



# Eosinophils and Cognitive Impairment in Schizophrenia: A New Perspective

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**Abstract:** Schizophrenia is a complex psychiatric disorder characterized by a wide array of cognitive impairments. While research has predominantly focused on the neurological aspects of schizophrenia, emerging evidence suggests that the immune system, specifically eosinophils, may play a significant role in the cognitive deficits associated with the disorder. This review presents a novel perspective on the interplay between eosinophils and cognitive impairment in schizophrenia. Eosinophils, traditionally associated with allergic responses and inflammation, have garnered limited attention within the realm of neuropsychiatry. Recent studies have hinted at a potential link between eosinophil activation and the pathogenesis of schizophrenia. In this comprehensive review, we delve into the world of eosinophils, elucidating their nature, functions, and interactions with the immune system. We examine the cognitive deficits observed in individuals with schizophrenia and discuss existing theories on the etiology of these impairments, focusing on immune system involvement. The paper also highlights the evolving body of research that supports the idea of eosinophilic influence on schizophrenia-related cognitive deficits. Furthermore, we explore potential mechanisms through which eosinophils may exert their effects on cognitive function in schizophrenia, including interactions with other immune cells and inflammatory pathways. By discussing the clinical implications and potential therapeutic avenues stemming from this newfound perspective, we underscore the practical significance of this emerging field of research. While this paper acknowledges the limitations and challenges inherent in studying eosinophils within the context of schizophrenia, it serves as a posit for novel thought in this vexing disease space as well as a call to action for future research endeavors. By providing a comprehensive survey of the existing literature and posing unanswered questions, we aim to inspire a reimagining of the relationship between eosinophils and cognitive impairment in schizophrenia, ultimately advancing our understanding and treatment of this debilitating disorder.

**Keywords:** eosinophils, cognitive impairment, schizophrenia

## Introduction

Schizophrenia, a severe and enigmatic neuropsychiatric disorder, has long captured the interest of researchers, clinicians, and society as a whole.<sup>1</sup> Formerly designated as dementia praecox and characterized by a complex interplay of symptoms that include hallucinations, delusions, disorganized thinking, and emotional dysregulation, schizophrenia extends its impact far beyond the boundaries of the mind.<sup>2</sup> One aspect of this disorder that has gained increasing attention in recent years is the cognitive impairment that frequently accompanies it.<sup>3</sup> Cognitive deficits in schizophrenia significantly hinder individuals' daily functioning, quality of life, and long-term outcomes.<sup>4</sup> Historically, research into the cognitive aspects of schizophrenia has predominantly traversed the neurological terrain, examining factors including neurotransmitter imbalances and brain structure abnormalities.<sup>5</sup> Yet, as we delve deeper into the intricacies of this complex disorder, an emerging perspective suggests that the immune system, often left in the shadows, may hold a key to understanding some of schizophrenia's cognitive mysteries.

This paper presents a novel perspective on the potential role of eosinophils, a subtype of white blood cells primarily known for their involvement in allergic responses and inflammation, in cognitive impairment associated with schizophrenia. While eosinophils have not been a central focus in the realm of neuropsychiatry, recent studies and evolving

hypotheses suggest that they may play a significant part in the pathogenesis and progression of schizophrenia.<sup>6</sup> The immune system's connection to mental health has been a burgeoning field of study, with mounting evidence pointing to immune dysregulation as a contributing factor in various neuropsychiatric disorders.<sup>7</sup> In schizophrenia, the notion of immune involvement has gradually shifted from the periphery to the center of attention, and eosinophils, with their multifaceted roles within the immune system, have been drawn into the spotlight.<sup>8</sup>

The objectives, herein, are to elucidate the nature and functions of eosinophils, to delve into the cognitive deficits that define schizophrenia, and to critically examine the evidence and hypotheses surrounding eosinophilic involvement in this disorder. Furthermore, we will explore potential mechanisms through which eosinophils might influence cognitive function in schizophrenia, as well as the clinical implications and therapeutic potential that this new perspective may offer. In this exploration, it becomes increasingly clear that schizophrenia is a disorder with a web of influences, and the role of eosinophils in cognitive impairment represents a new thread that warrants careful examination. By providing a posit for novel thought in this vexing disease space as well as integrating this emerging perspective into the broader context of schizophrenia research, we hope to contribute to a deeper understanding of the disorder and, in doing so, open doors to novel insights and potential interventions.

## Methods

The rationale for investigating the relationship between eosinophils and cognitive impairment in schizophrenia is listed in [Table 1](#). It includes a multifaceted approach for this new perspective and rooted in both clinical observations and emerging scientific evidence. The quality of included studies was assessed using appropriate tools such as the Newcastle-Ottawa Scale for observational studies or the Cochrane Risk of Bias tool for randomized controlled trials.

**Table 1** Selection Criteria and Approach for Publication Selection. Search Words Employed Included Medical Subject Headings (MeSH), Terms and Keywords: “Eosinophils”, “Schizophrenia”, “Cognitive Impairment”, “Neurocognitive Dysfunction”, “Cognitive Deficits”, “Psychosis”, “Blood Eosinophil Count”, “Peripheral Eosinophils”, “Immune System”, “Inflammation”, “Neuroinflammation”, “Cytokines”, “Interleukins”, “Tumor Necrosis Factor-Alpha”, “Interferon-Gamma”

Inclusion Criteria	Exclusion Criteria	Searched Databases	Study Selection Approach
Studies investigating the relationship between eosinophils and cognitive impairment in individuals diagnosed with schizophrenia.	Studies not focused on schizophrenia or cognitive impairment.	PubMed	Screening of titles and abstracts for relevance.
Studies published in peer-reviewed journals.	Studies conducted solely on animal models.	Scopus	Assessment of full-text articles against inclusion and exclusion criteria.
Studies with human subjects of any age, gender, or ethnicity.	Studies not available in English.	Good Scholar	Data extraction from selected studies.
Studies available in English.	Case reports, reviews, letters, commentaries, and editorials.	Embase	Quality assessment of included studies.
Studies employing observational, experimental, or interventional designs.	Studies lacking clear methodology or results.	Web of Science	Synthesis of findings through narrative or meta-analysis if appropriate.
Studies that assess eosinophil levels through blood tests or other reliable methods.	Studies with insufficient data for analysis.	Cochrane Library	
Studies that measure cognitive impairment using standardized neuropsychological tests or clinical assessments.	Duplicate publications or redundant data.		

