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Review

The Immunopathogenesis of Autoimmune Encephalitis-Related Psychosis, A Comprehensive Review of Humoral and Cellular Mechanisms

Le He *, Vasishta Polisetty and Timothy Nguyen

The Francis Crick Institute, London NW1 1AT, UK; vasishta.polisetty@crick.ac.uk (V.P.); timothy.nguyen@crick.ac.uk (T.N.)

* Corresponding author. E-mail: le.he@crick.ac.uk (L.H.)

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ABSTRACT: Autoimmune encephalitis has reshaped the understanding of neuropsychiatric disorders by highlighting the role of autoantibodies in psychosis symptoms, which often mimic primary psychosis conditions. This review synthesizes recent research on autoimmune encephalitis-related psychosis, broadening the focus from humoral immunity to T cell autoimmunity and the communication between the peripheral and central nervous systems. We discuss the identification of neuronal antigen targets, particularly the N-methyl-D-aspartate receptor (NMDAR), and their involvement in disease pathogenesis. Current treatments, such as plasma exchange and intravenous immunoglobulin, primarily target the pathogenicity of autoantibodies. However, emerging evidence suggests a crucial role for T cells, glia cell, and B cell in the immunopathogenesis of autoimmune encephalitis-related psychosis diseases. Autoimmune factors, including T and B cells, can either infiltrate the brain from the periphery or propagate via interacting with other cells, like glia, within the brain itself. This review advocates for a comprehensive approach to studying and treating these conditions, integrating both humoral and cellular mechanisms.

Keywords: Autoimmunity; Encephalitis; Psychiatric; Psychosis; NMDAR



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1. Introduction

Neuroinflammation is characterised by abnormal inflammation or an adaptive immune response against self-antigens in the central nervous system (CNS) that impairs neuronal activity [1–3]. These conditions can manifest with a wide range of neurological and psychosis symptoms, varying greatly in presentation and severity. Among these, the autoimmune encephalitides have emerged as a prime example of how autoantibody-mediated processes are linked to severe psychosis manifestations, often mimicking primary psychotic disorders [1].

The discovery of specific antigenic targets for autoimmune encephalitis has revolutionized the field of clinical neurology. With anti-N-methyl-D-aspartate (NMDA) receptor encephalitis being one of the most well characterized disorders, further research has identified and delineated a range of neuropsychiatric entities like LGI1, CASPR2, GABAR, *etc.* [4–6], and the association between autoantibodies and psychosis symptoms may expand our mechanistic understanding of mental disorders. Current treatment approaches for autoimmune encephalitis center around humoral mechanisms, such as plasma exchange (PLEX) and intravenous immunoglobulin (IVIG), to reduce the antibody titre from circulation. In contrast, other CNS autoimmune diseases and various animal models have shown that T cells, brain resident microglia, and astrocytes play a critical role in disease development.

In this review, we define psychosis symptom related diseases irrespective of neurological or psychosis diagnostic origin in the clinic. By synthesizing research on both humoral and cellular immune mechanisms underlying psychosis symptoms of suspected autoimmune origin, this review aims to contribute to the evolving conceptualization of these disorders. This integrated approach may help bridge the current gap between clinical observations and mechanistic understanding.

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2. Autoimmunity and Psychosis Disorder

Firstly, Autoimmune encephalitis-related psychosis is not yet a formally established diagnostic category in the clinic, in contrast, Autoimmune neuropsychiatric disorders is widely accepted terminology. In this review, we are using the term 'autoimmune encephalitis-related psychosis' to describe conditions where the body's immune system attacks the brain, leading to mental health issues. These psychosis symptoms might show up alongside typical neurological problems, or they might be the only visible sign that something's wrong, but not clear neurological problems. While autoimmune encephalitis with psychosis manifestation represents a clear disease entity, we acknowledge that the concept of autoimmune encephalitis-related psychosis without neurological involvement requires further validation.

Autoimmunity involves the immune system attacking the body's own tissues. The field of autoimmune research began in the 1940s with the discovery of antinuclear antibodies in patients with Systemic Lupus Erythematosus (SLE) [7]. This led to a focus on B cells and autoantibody (autoreactive antibody) detection in clinical studies. In contrast, autoreactive T cell research in the clinic was initially less developed due to technical challenges in studying their antigen specificity. We are going to elaborate on the humoral and cellular autoimmunity in the later paragraphs.

