuals at Clinical High Risk for Psychosis

A number of studies have reported altered inflammatory profiles in CHR individuals [35]. A recent review of Inflammation in CHR indicated IL-1 β , IL-7, IL-8, MMP-8, and cortisol predicted conversion to psychosis[36] and another study implicated IL12/IL23p40 as a marker for psychotic transition in CHR[37] individuals. However, there remains significant variability in the published literature. Studies examining brain imaging in CHR individuals found that grey matter volume in individuals with first-episode psychosis was inversely

correlated with neutrophil count and Positive and Negative Syndrome Scale (PANSS), a measure of symptom severity [38], though they did not assess neurocognition directly.

Only two studies directly examined inflammation and cognition in CHR, including one that used Translocator protein 18 (TSPO) as a proxy for microglial activation. TSPO is a conserved protein implicated in the regulation of many cellular processes including inflammation, oxidative stress and mitochondrial homeostasis that is commonly used as an indirect marker of microglial activation though it is expressed in multiple other cells and tissues. Da Silva *et al* examined TSPO expression via neuroimaging and did not find a correlation with neurocognitive performance[39]. In contrast, Ntouros *et al* found that IL-4 was correlated with deficits in social cognition[40]. While both studies employed small samples, they warrant follow up investigation.

Candidate Cytokines Involved in Neurocognition in Individuals at Clinical High Risk for Psychosis

Inflammation is most readily studied by examining peripheral cytokines. Though numerous studies have sought to describe cytokine alterations in schizophrenia and CHR, the literature is inconclusive likely due to examination of trait v. state markers, as well as large variability associated with sampling differences. However, changes in TNF- α , IL-1 β , IL-2 and IL-6 have been published in several cohorts with schizophrenia and we will discuss them in greater detail.

Tumor Necrosis Factor alpha (TNF- α)

Inflammatory cytokines, including TNF- α , are increased in schizophrenia and inversely correlated with cognition in this population[20, 41]. However, it is yet unclear whether the relationship between TNF- α and cognition extends to CHR population and whether this link can be manipulated to improve clinical outcomes. Several inflammatory cytokines, particularly TNF- α [42], have been found to be critical in synaptogenesis and neurodegeneration[43], a possible mechanism for the link to neurocognition. TNF- α is produced by resident brain astrocytes, microglia, and neurons in response to a variety of CNS stimuli and appears to play a role in cognitive dysfunction in schizophrenia, though its precise role in CHR is unclear. The role of TNF- α among CHR individuals may be of particular importance, as the brain continues to develop and mature through adolescence, a time when CHR individuals are often identified. TNF- α is an important player in brain development as it modulates synaptic pruning and plasticity[44] during pre-adolescence, adolescence and early adulthood. In mice, TNF- α regulates hippocampal formation and absence of TNF- α results in accelerated dentate gyrus development [45, 46]. Also, in *ex vivo* systems utilizing neuron/astrocyte co-cultures, treatment with exogenous TNF- α results in deficits of dendritic branching, a defect that can be reversed by ablation of the neuronal TNF-R gene[47]. Electrophysiological experiments have illustrated negative effects of TNF- α on rat neuronal function including decreases in long-term potentiation, a correlate of learning and memory in slices from the hippocampus and dentate gyrus [48]. Consistent with this finding, mice deficient in TNF- α exhibit decreased latency in finding the underwater platform in the Morris water maze (MWM) test compared to wild type mice,

suggesting improved hippocampal function in the absence of TNF- α [46]. Though a full discussion is beyond the scope of this review, TNF- α signaling has also been implicated in numerous ion channel pathways involved in schizophrenia and other psychiatric disorders including in α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) channel expression, as well as glutamate[49], NMDA[50] and GABA[51] signaling. Hence, clarifying the role of TNF- α in CHR is likely to lead to important insights into the pathophysiology of psychosis and new avenues for treatment.