## Schizophrenia and Cognitive Impairment

Schizophrenia is a complex and debilitating psychiatric disorder that is often characterized by a range of cognitive impairments. Cognitive impairment in schizophrenia can significantly impact an individual's daily functioning, quality of life, and overall outcomes.<sup>9–11</sup> People with schizophrenia often experience difficulties in working memory, which involves holding and manipulating information for short periods. This can hinder problem-solving and decision-making abilities.<sup>12</sup> Impaired attention and concentration are common, making it challenging for individuals to focus on tasks or filter out irrelevant information. Executive functions, including planning, organization, and decision-making, are often impaired, affecting a person's ability to set and achieve goals. Verbal memory impairments can affect the ability to remember and understand spoken information. Some individuals with schizophrenia may struggle with visual-spatial processing, impacting tasks that require spatial awareness.<sup>13</sup> Cognitive processing speed is often slower in individuals with schizophrenia, affecting the speed at which they can complete tasks and respond to stimuli.<sup>14</sup> Structural and functional brain abnormalities, such as reduced gray matter volume and altered connectivity, are thought to play a role in cognitive impairment. Dysregulation of neurotransmitters, including dopamine and glutamate, may contribute to cognitive deficits in schizophrenia.<sup>15</sup> Immune system dysregulation and neuroinflammation have also been implicated in cognitive impairment in schizophrenia.<sup>16</sup> Genetic predisposition and environmental stressors can further influence cognitive function in schizophrenia.<sup>17</sup> Some antipsychotic medications may have cognitive side effects, although newer medications aim to minimize these effects. Cognitive impairment in schizophrenia can impact various aspects of daily life, including employment, social relationships, and independent living. Individuals with schizophrenia may find it challenging to complete educational or vocational training, hold down a job, manage finances, or engage in social activities.<sup>18</sup> Comprehensive neuropsychological assessments can help identify specific cognitive deficits in individuals with schizophrenia. Cognitive remediation therapies, psychoeducation, and rehabilitation programs are often used to improve cognitive function and functional outcomes. Medications that target the underlying symptoms of schizophrenia can also indirectly benefit cognitive function.<sup>19</sup> Ongoing research aims to better understand the precise neural mechanisms underlying cognitive impairment in schizophrenia and to develop targeted interventions. Cognitive impairment is a significant aspect of schizophrenia that poses challenges for both individuals living with the condition and healthcare professionals. Addressing these cognitive deficits is an important component of comprehensive care and treatment for individuals with schizophrenia.<sup>20</sup>

## The Immunological Basis of Schizophrenia

The immunological basis of schizophrenia is an evolving area of research that suggests a complex interplay between the immune system and the development or exacerbation of schizophrenia.<sup>21</sup> While the exact mechanisms are not fully understood, growing evidence points to immune system dysregulation and inflammation as contributing factors in the pathogenesis of this psychiatric disorder. Studies have shown that individuals with schizophrenia often exhibit higher levels of pro-inflammatory markers, such as cytokines, in their blood and cerebrospinal fluid. These markers are indicative of immune system activation and inflammation.<sup>22,23</sup> Microglia, the resident immune cells in the brain, can become activated in response to infection, stress, or injury. This activation may contribute to neuroinflammation and affect brain function.<sup>24</sup> There is some evidence of autoimmune processes being involved in schizophrenia. Autoantibodies targeting brain proteins have been detected in some individuals with the disorder.<sup>25</sup> Some research has suggested that exposure to infections during prenatal development or childhood may increase the risk of developing schizophrenia later in life. This may be linked to maternal immune responses or the child's immune system.<sup>26</sup> Psychological stress can also lead to immune activation and the release of pro-inflammatory cytokines.<sup>27</sup> Stressful life events have been associated with an increased risk of developing schizophrenia.<sup>28</sup> The blood-brain barrier (BBB) separates the bloodstream from the brain and spinal cord. Disruption of the BBB may allow immune cells and molecules to enter the brain, potentially leading to neuroinflammation.<sup>29</sup> Chronic neuroinflammation may contribute to neurodegeneration and structural brain changes in individuals with schizophrenia.<sup>30</sup> It's important to note that while immune system dysregulation and inflammation are associated with schizophrenia, they are not the sole causative factors. The development of schizophrenia is likely influenced by a combination of genetic, environmental, and immunological

factors.<sup>31</sup> The understanding of the immunological basis of schizophrenia has led to the exploration of potential therapeutic interventions targeting the immune system or inflammation.<sup>32</sup> Some clinical trials are investigating the use of anti-inflammatory drugs as adjunctive treatments for schizophrenia. Research in this area is ongoing, and scientists continue to investigate the precise mechanisms through which the immune system and inflammation may contribute to the development and progression of schizophrenia. It's important to emphasize that while the immunological basis of schizophrenia is a promising avenue for research and potential treatments, it is just one facet of a multifactorial disorder. The exact role of the immune system and how it interacts with other genetic and environmental factors in schizophrenia remain areas of active investigation and debate in the scientific community.