Two major caveats challenge the initial hypothesis that neuronal autoimmunity induces psychosis. First, the CNS, including the brain, was traditionally considered immune-privileged, making it less likely to be targeted by the immune system [8,9]. However, increasing evidence has proven that the brain has its own lymphoid organs, like deep cervical lymph nodes and meninges, and maintains a tight communication with the peripheral immune system. Secondly, psychosis is often classified as a mental health disorder rather than being recognized as a manifestation of physical or neurological conditions [10]. Patients with autoimmune encephalitis frequently present with psychosis, complicating the differentiation from schizophrenia and providing direct evidence linking autoimmunity to psychosis. The discovery of autoimmune encephalitis has significantly contributed to the notion of autoimmune psychosis. Notably, as early as 1938, a case of cerebellar degeneration was reported in a patient with ovarian cancer [11]. Similarly, in 1968, a lung cancer patient exhibited distinct neurological symptoms, such as hallucinations and seizures, without evidence of brain metastases, leading to the identification of "limbic encephalitis" [12]. Therefore, there is a long history in the clinic for autoimmunity and psychosis association.

A major advancement in understanding the antigen specificity in these patients occurred in 2007 with the identification of NMDAR (N-methyl-D-aspartate receptor) as a neuronal antigen associated with psychosis symptoms in ovarian cancer patients [13]. Following this, anti-NMDAR autoreactive B cells and antibodies or oligoclonal bands were confirmed in patients' CSF with autoimmune encephalitis, establishing anti-NMDAR autoimmune encephalitis as a recognized neurological disorder [14,15]. In a 1114 schizophrenia patient cohort study, 3–4% patients also tested positive for serum anti-NMDAR [16]. It has been proposed that anti-NMDAR antibody may cause both encephalitis and psychosis as immunopsychiatric continuum factor [17]. The scope of autoimmunity pathogenicity was later extended to other neuronal surface antigens, including CASPR [18], AMPAR [19], and others. This autoimmune encephalitis typically presents with both neurological and psychosis symptoms. However, there is increasing recognition of a subgroup of patients who test serum or cerebrospinal fluid positive for antibodies against neuronal protein but exhibit minimal or no neurological symptoms. Based on these findings, scientists have proposed the term "autoimmune psychosis" to define patients whose psychosis symptoms may be caused by autoimmunity [1]. This review does not suggest that all primary psychosis disorders share an autoimmune etiology with conditions like NMDAR encephalitis. Rather, we examine how understanding immunopathogenic mechanisms across the spectrum of autoimmune neuropsychiatric conditions may inform our understanding of immune contributions to psychosis symptoms more broadly.

3. The Antineuronal Autoimmunity in Peripheral and Central Nerval System

In contrast to the well-documented presence of immune cells in the central nervous system (CNS) and the efficacy of immunotherapy, the mechanisms underlying the occurrence of autoimmunity in the brain remain intriguing. CNS autoimmunity may originate either peripherally or within the CNS itself. However, it is uncertain whether a distinct boundary exists between these origins.

The association between autoimmune encephalitis and peripheral conditions such as cancer or teratomas suggests that autoimmunity can traverse from the periphery to the CNS [20,21]. Notably, neuronal protein expression within teratoma tissues can induce antineuronal autoimmunity, with autoantibodies or autoreactive immune cells migrating to the CNS and causing damage. This is further supported by clinical observations where the resolution of teratomas correlates with the remission of psychosis symptoms in patients [20], indicating a peripheral origin of autoimmunity that later impacts the CNS. In addition, clinical cases have also shown anti-neuronal antibody, neurofascin 186

antibodies, in the peripheral can be associated with CNS [22], which also supports the immune cells peripheral entry to CNS. Autoreactive cells can infiltrate the CNS via several routes, including the blood-brain barrier, choroid plexus, meninges, or the olfactory pathway [23]. The efficacy of anti-VLA-4 antibody treatment, specifically natalizumab, in multiple sclerosis (MS) highlights the critical role of α4β1 integrin (VLA-4) in the pathogenesis of EAE [24]. Preclinical studies demonstrate that natalizumab significantly reduces disease severity when administered prior to EAE induction, but is less effective post-induction [25]. Clinically, early natalizumab intervention in MS patients leads to better outcomes, lower relapse rates, and rapid symptomatic relief [26,27]. The natalizumab treatment for autoimmune encephalitis in clinical trials also showed preliminary, promising results [28]. These findings underscore the difficulty of treating CNS autoimmunity once autoreactive cells have entered and begun self-perpetuation within the brain parenchyma. Nevertheless, questions remain regarding the specific sites within the brain where autoimmunity is sustained and amplified.