Interleukin 1 beta (IL-1 β)

Other cytokines have also been linked to schizophrenia. IL-1 β has been implicated in some studies examining inflammation in schizophrenia, which found that people with schizophrenia had higher levels of IL-1 β than controls, though there was no clear relationship between levels and symptomatology. Another study examining this relationship reported that IL-1 β levels in serum and CSF of individuals with schizophrenia were lower than controls[52]. Yet, another study found increased secretion of IL-1 β from monocytes derived from individuals with schizophrenia, which normalizes with antipsychotic medication treatment[52-54]. A meta-analysis from 8724 case-control and 201 samples from 16 studies failed to identify an association between *IL1 β* C511T single nucleotide polymorphism (SNP) of the IL-1 β gene and schizophrenia[55]. However, a study in a different population found that the *IL1 β* C-511T and C395T polymorphisms were moderately associated with schizophrenia in a group of Caucasian individuals[56], suggesting that the relationship might be specific only to certain racial or ethnic groups. IL-1 β has also been shown to be important in cognition independent of schizophrenia as it is increased in long term potentiation of synaptic transmission, a process that underlies learning and memory and appears to play a crucial role in hippocampal neurogenesis[57, 58]. Mouse studies have also shown that IL-1 β is critical for dopaminergic neuron differentiation in progenitor cells[59] and decreasing IL-1 β improved cognition in a rat model of vascular dementia[60].

Interleukin 2 (IL-2)

Interleukin-2 (IL-2), an anti-inflammatory cytokine with neuroprotective properties, has been shown to be altered in people with schizophrenia, though it is uncertain whether levels are increased or decreased, and whether it varies based on ethnicity and symptoms present[32, 41, 52, 61]. Genetic studies have linked the polymorphism G330T in the IL-2 gene with an increased risk of schizophrenia[41, 62]. A study examining IL-2 in individuals with schizophrenia found that it is positively correlated with several cognitive measures including digit span test, nonverbal intelligence and negatively correlated with the negative subscale of PANSS, specifically blunted affect, poor rapport and abstract thinking[41].

Interleukin 6 (IL-6)

IL-6 is a pleiotropic cytokine with pro and anti-inflammatory properties and is postulated to be a state marker for psychosis exacerbation. It is produced by activated astrocytes, microglial cells, and neurons and IL-6 receptors have been localized in the central nervous system. Cross-sectional studies have shown that IL-6 is associated with negative effects on cognition in healthy individuals[63, 64] and mild transient elevations of IL-6 induced in

healthy adults are associated with negative performance on memory tests[65] and increased reaction time coupled with altered substantia nigra activity[66]. Serum IL-6 levels are significantly higher in individuals with schizophrenia compared to controls and there is an inverse relationship between serum IL-6 in schizophrenia and cognition even when corrected for total PANSS score, depression severity and chlorpromazine equivalents [21]. This is consistent with animal studies which showed that IL-6 alters survival and transmission of catecholaminergic, serotonergic and dopaminergic neurons in the hippocampus and prefrontal cortex[67]. Two studies in individuals with schizophrenia indicated increased IL-6 mRNA in the prefrontal cortex of [68, 69], while a recent study indicated that IL-6 may modulate cognition in schizophrenia via its action in the choroid plexus and the blood brain barrier[70]. Though ample evidence implicates IL-6 in neurocognition in schizophrenia, it is unclear what role it plays in neurocognitive dysfunction in CHR.