## Eosinophils: Form and Function

Eosinophils are a type of white blood cell, specifically a granulocyte, that plays a crucial role in the immune system. They are characterized by their distinct bi-lobed nucleus and granules within the cytoplasm that stain bright red or orange when exposed to certain dyes, such as eosin, hence the name eosinophils.<sup>33</sup> Eosinophils are particularly effective in combating parasitic infections, such as helminths (worms) and certain protozoa. They release cytotoxic substances, including enzymes and proteins like major basic protein (MBP) and eosinophil peroxidase, which can kill parasites or limit their growth.<sup>34</sup> Eosinophils play a role in allergic reactions and asthma. When an allergic reaction occurs, the immune system releases substances that attract eosinophils to the site of inflammation. These cells then release their granule contents, contributing to tissue damage and inflammation in allergic conditions.<sup>35</sup> Eosinophils also participate in modulating inflammatory responses. They release cytokines, which are signaling molecules that regulate the activity of other immune cells, contributing to the overall immune response. In response to stimuli, eosinophils may release a range of granule proteins, including major basic proteins (MBPs) 1 and 2, eosinophil cationic protein (ECP), eosinophil peroxidase (EPX), eosinophil derived neurotoxin (EDN), cytokines, and cytosolic Charcot-Leyden crystal protein/galectin-10 (CLC/Gal-10) among others.<sup>36</sup> While eosinophils are known for their role in host defense and inflammation, they also have roles in tissue repair and remodeling. They can produce growth factors that aid in tissue regeneration and repair after injury or inflammation. Although eosinophils are essential for the body's defense against certain infections and for managing allergic reactions, abnormal levels of eosinophils can indicate underlying health issues including eosinophilic granulomatosis with polyangiitis (EGPA), eosinophilic esophagitis (EOE), and hypereosinophilic syndrome (HES) Furthermore, eosinophilic dysfunction might be indicative of various conditions, including allergies, parasitic infections, autoimmune diseases, or certain cancers.

## Eosinophils in Schizophrenia and Cognitive Impairment

The involvement of eosinophils in schizophrenia and cognitive impairment is an area of ongoing research, although the specific role of eosinophils in these conditions is not yet fully understood. Schizophrenia is a complex mental disorder characterized by disturbances in thinking, perception, emotions, and behavior. Cognitive impairment often accompanies schizophrenia and can manifest as deficits in memory, attention, and executive function. Eosinophils, being part of the immune system, have garnered attention in this context due to their involvement in inflammatory responses and immune modulation.<sup>37</sup> For example, T cell dysfunction has been reported in schizophrenia<sup>38</sup> and eosinophils have the ability to regulate T cell function with respect to polarization of T cells to either the Th2 or Th1 pathway in that they express both Th1- and Th2-associated cytokines.<sup>37</sup> Elevated levels of certain eosinophil-related cytokines and immune cells have been reported in some studies. These findings suggest a possible association between inflammation and the pathophysiology of schizophrenia due to modulation by eosinophils. Eosinophils might contribute to neuroinflammation, potentially impacting brain function and cognitive processes by influencing integrity of the BBB.

## Emerging Research on Eosinophils in Schizophrenia

Emerging research on eosinophils in schizophrenia is shedding light on the potential role of these white blood cells in the pathogenesis of the disorder. While the field is still evolving, several recent studies and findings have provided new insights into the connection between eosinophils and schizophrenia.<sup>32</sup> Some studies have reported alterations in eosinophil counts in individuals with schizophrenia. While the findings are not consistent across all studies, the variations

suggest the potential involvement of eosinophils in the immune response in schizophrenia.<sup>39,40</sup> Eosinophils are traditionally associated with allergic and inflammatory responses.<sup>41</sup> Emerging research suggests that immune system dysregulation and inflammation are linked to the pathophysiology of schizophrenia. Altered cytokine levels in schizophrenia have been widely reported, and eosinophils may be a source of these cytokines.<sup>42,43</sup> Eosinophils are also implicated in BBB disruption which may permit immune cells, including eosinophils, to enter the brain, leading to neuroinflammation, which is associated with schizophrenia.<sup>44</sup> Research is starting to explore different subtypes of eosinophils, each with distinct functions. These subtypes may have varying roles in the immune response and may be differentially regulated in individuals with schizophrenia. Studies by Cabrera Lopez et al have identified differences in eosinophil surface proteins as either 1) resident eosinophils (Siglec-8<sup>+</sup>CD62L<sup>+</sup>IL-3R<sup>lo</sup>) or 2) inflammatory eosinophils (iEos; Siglec-8<sup>+</sup>CD62L<sup>lo</sup>IL-3R<sup>hi</sup>) via flow cytometry and confocal microscopy.<sup>45</sup> Eosinophils do not work in isolation. They interact with other immune cells, such as microglia and T cells, which are also implicated in the immune response in schizophrenia. Emerging research is beginning to examine these complex interactions. Understanding the role of eosinophils in schizophrenia may have therapeutic implications. Targeting eosinophils or related pathways could potentially lead to novel treatments for the disorder. Emerging research in this area faces several challenges, including the need for larger and more comprehensive studies, as well as the elucidation of the specific mechanisms by which eosinophils contribute to schizophrenia. Future research will likely focus on clarifying these aspects. As the understanding of eosinophils in schizophrenia continues to evolve, it holds the promise of providing new perspectives on the immune system's involvement in the disorder and potential avenues for the development of targeted interventions. Further studies and collaboration between researchers in immunology and psychiatry are essential to fully uncover the role of eosinophils in the complex landscape of schizophrenia.