The recent discovery of meningeal lymphatic vessels (MLVs) has significantly advanced our understanding of the brain's immune privilege. MLVs function not only as a drainage system for CNS components but also as an immune cell hub, akin to a lymphoid organ. For instance, B cells can complete their development and maturation cycle within the MLVs [29]. Further research has identified dural-associated lymphoid tissue, particularly in the rostral-rhinal hub region of the meninges, as a key site for B cell maturation [30]. In experimental autoimmune encephalomyelitis (EAE) animal models, meningeal inflammation is evident before the onset of inflammation in the brain parenchyma [31,32]. Post-mortem studies of CNS autoimmune diseases, such as multiple sclerosis (MS) and autoimmune encephalitis, consistently reveal meningeal inflammation [33–35]. Additionally, peripheral antigens can accumulate in the meninges, leading to the activation of immune cells [30]. This not only validates the meninges as a critical site for CNS autoimmune pathogenesis but also suggests that, in addition to the infiltration of peripheral autoreactive immune components into the brain, self-antigens from the periphery may induce autoimmunity within the CNS via the meninges.

Moreover, since the meninges also serve as a drainage pathway for the CNS, the possibility of autoimmunity occurring independently within the CNS itself is plausible. Therefore, the role of the meninges in blurring the distinction between peripheral and CNS origins of autoimmunity highlights the complexity of CNS autoimmune pathogenesis. The mechanisms by which peripheral immune cells or autoantigens enter the meninges and contribute to autoimmunity warrant further investigation.

4. Autoantibody Pathogenicity for Neuropsychiatric Symptoms

Among all self-antigens associated with psychosis, the N-methyl-D-aspartate receptor (NMDAR) has been the focus of extensive research. The NMDAR is a neuron-specific ion channel composed of four subunits: two mandatory Grin1 subunits and two additional subunits selected from six different options. Serum or cerebrospinal fluid Autoantibodies targeting the NMDAR or other neuronal proteins are screened in some clinical settings for autoimmune encephalitis patients, and patients with schizophrenia or first-episode psychosis [1,36]. This practice is strongly supported by the NMDAR hypofunction theory induced by autoantibody binding [Figure 1]. Specifically, the NMDAR antagonist ketamine, when administered at relevant doses, blocks NMDAR ion channel function and induces hallucinations. Similarly, the binding of anti-NMDAR autoantibodies to the receptor leads to its internalization, resulting in hypofunction [14]. This internalization is mediated by the cross-linking of NMDARs by the two Fab arms of intact antibodies, an effect not observed with the isolated Fab fragments [37]. Additionally, *in vitro* studies demonstrate that anti-NMDAR autoantibodies preferentially bind to extrasynaptic NMDARs, thereby reducing receptor density at the synapse [38]. Although NMDAR hypofunction is a primary mechanism of interest, research on other self-antigens halve also heavily emphasized the role of autoantibodies in psychosis symptoms.

In addition to inducing receptor internalization, autoantibodies can interact with other immune cells. For instance, the anti-GluN1 antibody-NMDAR complex can be phagocytosed and removed from neurons by microglia in an *in vitro* co-culture system [39]. This microglial engulfment, triggered by the Fc portion of the anti-NMDAR antibody, involves two distinct pathways. The first pathway relies on direct engagement of the antibody's Fc region with the microglial Fc receptor (CD64), while the second pathway involves the formation of an antibody-complement immune complex that binds to the microglial complement receptor (CD11b). These pathways appear to have compensatory roles in facilitating microglial phagocytosis [39]. Notably, astrocytes and oligodendrocytes also express Fc and complement receptors; however, in vivo evidence for their interaction with antibodies to modulate neuronal activity remains lacking [40,41].

Microglial activation has also been observed in patients with anti-NMDAR encephalitis. Elevated levels of soluble-TREM2, CD44, and MMP9 in patient serum and cerebrospinal fluid (CSF) support this observation [42]. Additionally, a recent study demonstrated microglial activation in the hippocampal region of mice immunized with NMDAR peptides.

In these mice, IgG and NMDAR particles were found colocalized within microglia, further suggesting a role for microglia in the pathological process [43]. Thus, autoantibodies not only induce microglial phagocytosis but also activate microglia, contributing to the establishment of a pro-inflammatory environment. However, the precise neuronal consequences of microglial activation in the CNS and the associated behavioural changes in patients remain unclear [Figure 1].