Evidence from Interventional Studies in Schizophrenia and Related Disorders

Pharmacological Anti-Inflammatory Treatments

Inflammation is increased in schizophrenia and correlated with greater neurocognitive dysfunction. Evidence suggests that antipsychotic medications may act, at least in part, via an anti-inflammatory mechanisms[71]. As such, efforts are underway to develop other anti-inflammatory treatments that improve symptom burden and decrease morbidity and mortality in schizophrenia. An open label trial using Tocilizumab, an IL-6 receptor monoclonal antibody, in individuals with schizophrenia showed improvements in cognition[72]. However, another study studying the effect of treatment with Tocilizumab, did not observe alterations in clinical measures including neurocognition, symptoms, clinical status, and global functioning in a 12-week randomized controlled trial[73]. A double-blind randomized controlled trial using minocycline, an antibiotic that is anti-inflammatory, as an augmentation agent to antipsychotics showed improvement in negative symptoms and executive function compared to antipsychotic treatment alone[74], though this was not replicated by later studies[75, 76]. Trials of NSAIDs as treatment adjuncts have shown little, if any, benefit in individuals with schizophrenia[77]. However, a meta-analysis of clinical effects of NSAIDs in schizophrenia revealed significant effects on total symptom burden, though another found a significant benefit only in individuals with a short duration of illness[77, 78]. One previous study found a trend towards improvements on the PANSS cognition score with Celecoxib, a cyclooxygenase 2 (COX-2) inhibitor adjunctive treatment though this was not statistically significant [79]. A pilot double blind placebo-controlled randomized parallel group study examined N-methyl-D-aspartate (NMDAR) receptor antagonist D-serine which acts in part via modulation of IL-6 and found that treatment with D-serine led to an improvement in negative symptoms though the study was small and effects on IL-6 and cognition were not statistically significant[80]. A recent meta-analysis examining anti-inflammatory medication in schizophrenia concluded that there is some evidence for benefit as an adjunct to antipsychotic medication though more studies are needed[81]. There is a lack of data about the safety and efficacy of these pharmacological treatments in the CHR population though numerous studies are ongoing.

Aerobic Exercise

Individuals with schizophrenia display highly sedentary lifestyle [82-85], as evident by increased morbidity and mortality as a result of cardiovascular complications. Our group have shown that Aerobic Exercise (AE) interventions using active-play video games were both feasible and safe in individuals with schizophrenia and led to significant improvements in cognitive functioning [82-84], along with cardiovascular benefits[85] [86]. A recent meta-analysis confirmed the cognitive benefits of AE [87]. Previous reports have suggested that the proposed mechanism for neurocognitive improvement is via upregulation of Brain Derived Neurotrophic Factor (BDNF), which has been shown to enhance neurogenesis and neuroplasticity. BDNF also plays a role in other models of cognitive impairment including Alzheimer's dementia[88] and cognitive impairment associated with multiple sclerosis[89]. BDNF is negatively regulated by TNF- α , which we have shown is inversely associated with cognition and functioning in individuals with schizophrenia[30].

Imaging studies have indicated AE increases hippocampal volume in individuals with schizophrenia as well as healthy subjects[94], although these findings are not universal. Related to these findings, AE training also leads to a release of anti-inflammatory factors in insulin-responsive tissues including skeletal muscle, liver and adipose tissue which leads to improvements in whole body glucose metabolism[94]. Furthermore, studies indicate that people with schizophrenia have alterations in T cell and monocyte activation that are independent of cardiometabolic disease[32]. These health benefits are critical given people with schizophrenia have a 12-fold higher mortality from all causes compared with the general population and estimates indicate that life expectancy is reduced by 20 years, with much of this effect being driven by cardiovascular-related mortality[96].

Similar to individuals with schizophrenia, CHR individuals also show baseline abnormalities in cardiometabolic risk factors such as insulin and lipid dysregulation, low levels of physical activity, as well as high rates of smoking and alcohol abuse compared with controls. These cardiometabolic abnormalities may relate to conversion risk[90], CHR individuals have been found to be more sedentary than controls, with lower self-perceptions of fitness being associated with increased symptom burden[91] and changes in parahippocampal gyri on MRI[91]. Preliminary evidence indicates that AE is a safe and feasible intervention for CHR individuals with improvements in positive symptoms, negative symptoms, social functioning and neurocognition noted, though inflammation was not assessed[93].

Inflammation, Cognition, and Aerobic Exercise: Findings from Animal Studies

Rodent studies provide evidence regarding the mechanism of the pro-cognitive effects of AE, which seem to be via promoting hippocampal neurogenesis. The pro-cognitive features of AE were first reported when it was discovered that mice housed with a running wheel had increased cell proliferation and survival in the hippocampus as well as improved spatial memory compared to mice housed without[97]. It has since been described that AE increases hippocampal neurogenesis and improves memory tasks in rodents[98]. Much of the mouse studies examining the role of AE in cognition have used Alzheimer's Disease

(AD), a neurodegenerative disorder in which neuroinflammation is a major feature as their model of cognitive impairment. However, neuroinflammation also modulates cognition in socially defeated mice, a model of stress and depression via IL-1 β , TNF- α , IL-6 and VEGF and the negative cognitive phenotype is rescued by the anti-inflammatory medication, minocycline [99]. Inflammation negatively modulates hippocampal neurogenesis and AE is a robust positive modulator, likely via upregulation of BDNF and decreased inflammation as measured by microglial activation[100]. Increased angiogenesis also accounts for some of the improvement in cognition, as AE increases blood vessel density, number as well as cerebral blood flow in animal models[101].