## Mechanisms and Pathways of Eosinophils in Schizophrenia and Cognitive Impairment

The mechanisms and pathways through which eosinophils may be involved in schizophrenia and cognitive impairment are still the subject of ongoing research.<sup>46</sup> While our understanding is not yet complete, emerging evidence suggests several potential mechanisms and pathways that may link eosinophils to cognitive impairment in individuals with schizophrenia. Eosinophils are known to produce cytokines, such as interleukins (eg, IL-4 and IL-5) and chemokines.<sup>47</sup> These cytokines can modulate the immune response and have the potential to affect neural function. In schizophrenia, an imbalance of cytokines, particularly pro-inflammatory cytokines, has been observed.<sup>48</sup> Eosinophil-derived cytokines may contribute to this imbalance, leading to inflammation in the brain, which is associated with cognitive impairment. Eosinophils are involved in immune responses and can potentially migrate to sites of inflammation, including the brain.<sup>49</sup> The disruption of the BBB, which separates the bloodstream from the brain, can allow immune cells, including eosinophils, to enter the brain. This migration may lead to neuroinflammation, affecting neural pathways and cognitive function.<sup>44</sup> Eosinophils, when activated, release inflammatory molecules, and they may contribute to the overall neuroinflammatory response in individuals with schizophrenia.<sup>50</sup> Chronic neuroinflammation has been associated with structural brain changes and cognitive deficits. Eosinophils can produce neurotransmitters like serotonin. Alterations in serotonin signaling have been implicated in schizophrenia and cognitive dysfunction.<sup>51</sup> Eosinophil-derived neurotransmitters may influence neurotransmitter imbalances in the brain. Eosinophils do not operate in isolation. They interact with other immune cells, such as microglia (the brain's resident immune cells), T cells, and astrocytes. The interplay between eosinophils and other immune cells may contribute to the immune response in the brain, affecting cognitive function. Autoimmune processes may be involved in schizophrenia, and eosinophils could play a role in this context. Autoantibodies targeting brain proteins have been identified in some individuals with schizophrenia.<sup>52</sup> Eosinophils may contribute to these autoimmune responses.

Research into different subtypes of eosinophils may reveal distinct functions. Some subtypes may be more pro-inflammatory, while others may have anti-inflammatory properties. Understanding the balance of eosinophil subtypes and their regulation in the context of schizophrenia and cognitive impairment is an area of interest. Genetic factors, such as genetic predisposition to immune dysregulation, and environmental stressors may interact with eosinophil-related

mechanisms, contributing to cognitive deficits in individuals with schizophrenia.<sup>53,54</sup> Although some reports have not shown differences in blood eosinophil concentrations in patients with schizophrenia, compared with healthy donors, Hallgren et al have reported elevated serum levels of lactoferrin and eosinophil cationic protein in schizophrenic patients<sup>55</sup> and others have reported a significant increase in blood eosinophil levels in patients with schizophrenia. Further, eosinophils were the only blood cells that were significantly reduced in women with schizophrenia compared to men with schizophrenia. Whether or not elevated eosinophils modulate neuro-cognitive function in schizophrenia in a manner similar to other diseases of cognitive dysfunction such as eosinophilia-myalgia syndrome,<sup>56</sup> remains to be determined.

In contrast, in those studies there were no differences in basophils in patients with schizophrenia compared with healthy controls.<sup>38</sup> Interestingly, elevated eosinophils have been associated with improved nerve growth or cognition in other studies. In a murine model of atopic dermatitis, eosinophils dramatically increased branching of sensory neurons isolated from the dorsal root ganglia (DRG) of the experimental mice suggesting a pathophysiological role for eosinophils in cutaneous nerve growth in atopic dermatitis.<sup>57</sup> In addition, although there have been reports of cognitive impairment with verbal learning and memory in over half of patients with severe eosinophilic asthma,<sup>58</sup> there are eosinophilic asthma patients who remain cognitively intact suggesting that there are other factors that likely modulate cognitive function in the presence of eosinophils. Furthermore, elevated eosinophils are well described in the arena of opportunistic and other infections<sup>59</sup> and do not always present with cognitive concerns, suggesting that there are likely multiple factors that need to be engaged to foster cognitive decay in the presence of hyper-eosinophilia. It's important to note that the exact contribution of eosinophils and the mechanisms involved are still being investigated. As research in this area progresses, a more comprehensive understanding of how eosinophils may impact cognitive impairment in schizophrenia will likely emerge. Further studies are needed to elucidate the specific roles and interactions of eosinophils within the complex immune and neural systems in individuals with schizophrenia.

## Therapeutic Implications

The clinical implications and therapeutic potential of eosinophils in schizophrenia are areas of growing interest and research. Investigating the relationship between eosinophils and cognitive impairment in schizophrenia may have therapeutic implications. If eosinophils are found to play a significant role in mediating inflammation and cognitive dysfunction in schizophrenia, targeting eosinophilic inflammation could represent a novel therapeutic approach. This could involve repurposing existing anti-inflammatory drugs or developing new treatments specifically targeting eosinophils or their downstream inflammatory pathways.

While the field is still in its early stages, understanding the role of eosinophils in schizophrenia may have important implications for diagnosis, treatment, and the development of novel therapeutic strategies.<sup>60</sup> Eosinophil levels and activation status may serve as potential biomarkers to distinguish different subtypes of schizophrenia. This could aid in tailoring treatment approaches to individual patients based on their immune profiles.<sup>61</sup> Eosinophil profiles and their interaction with other immune markers could potentially be used to predict disease progression or treatment response in individuals with schizophrenia.<sup>58</sup> Eosinophils might offer insights into early stages of schizophrenia development, allowing for early detection and intervention, which could improve treatment outcomes.<sup>62</sup> Understanding the eosinophilic involvement in schizophrenia may help identify individuals at higher risk of developing comorbidities related to immune dysregulation and inflammation, including autoimmune disorders.

Targeting eosinophils or modulating their activity may offer a novel therapeutic approach for individuals with schizophrenia. Immune-modulating therapies, such as anti-inflammatory medications, may help reduce neuroinflammation and potentially improve cognitive function.<sup>63,64</sup> By considering the eosinophil profile of individuals with schizophrenia, personalized treatment plans can be developed. Some patients may benefit from immune-targeted therapies, while others may require different interventions. Eosinophil-targeted treatments could be used as adjunctive therapies alongside standard antipsychotic medications to address specific aspects of the disorder, such as cognitive impairment and inflammation.<sup>65</sup> Therapies aimed at mitigating eosinophil-related neuroinflammation could have neuroprotective effects, potentially preventing or minimizing structural brain changes associated with schizophrenia. The emerging field of psychoneuroimmunology focuses on understanding the connections between the immune system and mental health.