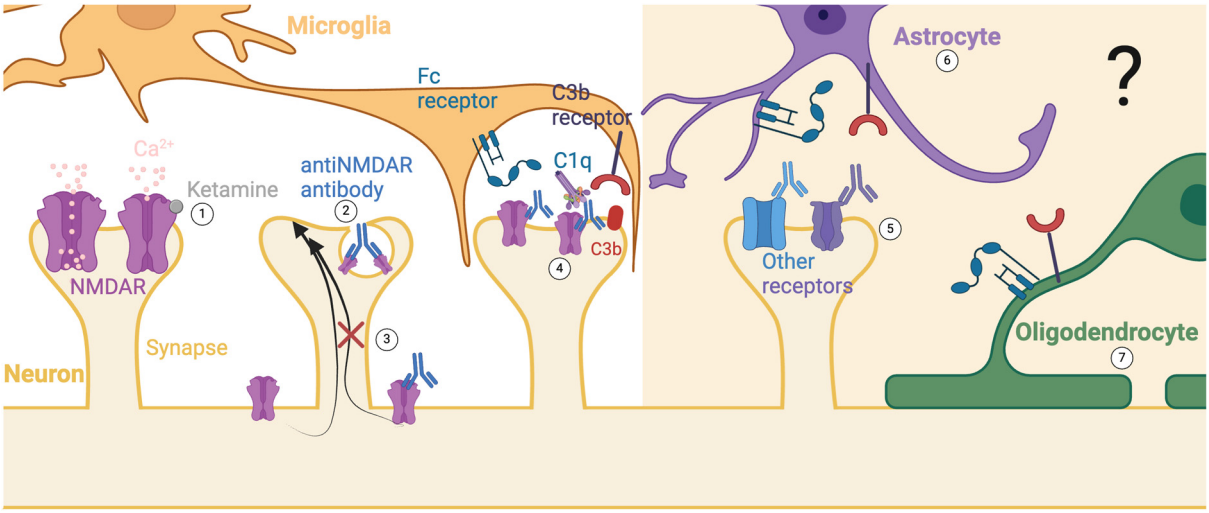


Figure 1. The antibody pathogenicity for autoimmune psychosis: ① The NMDAR antagonist Ketamine induces hypofunction of the NMDAR by blocking Ca^{2+} influx through the receptor into the cell. Anti-NMDAR antibodies bind to the receptor and cause NMDAR hypofunction through two mechanisms: ② cross-linking receptors, leading to their internalization, and ③ binding to extra-synaptic receptors, preventing their migration and contributing to receptor scarcity at the synapse. ④ The antibody-NMDAR complex can be phagocytosed by microglia via the antibody's Fc part, either through Fc receptors or complement receptors. Unknown aspects remain, ⑤ such as whether the same mechanism applies to other receptor and its antibody. Additionally, there is a significant need to understand the roles of ⑥ astrocytes and ⑦ oligodendrocytes in this process.

5. The Hidden Auto-Reactive T Cell

T cells, alongside B cells, constitute the two central pillars of adaptive immunity. Unlike B cells, which bind directly to antigens regardless of their size, T cells recognize segmented antigens presented by major histocompatibility complex (MHC) molecules on antigen-presenting cells (APCs). T cells contribute to autoimmune pathogenesis through two primary mechanisms: the secretion of pro-inflammatory cytokines or the direct killing of antigen-presenting cells [Figure 2]. Under healthy conditions, T cells actively survey the CNS and comprise approximately 80% of immune cells in the cerebrospinal fluid (CSF) that bathes the brain and spinal cord [44]. Thus, it is plausible that T cells might play a part in the development of CNS autoimmune diseases.

The adaptive transfer of antibodies to naïve animals is a well-established method for confirming the causality of autoantibodies. This approach has been extensively utilized in myasthenia gravis research, demonstrating that autoantibodies against the acetylcholine receptor (AChR) are causal for muscle weakness [45,46]. While antibody pathogenicity is a central focus in autoimmune psychosis diseases, the results from passive transfer experiments in these contexts have been less conclusive in establishing antibody causality. For instance, when anti-NMDAR (N-methyl-D-aspartate receptor) antibodies derived from patients are transferred into recipient mice, only mild behavioral changes are observed, both during development and in adulthood [47,48]. These changes are not as severe as the psychosis symptoms seen in patients with autoimmune encephalitis, suggesting that an additional factor, like T cells, could be a critical missing component contributing to the disease pathogenesis. Supporting this, studies have shown that T cells are essential for inducing behavioral phenotypes in mice immunized with the NMDAR holoreceptor [49]. In the clinic, some autoimmune encephalitis patients' CSF samples also shown with oligoclonal bands but without significant pleocytosis or protein, suggesting a potential causal role of cytotoxic T cell [50]. This highlights the potential role of T cells in the development of autoimmune psychosis conditions and suggests that both antibodies and T cells may be required to fully replicate the disease phenotype in animal models.

Among autoimmune diseases, multiple sclerosis (MS) is widely recognized as an autoimmune disorder mediated by T cells that erroneously recognize and attack the body's myelin, the protective sheath surrounding nerve fibers. Post-mortem analysis of brain tissue from MS patients reveals increased T cell infiltration, with a predominance of $CD8^+$ T

cells over $CD4^+$ T cells [51–55]. Intriguingly, there is a strong correlation between MS and Epstein-Barr virus (EBV) infection. In early-stage MS patients, approximately 13% of T cells in the CSF are specific for EBV-infected autologous B cells [56]. Furthermore, in the experimental autoimmune encephalomyelitis (EAE) mouse model for MS, the adoptive transfer of T cells from diseased mice to healthy recipients induces disease, underscoring the pathogenic potential of autoreactive T cells.