Summary and Future Directions

People with schizophrenia have alterations in inflammation and cognition. These changes are increasingly being identified early in the CHR population and are correlated with increased risk of conversion to psychosis. Consistent with these findings, both changes in cognition and altered inflammatory profiles in CHR individuals have been linked to increased risk of psychotic transition, though the interplay between them has not been fully elaborated. Specifically, number of inflammatory cytokines have been linked to increased risk of psychosis, most notably TNF- α , IL-1 β , IL-2, and IL-6, though the published literature is inconsistent.

Evidence from clinical trials of anti-inflammatory pharmaceutical compounds have shown limited improvement in individuals with schizophrenia. However, a number of clinical trials employing AE training show promise, with benefits evident for neurocognition and physical health outcomes. Additionally, AE offers a number of other advantages including relatively low cost, a non-stigmatizing activity with minimal side effects. Though preliminary reports indicate that AE is a safe and viable intervention in individuals at CHR for psychosis[93], more studies are needed to better understand the impact of AE on neurocognition, inflammation, symptom progression, and conversion rates. Specifically, the link between inflammation and cognition in CHR individuals warrants further exploration as it could potentially provide a more sensitive and specific predictor of psychosis risk. Furthermore, manipulating this interaction with AE could be a novel target for improving outcomes in this population both by delaying and/or preventing symptom progression. Such AE interventions would improve the trajectory for affected individuals, as a significant portion of morbidity in schizophrenia is related to cognitive symptom burden, which hastens functional decline. Future studies should optimize protocols for AE in CHR and confirm if this intervention may improve neurocognition and conversion risk outcomes in this population.

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Table

Studies examining the association between inflammation and cognition in clinical high risk individuals
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), translocator protein 18 kDa (TSPO), Theory of Mind (ToM) and Emotion Perception (EP), Social Cognition (SC), Ultra High Risk (UHR)

Study	Study type/subpopulation	Immune-inflammatory markers	Measures of cognition	Main findings
Da Silva 2019 ^[1]	29 CHR and 15 healthy volunteers) underwent a highresolution PET scan to quantify TSPO expression and were genotyped for the TSPO <i>rs6971</i> polymorphism. Control group was 1:2 M:F and CHR group was evenly split M:F with average age 21.	TSPO	RBANS	no significant correlation between GABA+ levels or residuals of the association with TSPO expression and the severity of prodromal symptoms or cognition
Ntouros 2018 ^[2]	25 First Episode Psychosis (FEP) and 16 relapsed schizophrenic patients (CHRON) compared to 12 subjects in Ultra-high Risk (UHR) and 23 healthy controls (CTR). All subjects were male and age 18-40	Cortisol, IGF-1, TNF- α , TNF- β , IL-1 β , IL-2, IL-4, IL-5, IL-8, IL-10 and IL-12	ToM, EP	SC domains are impaired in patients with psychosis as well as in UHR compared to controls. IL-4 correlates with SC and ToM suggesting a protective effect

¹Da Silva T, Hafizi S, Rusjan PM, Houle S, Wilson AA, Price I, Sailasuta N, Mizrahi R: GABA levels and TSPO expression in people at clinical high risk for psychosis and healthy volunteers: a PET-MRS study. *J Psychiatry Neurosci* 2019, 44(2): 111-119.

²Ntouros E, Karanikas E, Floros G, Andreou C, Tsoura A, Garyfallos G, Bozikas VP: Social cognition in the course of psychosis and its correlation with biomarkers in a male cohort. *Cogn Neuropsychiatry* 2018, 23(2): 103-115.