Incorporating eosinophil-related research into this framework could lead to innovative treatment strategies. Targeted interventions based on eosinophil research could be designed to address cognitive deficits associated with schizophrenia, potentially enhancing cognitive function and quality of life.<sup>66</sup> It's important to emphasize that research into the therapeutic potential of eosinophils in schizophrenia is ongoing, and more studies are needed to validate the efficacy and safety of these approaches. Additionally, personalized treatment plans should take into account each patient's unique immunological profile and needs. As the field continues to evolve, it holds promise for providing new insights and treatment options for individuals with schizophrenia.

## Future Directions of Eosinophils in Schizophrenia

The study of eosinophils in schizophrenia is an evolving field, and future research directions hold the promise of further elucidating the role of eosinophils in the disorder.<sup>67</sup> Research may delve deeper into understanding the various subtypes of eosinophils and their specific functions in the context of schizophrenia. Investigating the roles of distinct eosinophil subpopulations could provide insights into their differential impact on the disorder. Ongoing research may aim to identify eosinophil-related biomarkers that can be used for diagnostic and prognostic purposes in schizophrenia. The discovery of specific eosinophil-related markers may help in patient stratification and personalized treatment approaches. Additionally, elucidating the underlying mechanisms linking eosinophils to cognitive impairment may pave the way for the development of personalized treatment strategies targeting specific immune pathways implicated in schizophrenia.

It is important to caution that it is necessary to consider the influence of other acquired factors such as drugs (ie clozapine) and deleterious habits (ie smoking) as well as innate genetic polymorphisms that may further affect the relationship of eosinophils in schizophrenia. Future studies should investigate the causal relationship between eosinophils and schizophrenia. This may involve longitudinal research to determine whether eosinophil activity precedes the onset of schizophrenia or is a consequence of the disorder. Research can explore the intricate interactions between eosinophils and other immune cells, such as microglia, T cells, and astrocytes. Understanding these interactions and their implications for schizophrenia pathogenesis is critical. Further investigation into the potential autoimmune processes in schizophrenia, including the role of eosinophils in producing autoantibodies against brain proteins, is needed. Studies may focus on the interplay between genetic predisposition and environmental factors in eosinophil-related mechanisms, potentially revealing why some individuals with certain genetic backgrounds are more susceptible to eosinophil-related immune dysregulation in schizophrenia. Future research could explore the precise mechanisms through which eosinophils contribute to neuroinflammation and cognitive impairment in schizophrenia. This may involve both *in vitro* and *in vivo* studies. Clinical trials and experimental therapies that target eosinophil-related pathways could be developed and tested for their efficacy in improving cognitive function and overall outcomes in individuals with schizophrenia. Based on eosinophil-related markers and profiles, researchers may work toward identifying subgroups of individuals with schizophrenia who are more likely to benefit from specific treatment strategies, including immune-modulating therapies. Collaboration between researchers in immunology, psychiatry, neuroscience, and other related fields is essential to gain a comprehensive understanding of the role of eosinophils in schizophrenia. Multidisciplinary approaches can help connect findings from different areas of expertise. As the field of eosinophils in schizophrenia research progresses, it will be important to integrate findings from these future directions into a broader understanding of the disorder. By providing a posit for novel thought in this vexing disease space, additional collaboration, innovative research methods, and a focus on personalized medicine may help uncover new insights and therapeutic strategies for individuals with schizophrenia.

## Clinical and Health Implications

The potential involvement of eosinophils and immune dysregulation in conditions like schizophrenia and cognitive impairment could have significant implications for health policy makers:

## Research Funding Allocation

Encouraging and supporting research initiatives focused on understanding the role of eosinophils and the immune system in schizophrenia and cognitive impairment is crucial. Health policy makers can allocate funding toward studies investigating the mechanisms underlying immune dysregulation in these conditions. This could include supporting interdisciplinary research involving immunologists, neuroscientists, psychiatrists, and other relevant fields.

## Integrated Healthcare Approaches

Policy makers could advocate for integrated healthcare approaches that consider the interaction between the immune system and mental health. This might involve promoting collaboration between mental health professionals and immunologists to develop comprehensive treatment strategies that target both neurological and immune aspects of these disorders.

## Early Detection and Intervention

Supporting initiatives for early detection and intervention of immune-related mechanisms in schizophrenia and cognitive impairment could improve patient outcomes. Policy makers can facilitate the development of screening programs and diagnostic tools that assess immune biomarkers, including eosinophil-related markers, to identify individuals at risk or in the early stages of these conditions.

## Treatment Strategies

Understanding the role of eosinophils and immune pathways may lead to the development of novel treatment strategies. Health policy makers can prioritize the evaluation and potential implementation of therapies targeting immune dysregulation, such as immunomodulatory treatments, alongside traditional approaches for managing schizophrenia and cognitive impairment.

## Education and Awareness

Increasing awareness among healthcare professionals, policymakers, and the general public about the potential link between the immune system and mental health disorders like schizophrenia could lead to improved recognition, diagnosis, and management of these conditions. Policy makers can support educational campaigns to disseminate information about emerging research findings in this area.

## Ethical Considerations and Regulations

Policy makers also play a role in establishing ethical guidelines and regulations for the development and implementation of new treatments targeting immune pathways. This includes ensuring patient safety, informed consent, and ethical considerations surrounding the use of innovative therapies in mental health care.