While direct evidence of autoreactive T cells interacting with neurons to cause autoimmune psychosis symptoms is lacking, patients experiencing first-episode psychosis often exhibit elevated levels of T cell secreted pro-inflammatory cytokines such as IL-6, IFN-γ, and TNF-α [57]. These cytokines may modulate neuronal function or recruit and activate other immune cells, thereby altering the immune environment in the CNS. There was an increased percentage of monocytes and T cell within the CSF in psychosis patients [58]. This data suggested that the T cell promotes monocyte CNS infiltration via cytokines.

T cells also play a critical role in supporting B cell function, particularly in the process of B cell receptor (BCR) affinity maturation. This collaboration results in the production of high-affinity antibodies that effectively neutralize specific antigens. Through BCR or antibody sequencing, somatic hypermutation—a hallmark of B cell activation—has been observed in CSF derived B cells or plasma cells of autoimmune anti-NMDAR [14] or anti-LGI [59–61] 1 encephalitis patients. These findings highlight the role of T cells in facilitating autoimmune development by aiding B cells.

The potential role of autoreactive T cells in autoimmune psychosis diseases is further suggested by the involvement of intracellular antigens in autoimmune encephalitis. While membrane receptors such as NMDAR, AMPAR, and LGI1 are well-known targets, intracellular antigens such as Hu [62], Ma2 [21,63,64], CRMP5 [65], and Amphiphysin [66] have also been implicated. For instance, Hu is an intracellular RNA-binding protein that cannot be targeted by antibodies alone but becomes accessible to T cells when presented via MHC molecules. Although autoantibodies against these intracellular antigens are commonly detected, identifying autoreactive T cells specific to these antigens remains challenging. This difficulty stems from technical limitations in identifying pathogenic autoantigen epitopes and constructing MHC-antigen complexes to probe T cell specificity. Nevertheless, the presence of intracellular autoantibodies indirectly suggests the involvement of autoreactive T cells, as these autoantibodies often arise in response to intracellular antigens processed and presented to T cells.

In conclusion, the evidence strongly supports the pivotal role of autoreactive T cells in driving autoimmune diseases, including those affecting the CNS. Advancements in technology and methodology will be crucial to unravel the precise mechanisms by which these T cells contribute to disease pathogenesis, particularly in autoimmune psychosis conditions [Figure 2].

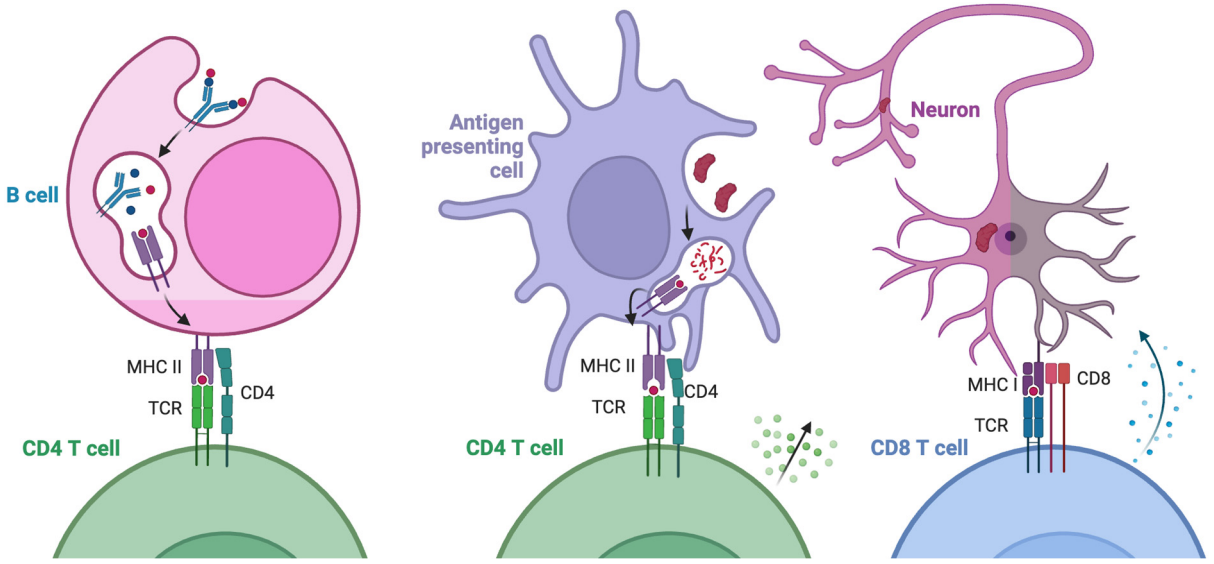


Figure 2. T cells play crucial roles in modulating immune responses. Firstly, $CD4^+$ T follicular helper (Tfh) cells support B cells in undergoing somatic hypermutation of their receptors, leading to the production of high-affinity antibodies against antigens. Secondly, $CD4^+$ T cells are presented with antigen peptides by antigen-presenting cells and secrete cytokines or chemokines, significantly modulating the immune environment. Thirdly, $CD8^+$ T cells can directly interact with neurons via the MHC I-antigen complex and induce neuronal death.

6. The Inflammation and Glia Cells

Brain resident glia cell bridges the autoreactive T or B cells and the neuronal antigen. There is also growing evidence showing that the glia cell can also be activated by autoimmune processes, helping create a self-reinforcing inflammatory environment that alters neuronal activity.

Microglia, the CNS's primary immune cells, rapidly respond to autoantibodies and inflammatory cytokines. In anti-NMDAR encephalitis, microglia phagocytose antibody-receptor complexes via FcγR (CD64) and complement receptors (CD11b), leading to synaptic stripping and NMDAR hypofunction [67,68]. Activated microglia also secrete IL-1β, TNF-α, and CCL2, which amplify neuroinflammation and recruit peripheral immune cells [69,70]. Notably, microglial TREM2 and MMP9 are elevated in patient CSF, correlating with psychosis severity [67]. Preclinical models show that microglial depletion (via PLX5622) reverses inflammation-induced anhedonia and cognitive deficits, underscoring their central role in behavior [71].

Astrocytes transition from homeostatic supporters to inflammatory mediators in autoimmune conditions. Pro-inflammatory A1 astrocytes, induced by microglial TNF-α and IL-1α, release reactive oxygen species and glutamate, exacerbating neuronal damage [69,72]. Conversely, A2 astrocytes promote tissue repair via BDNF and glial scar formation. For inflammation-induced depression-like behavior, astrocytic calcium dysregulation (e.g., Orai1-mediated signaling) disrupts tripartite synapse function, impairing glutamate clearance and amplifying excitotoxicity [73].

Oligodendrocytes extend beyond myelination to actively modulate neuroinflammation. They express TLR3 and MHC-I, enabling direct interactions with autoreactive T cells [74,75]. In multiple sclerosis models, Th17 cells induce oligodendrocyte process retraction via glutamate release and CD29 integrin signaling, impairing remyelination [74]. Oligodendrocyte precursor cells (OPCs) further exacerbate inflammation by secreting CCL2 and CXCL10, which recruit microglia and T cells [76,77]. Myelin breakdown releases DAMPs (e.g., MBP peptides), perpetuating autoimmune responses and disrupting axonal conduction—a potential substrate for psychosis [76,77].

Glia cell also form a network, which in turn regulates each other's and immune cell's activity. Microglia-astrocyte crosstalk amplifies neuroinflammation: microglial IL-1α and TNF-α drive A1 astrocyte polarization, while astrocytic CCL2 enhances microglial motility and phagocytosis [69,72]. This loop sustains cytokine storms that reduce synaptic density in prefrontal and hippocampal regions, regions critical for mood and cognition [70,71]. OPCs modulate microglial activation states via chemokine release (e.g., CXCL1). Depleting OPCs in Parkinson's models increases dopaminergic neuron loss, highlighting their protective role [77]. However, in acute inflammation, OPCs exacerbate macrophage and Th17 infiltration, creating a vicious cycle of demyelination and neurotoxicity [74,76].

7. The Treatment and Mechanism

The autoimmune psychosis disease mechanism strongly focuses on antibody-mediated pathogenicity. Consequently, treatments and clinical trials on autoimmune psychosis disease are primarily focused on dampening antibody-driven autoimmunity. For instance, first-line treatments such as plasma exchange (PLEX) and intravenous immunoglobulins (IVIg) aim to remove pathogenic autoantibodies.

PLEX involves withdrawing blood from one vein, separating the plasma from blood cells via membrane filtration or centrifugation, and reinfusing the blood with a plasma substitute into another vein. This process removes antibodies and other factors, like cytokines, that promote autoimmunity [78]. PLEX was demonstrated to produce positive outcomes in 1976 for treating myasthenia gravis, an autoimmune neurological disorder caused by autoantibodies targeting acetylcholine receptors [79].