## Conclusion

The exploration of eosinophils and their potential involvement in cognitive impairment in schizophrenia marks a new and promising perspective in the field of neuropsychiatry. While our understanding is still in its infancy, the emerging research offers a fresh outlook on the complex interplay between the immune system and the cognitive deficits that characterize this enigmatic disorder. Eosinophils, traditionally associated with allergic responses and inflammation, are now being considered as potential contributors to the intricate immune dysregulation observed in individuals with schizophrenia. The mechanisms through which eosinophils may influence cognitive function are multifaceted and interconnected, involving cytokine production, neuroinflammation, blood-brain barrier disruption, and complex interactions with other immune cells.

This new perspective holds potential clinical implications, as it posits towards the putative application for eosinophil profiles to serve as biomarkers, predictive indicators, and tools for personalized treatment in schizophrenia. Furthermore, the therapeutic potential of targeting eosinophil-related pathways offers hope for innovative interventions that may



alleviate cognitive impairment and enhance the quality of life for those affected by the disorder. It is essential to recognize the ongoing nature of this research. While the role of eosinophils in schizophrenia and cognitive impairment has been illuminated, numerous questions remain unanswered. Future investigations will need to delve deeper into the specifics of eosinophil subtypes, the causality and temporality of their involvement, and their interaction with other immune cells. The collaboration between researchers from diverse fields—immunology, psychiatry, neuroscience, and beyond—will be pivotal in advancing our understanding of the role of eosinophils in schizophrenia. The potential for a more nuanced and personalized approach to diagnosis and treatment hinges on the collective efforts of the scientific community.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Kelly S, Jahanshad N, Zalesky A, et al. Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI working group. *Mol Psychiatry*. 2018;23(5):1261–1269. doi:10.1038/mp.2017.170
2. Strik W, Stegmayer K, Walther S, Dierks T. Systems neuroscience of psychosis: mapping schizophrenia symptoms onto brain systems. *Neuropsychobiology*. 2018;75(3):100–116. doi:10.1159/000485221
3. Millan MJ, Agid Y, Brüne M, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov*. 2012;11(2):141–168. doi:10.1038/nrd3628
4. Fett AK, Velthorst E, Reichenberg A, et al. Long-term changes in cognitive functioning in individuals with psychotic disorders: findings from the Suffolk County Mental Health Project. *JAMA psychiatry*. 2020;77(4):387–396. doi:10.1001/jamapsychiatry.2019.3993
5. Lawrence RE, First MB, Lieberman JA. Schizophrenia and other psychoses. In: *Psychiatry*. Wiley Online Library; 2015:791–856.
6. Vidal PM, Pacheco R. The cross-talk between the dopaminergic and the immune system involved in schizophrenia. *Front Pharmacol*. 2020;11:394. doi:10.3389/fphar.2020.00394
7. Delaney S, Hornig M. Environmental exposures and neuropsychiatric disorders: what Role does the Gut–immune–brain axis play? *Curr Environ Health Rep*. 2018;5(1):158–169. doi:10.1007/s40572-018-0186-z
8. Bjelobaba I, Savic D, Lavrnja I. Multiple sclerosis and neuroinflammation: the overview of current and prospective therapies. *Curr Pharm Des*. 2017;23(5):693–730. doi:10.2174/1381612822666161214153108
9. Obeagu EI. Gender-based assessment of tumour necrosis factor–alpha and interleukin–6 of patients with Schizophrenia in Nigeria. *Int J Adv Res Biol Sci*. 2022;9(9):29–35.
10. Obeagu EI, Johnson AD, Arinze-Anyiam OC, Anyiam AF, Ramos GF, Esimai BN. Neutrophils to Lymphocytes Ratio and Some Cytokines in Patients with Schizophrenia in Southeast, Nigeria. *Int J Res Rep Hematol*. 2022;5(2):107–112.
11. Obeagu EI, Esimai BN, Ugwu LN, Ramos GF, Adetoye SD, Edupute EC. Neutrophil to Lymphocyte ratio and some cytokines in patients with schizophrenia after antipsychotic therapy in Southeast, Nigeria. *Asian J Med Princ Clin Prac*. 2022;5(4):47–52.
12. Forbes NF, Carrick LA, McIntosh AM, Lawrie SM. Working memory in schizophrenia: a meta-analysis. *Psychological Medicine*. 2009;39(6):889–905. doi:10.1017/S0033291708004558
13. Scala S, Pousada A, Stone WS, et al. Verbal and visual–spatial memory impairment in youth at familial risk for schizophrenia or affective psychosis: a pilot study. *Schizophr Res*. 2013;144(1–3):122–128. doi:10.1016/j.schres.2012.11.027
14. Kalkstein S, Hurford I, Gur RC. Neurocognition in schizophrenia. In: *Behavioral Neurobiology of Schizophrenia and Its Treatment*. Springer; 2010:373–390.
15. Coyle JT, Basu A, Benneyworth M, Balu D, Konopaske G. Glutamatergic synaptic dysregulation in schizophrenia: therapeutic implications. In: *Novel Antischizophrenia Treatments*. Springer; 2012:267–295.
16. Fourrier C, Singhal G, Baune BT. Neuroinflammation and cognition across psychiatric conditions. *CNS Spectr*. 2019;24(1):4–15. doi:10.1017/S1092852918001499
17. Brown AS. The environment and susceptibility to schizophrenia. *Progr Neurobiol*. 2011;93(1):23–58. doi:10.1016/j.pneurobio.2010.09.003
18. Harvey PD, Strassnig M. Predicting the severity of everyday functional disability in people with schizophrenia: cognitive deficits, functional capacity, symptoms, and health status. *World Psychiatry*. 2012;11(2):73–79. doi:10.1016/j.wpsyc.2012.05.004
19. Reichenberg A. The assessment of neuropsychological functioning in schizophrenia. *Dialogues Clin Neurosci*. 2010;12(3):383–392. doi:10.31887/DCNS.2010.12.3/reichenberg
20. Millier A, Schmidt U, Angermeyer MC, et al. Humanistic burden in schizophrenia: a literature review. *J Psychiatr Res*. 2014;54:85–93. doi:10.1016/j.jpsychires.2014.03.021
21. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *Lancet Psychiatry*. 2015;2(3):258–270. doi:10.1016/S2215-0366(14)00122-9
22. Orlovska-Waast S, Köhler-Forsberg O, Brix SW, et al. Cerebrospinal fluid markers of inflammation and infections in schizophrenia and affective disorders: a systematic review and meta-analysis. *Mol Psychiatry*. 2019;24(6):869–887. doi:10.1038/s41380-018-0220-4
23. Gallego JA, Blanco EA, Husain-Krautter S, et al. Cytokines in cerebrospinal fluid of patients with schizophrenia spectrum disorders: new data and an updated meta-analysis. *Schizophr Res*. 2018;202:64–71. doi:10.1016/j.schres.2018.07.019
24. Woodburn SC, Bollinger JL, Wohleb ES. The semantics of microglia activation: neuroinflammation, homeostasis, and stress. *J Neuroinflammation*. 2021;18(1):1–6. doi:10.1186/s12974-021-02309-6
25. Benros ME, Eaton WW, Mortensen PB. The epidemiologic evidence linking autoimmune diseases and psychosis. *Biol Psychiatry*. 2014;75(4):300–306. doi:10.1016/j.biopsych.2013.09.023

26. Karlsson H, Dalman C. Epidemiological studies of prenatal and childhood infection and schizophrenia. In: *Neuroinflammation and Schizophrenia*. Springer; 2020:35–47.
27. Marsland AL, Walsh C, Lockwood K, John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. *Brain Behav Immun*. 2017;64:208–219. doi:10.1016/j.bbi.2017.01.011
28. Pries LK, van Os J, Ten Have M, et al. Association of recent stressful life events with mental and physical health in the context of genomic and exposomic liability for schizophrenia. *JAMA psychiatry*. 2020;77(12):1296–1304. doi:10.1001/jamapsychiatry.2020.2304
29. Dingezweni S. The blood–brain barrier. *South Afr J Anaesth Analg*. 2020;26(6):S32–34. doi:10.36303/SAJAA.2020.26.6.S3.2533
30. Aricioglu F, Ozkartal CS, Unal G, Dursun S, Cetin M, Müller N. Neuroinflammation in schizophrenia: a critical review and the future. *Klinik Psikofarmakoloji Bülteni-Bull Clin Psychopharmacol*. 2016;26(4):429–437. doi:10.5455/bcp.20161123044657
31. Kinney DK, Hintz K, Shearer EM, et al. A unifying hypothesis of schizophrenia: abnormal immune system development may help explain roles of prenatal hazards, post-pubertal onset, stress, genes, climate, infections, and brain dysfunction. *Med Hypotheses*. 2010;74(3):555–563. doi:10.1016/j.mehy.2009.09.040
32. Prestwood TR, Asgariroozbehani R, Wu S, et al. Roles of inflammation in intrinsic pathophysiology and antipsychotic drug-induced metabolic disturbances of schizophrenia. *Behav Brain Res*. 2021;402:113101. doi:10.1016/j.bbr.2020.113101
33. Ramirez GA, Yacoub MR, Ripa M, et al. Eosinophils from physiology to disease: a comprehensive review. *Biomed Res Int*. 2018;2018:1–28. doi:10.1155/2018/9095275
34. Klion AD, Nutman TB. The role of eosinophils in host defense against helminth parasites. *J Allergy Clin Immunol*. 2004;113(1):30–37. doi:10.1016/j.jaci.2003.10.050
35. McBrien CN, Menzies-Gow A. The biology of eosinophils and their role in asthma. *Front Med*. 2017;4:93. doi:10.3389/fmed.2017.00093
36. Wechsler ME, Munitz A, Ackerman SJ, et al. Eosinophils in health and disease: a state-of-the-art review. *Mayo Clin Proc*. 2021;96(10):2694–2707. PMID: 34538424. doi:10.1016/j.mayocp.2021.04.025
37. Akuthota P, Wang HB, Spencer LA, Weller PF. Immunoregulatory roles of eosinophils: a new look at a familiar cell. *Clin Exp Immunol*. 2008;38(8):1254–1263. doi:10.1111/j.1365-2222.2008.03037.x
38. Ermakov EA, Melamud MM, Buneva VN, Ivanova SA. Immune system abnormalities in schizophrenia: an integrative view and translational perspectives. *Front Psychiatry*. 2022;13:880568. doi:10.3389/fpsy.2022.880568
39. Jackson AJ, Miller BJ. Meta-analysis of total and differential white blood cell counts in schizophrenia. *Acta Psychiatrica Scandinavica*. 2020;142(1):18–26. doi:10.1111/acps.13140
40. Juchnowicz D, Dzikowski M, Rog J, et al. The usefulness of a complete blood count in the prediction of the first episode of schizophrenia diagnosis and its relationship with oxidative stress. *PLoS One*. 2023;18(10):e0292756. doi:10.1371/journal.pone.0292756
41. Possa SS, Leick EA, Prado CM, Martins MA, Tibério IF. Eosinophilic inflammation in allergic asthma. *Front Pharmacol*. 2013;4:46. doi:10.3389/fphar.2013.00046
42. Davoine F, Lacy P. Eosinophil cytokines, chemokines, and growth factors: emerging roles in immunity. *Front Immunol*. 2014;5:570. doi:10.3389/fimmu.2014.00570
43. Dawidowski B, Górmia A, Podwalski P, Lebiecka Z, Misiak B, Samochowiec J. The role of cytokines in the pathogenesis of schizophrenia. *J Clin Med*. 2021;10(17):3849. doi:10.3390/jcm10173849
44. Salimi H, Klein RS. Disruption of the blood-brain barrier during neuroinflammatory and neuroinfectious diseases. In: *Neuroimmune Diseases: From Cells to the Living Brain*. Springer; 2019:195–234.
45. Cabrera López C, Sánchez Santos A, Lemes Castellano A, et al. Eosinophil subtypes in adults with asthma and adults with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2023;208(2):155–162. PMID: 37071848. doi:10.1164/rccm.202301-0149OC
46. Stuart MJ, Baune BT. Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. *Neurosci Biobehav Rev*. 2014;42:93–115. doi:10.1016/j.neubiorev.2014.02.001
47. Lampinen M, Carlson M, Håkansson LD, Venge P. Cytokine-regulated accumulation of eosinophils in inflammatory disease. *Allergy*. 2004;59(8):793–805. doi:10.1111/j.1398-9995.2004.00469.x
48. Shnyder NA, Khasanova AK, Strelnik AI, et al. Cytokine imbalance as a biomarker of treatment-resistant schizophrenia. *Int J Mol Sci*. 2022;23(19):11324. doi:10.3390/ijms231911324
49. Kita H. Eosinophils: multifaceted biological properties and roles in health and disease. *Immunol Rev*. 2011;242(1):161–177. doi:10.1111/j.1600-065X.2011.01026.x
50. Roomruangwong C, Noto C, Kanchanatawan B, et al. The role of aberrations in the immune-inflammatory response system (IRS) and the compensatory immune-regulatory reflex system (CIRS) in different phenotypes of schizophrenia: the IRS-CIRS theory of schizophrenia. *Mol Neurobiol*. 2020;57(2):778–797. doi:10.1007/s12035-019-01737-z
51. Terry AV, Buccafusco JJ, Wilson C. Cognitive dysfunction in neuropsychiatric disorders: selected serotonin receptor subtypes as therapeutic targets. *Behav Brain Res*. 2008;195(1):30–38. doi:10.1016/j.bbr.2007.12.006
52. Just D, Månberg A, Mitsios N, et al. Exploring autoantibody signatures in brain tissue from patients with severe mental illness. *Transl Psychiatry*. 2020;10(1):401. doi:10.1038/s41398-020-01079-8
53. Wang LJ, Li SC, Li SW, et al. Gut microbiota and plasma cytokine levels in patients with attention-deficit/hyperactivity disorder. *Transl Psychiatry*. 2022;12(1):76. doi:10.1038/s41398-022-01844-x
54. Banchereau J, Briere F, Caux C, et al. Immunobiology of dendritic cells. *Annu Rev Immunol*. 2000;18(1):767–811. doi:10.1146/annurev.immunol.18.1.767
55. Hällgren R, Venge P, Wistedt B. Elevated serum levels of lactoferrin and eosinophil cationic protein in schizophrenic patients. *Br J Psychiatry*. 1982;140(1):55–60. PMID: 6120735. doi:10.1192/bjp.140.1.55
56. Armstrong C, Lewis T, D’Esposito M, Freundlich B. Eosinophilia-myalgia syndrome: selective cognitive impairment, longitudinal effects, and neuroimaging findings. *J Neurol Neurosurg Psychiatry*. 1997;63(5):633–641. PMID: 9408106; PMCID: PMC2169832. doi:10.1136/jnnp.63.5.633
57. Foster EL, Simpson EL, Fredrikson LJ, et al. Eosinophils increase neuron branching in human and murine skin and in vitro. *PLoS One*. 2011;6(7):e22029. doi:10.1371/journal.pone.0022029
58. Bernhoff C, Jespersen AE, Dyhre-Petersen N, Klein DK, Miskowiak KW, Porsbjerg CM. Cognitive impairment is common in patients with severe asthma that are commenced on a biological treatment. *Eur Respir J*. 2022;60(suppl 66):4644. doi:10.1183/13993003.congress-2022.4644