IVIg is a treatment that uses pooled immunoglobulin G from thousands of healthy donors to induce anti-inflammatory and immunomodulatory effects. It was first applied to immunedeficient patients to provide temporary passive immunity, and its ability to mitigate autoimmune processes may be through multiple mechanisms [80]. Firstly, it can compete with autoantibodies for binding to antigens and complement system factors. In addition, it accelerates autoantibody catabolism by saturating the neonatal Fc receptor (FcRn), thereby enhancing autoantibody clearance. Efgartigimod, a novel FcRn antagonist, has shown promising results in clinical trials for various autoimmune diseases. A case report has demonstrated its efficiency in eliminating psychosis symptoms of autoimmune encephalitis patients [81]. Therefore, both PLEX and IVIg have the potential to be used to treat autoimmune disease, like autoimmune encephalitis [82–84]. Corticosteroids, another first-line therapy, are potent immunosuppressive agents that reduce inflammation globally.

Antibody depletion is particularly relevant if the antigen is extracellular. Regarding the intracellular antigen, the autoimmunity may be primarily driven by the T cells [85]. In this scenario, the antibody is a by-product of the

autoimmunity, and removing it may not contribute to the autoimmunity attenuation. The T cell depletion therapy is not there yet in the clinic. But we know B cells play an important role in antigen-specific T cell's activation, and there are different treatment choices to remove B cell in the clinic.

Once the first-line therapies fail, second-line treatments such as rituximab are employed. Rituximab, a monoclonal antibody targeting CD20, depletes B cells and is considered a more aggressive intervention. This antibody binds to B cells and induces their apoptosis either directly or by engaging effector cells such as natural killer (NK) cells, macrophages, or other immune cells. This interaction triggers antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC), leading to B cell depletion [86]. It was initially approved by the FDA for treating B-cell non-Hodgkin lymphomas resistant to other chemotherapy regimens. Rituximab effectively depletes B cells with minimal impact on plasma cells, as plasma cells exhibit limited CD20 expression. Since the early 2000s, rituximab has been repurposed for autoimmune diseases, demonstrating efficacy in conditions such as rheumatoid arthritis [87], systemic lupus erythematosus (SLE) [88], and autoimmune encephalitis [89,90]. Inspired by these successes, rituximab and other B-cell depletion strategies are being actively explored for treating psychosis and schizophrenia in clinical trials to treat antineuronal antibody positive patients [91,92].

Chimeric antigen receptor T (CAR-T) cell therapy, which can be employed to eliminate pathogenic B cells, is a rapidly evolving treatment [93]. Unlike B cell-targeting antibodies, CAR-T cells directly deplete B cells without the need for other immune cells, achieving more extensive and profound B cell depletion within the affected tissue. The development of allogeneic CAR-T cells has also paved the way for large-scale industrial manufacturing [94]. Additionally, CAR-T cells may cross the blood-brain barrier more efficiently than antibodies, potentially offering superior B cell depletion for CNS autoimmune diseases [95]. Two case reports have confirmed the safety and efficacy of CAR-T therapy in treating neurological autoimmune diseases [96,97]. Furthermore, nine registered clinical trials are currently investigating its potential for treating CNS autoimmune diseases [93]. Over the coming years, we anticipate gaining a deeper understanding of CAR-T therapy's efficacy in addressing autoimmune psychosis diseases.

8. The B Cells on CNS Autoimmunity

B cells, as a whole, exhibit a dual role in autoimmune disorders, acting as both promoters and suppressors of neuroinflammation [98–100]. While their role as antibody-producing cells after further development is well-established, emerging evidence highlights their capacity to modulate immune responses through antigen presentation and cytokine secretion—functions critical to understanding the variable efficacy of B cell-targeted therapies in autoimmune psychosis [101,102].

B cells process and present antigens via MHC class II with 10,000-fold greater efficiency than nonspecific mechanisms, enabling them to dominate immune responses even against low-abundance neuronal antigens [103]. In the multiple sclerosis (MS) disease animal model, meningeal B cells form ectopic lymphoid structures that present myelin antigens to autoreactive T cells, sustaining neuroinflammation through several mechanisms [98,99]. These B cell-T cell interactions amplify the immune response as B cells sustain T cell reactivation through CD86/CD80 stimulation, produce GM-CSF to recruit pro-inflammatory myeloid cells, and secrete IL-6 to promote Th17 differentiation [98,99]. Clinically, anti-CD20 therapies like rituximab achieve 79–89% relapse-free rates in MS by depleting pathogenic meningeal B cell clusters while sparing regulatory subsets [98,99]. Paradoxically, these therapies leave plasma cells intact, demonstrating that antibody production alone cannot explain B cells' contribution to autoimmunity [100].

Experimental autoimmune encephalomyelitis (EAE) reveals context-dependent B cell functions [98–100]. The pathogenic role partially relies on B cells MHC II dependent antigen presentation function [104]. Depleting these cells during established EAE reduces disease severity [105]. Conversely, CD1dhiCD5+B10 cells (IL10 expressing B cells) demonstrate a protective role by suppressing EAE initiation via IL-10 [106]. Early B cell depletion removes this population, increasing CNS monocyte infiltration [99,107]. Notably, adoptive transfer of B10 cells normalizes EAE in B cell-depleted mice, confirming their regulatory function [106].

In addition to depleting B cell directly via targeting the protein on its cell surface, like CD19, other principles have also been applied for B cell depletion. Like Atacicept, it is a recombinant protein drug that combines with the extracellular part of TACI and Fc part of IgG1. The Atacicept application absorbs B cell survival cytokines: BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand), causing B cell death. However, the phase II trial of Atacicept on Multiple Sclerosis [108]. Despite reducing peripheral B cells and immunoglobulins, atacicept increased annualized relapse rates by 126–158% in MS patients [109]. Mouse study reveals Atacicept depletes IL-10^{+} B10 cells while sparing meningeal pathogenic B cells, disrupting immune homeostasis [99]. This contrasts with SLE, where

BAFF/APRIL inhibition benefits patients by targeting antibody-driven pathology [110]. In EAE, preventive B cell depletion exacerbates disease via B10 cell loss, whereas depletion during established disease suppresses symptoms by removing antigen-presenting B cells [106]. This temporal duality underscores the need for precision timing in B cell-targeted therapies for patients.

The role of B cells in autoimmune psychosis remains relatively elusive due to the lack of robust animal models and clinical evidence. In an anti-NMDAR autoimmune encephalitis model, behavioral abnormalities, including shortened lifespan and hyperactivity following active immunization, were ameliorated in B cell-deficient mouse strains [49]. This finding demonstrates the pathogenic role of B cells, independent of their functions in antigen presentation or antibody production. Recent clinical trials investigating B cell depletion therapies (primarily rituximab) in psychosis-related disorders have shown promising but preliminary results, with variable success rates [36,92,111,112]. These variable outcomes may be explained by the dichotomous functions of B cells in CNS autoimmunity, which underscore the critical need for additional animal models and expanded clinical studies.

9. Conclusions and Future Research

This review traces the history and evolving understanding of autoimmune mechanisms underlying psychosis disorders. Neuroinflammatory conditions, such as autoimmune encephalitis and related autoimmune encephalitis-related psychosis, exemplify the complex interaction between the immune system and the CNS. The identification of specific autoantibodies linked to psychosis symptoms has advanced the concept of autoimmune encephalitis-related psychosis in both basic research and clinical practice. However, the role of autoantibodies in treatment is not definitive, as these antibodies may sometimes be disease-irrelevant. Therefore, despite acknowledging that autoimmunity can cause psychosis disorders, the clinical practice of diagnosing and treating autoimmune-induced psychosis patients remains limited. This knowledge and practice gap is largely due to our insufficient mechanistic understanding of these diseases.

In addition to the established autoantibody causality, this review explores the potential roles of T cells and the origins of autoimmunity—whether peripheral or CNS-based—as alternative perspectives on autoimmune encephalitis-related psychosis. Extended from the T cell, this review also illustrated that the brain resident glia cells play an important role in sensing inflammation and modulating neuronal activity. Based on the current clinical treatment test, the B cell function was also further exploited. It is clear that the need for animal models to understand T cell causality, the role of B cell, and also different glia cells. Though, there are animal models that have demonstrated that anti-NMDAR autoimmunity can cause behavioural symptoms. However, these models have not been consistently replicated across laboratories, potentially due to technical challenges. We believe that a more accessible animal model would greatly facilitate mechanistic research. Furthermore, animal studies provide critical insights into the efficacy and safety of new treatment approaches, accelerating the translation of findings into clinical applications.

A deeper exploration of CNS immunity, especially the role of meningeal functions during disease progression, represents a crucial frontier in this field. The meninges, serving as the interface between the peripheral immune system and the CNS, may hold the key to understanding how autoimmunity transitions from the periphery to the CNS. If autoimmunity requires propagation within the meninges rather than the periphery, targeted treatment at the meningeal level might be more effective than global approaches. Investigating the immunological dynamics within the meninges during autoimmune psychosis diseases promises to reveal how autoimmunity develops and persists in the CNS.

Future research should integrate clinical findings, animal models, and immunological insights to establish a comprehensive framework for understanding autoimmune-mediated psychosis disorders. Leveraging advanced tools like single-cell sequencing, spatial transcriptomics, and high-resolution imaging can uncover the complex mechanisms underlying autoimmune psychosis diseases. This knowledge will enhance our diagnostic and treatment capabilities and pave the way for innovative strategies to prevent the onset and progression of these disorders.

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Informed Consent Statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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