59. Chou A, Serpa JA. Eosinophilia in patients infected with human immunodeficiency virus. *Curr HIV/AIDS Rep.* 2015;12(3):313–316. PMID: 26126686; PMCID: PMC4681518. doi:10.1007/s11904-015-0272-x
60. Røge R, Møller BK, Andersen CR, Correll CU, Nielsen J. Immunomodulatory effects of clozapine and their clinical implications: what have we learned so far? *Schizophr Res.* 2012;140(1–3):204–213. doi:10.1016/j.schres.2012.06.020
61. Luo C, Pi X, Hu N, et al. Subtypes of schizophrenia identified by multi-omic measures associated with dysregulated immune function. *Mol Psychiatry.* 2021;26(11):6926–6936. doi:10.1038/s41380-021-01308-6
62. Noto C, Maes M, Ota VK, et al. High predictive value of immune-inflammatory biomarkers for schizophrenia diagnosis and association with treatment resistance. *World J Biol Psychiatry.* 2015;16(6):422–429. doi:10.3109/15622975.2015.1062552
63. Upthegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. *Schizophr Res.* 2014;155(1–3):101–108. doi:10.1016/j.schres.2014.03.005
64. Bencherif M, Lippiello PM, Lucas R, Marrero MB. Alpha7 nicotinic receptors as novel therapeutic targets for inflammation-based diseases. *Cell Mol Life Sci.* 2011;68(6):931–949. doi:10.1007/s00018-010-0525-1
65. Lee LY, Hew GS, Mehta M, et al. Targeting eosinophils in respiratory diseases: biological axis, emerging therapeutics and treatment modalities. *Life Sci.* 2021;267:118973. doi:10.1016/j.lfs.2020.118973
66. Arciniegas DB, Held K, Wagner P. Cognitive impairment following traumatic brain injury. *Curr Treat Options Neurol.* 2002;4(1):43–57. doi:10.1007/s11940-002-0004-6
67. Salarda EM, Zhao NO, Lima CN, Fries GR. Mini-review: the anti-aging effects of lithium in bipolar disorder. *Neurosci Lett.* 2021;759:136051. doi:10.1016/j.neulet.2021.136051

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