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NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS: INTEGRATING MECHANISMS, DIAGNOSTIC ATTRIBUTION AND MANAGEMENT STRATEGIES

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ABSTRACT

Objective: To synthesize contemporary evidence on the pathogenesis, clinical spectrum, diagnostic challenges and therapeutic approaches in neuropsychiatric systemic lupus erythematosus (NPSLE), with particular emphasis on diffuse cognitive and psychiatric manifestations.
Methods: A narrative review was conducted using PubMed and Scopus to identify peer-reviewed studies published between 2019 and 2025. Mechanistic, clinical, neuroimaging and biomarker-focused research was included, with selective incorporation of earlier foundational work relevant to core pathogenic concepts.
Findings: Current evidence indicates that NPSLE arises from convergent mechanisms involving blood–brain barrier dysfunction, autoantibody-mediated neuronal injury, complement activation and microglial-driven synaptic loss. While focal presentations such as stroke or seizures typically reflect antiphospholipid-mediated vascular pathology, diffuse manifestations - including cognitive dysfunction, mood disorders and acute confusional states - primarily result from neuroinflammatory, excitotoxic and microglial-dependent processes. Despite progress in identifying candidate biomarkers such as anti-NR2, anti-ribosomal-P and CSF neopterin, no validated tool reliably differentiates inflammatory from non-inflammatory neuropsychiatric events. Advances in neuroimaging modalities (DTI, MRS, TSPO-PET) show promise but remain insufficiently standardized for routine clinical use. Acute inflammatory presentations may respond to high-dose glucocorticoids and immunosuppressants, however, chronic cognitive dysfunction remains largely refractory to current therapeutic strategies.
Conclusions: Although significant progress has been made in defining the immunological and neurobiological underpinnings of NPSLE, translation into precise diagnostic tools and durable treatment remains limited. The development of integrated biomarker panels, harmonized neuroimaging protocols and mechanism-based therapeutic strategies is essential to improving attribution accuracy and long-term outcomes in patients with NPSLE.

KEYWORDS

Systemic Lupus Erythematosus (SLE), Neuropsychiatric Lupus (NPSLE), Autoimmunity, Neuroinflammation, Cognitive Dysfunction, Lupus Psychosis

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1. Introduction

1.1 Background and Epidemiology

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by the loss of tolerance to self-antigens, the production of autoantibodies, and immune complex deposition, leading to inflammation and tissue damage in multiple organs (Fanouriakis et al., 2024). Among the diverse clinical manifestations of SLE, involvement of the nervous system - collectively termed Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) - remains one of the most complex and least understood aspects of the disease, associated with significant morbidity and mortality (Sarwar et al., 2021).

The prevalence of NPSLE varies widely in the literature, ranging from 14% to over 80% in prospective cohorts. This discrepancy is largely attributable to the heterogeneity in case definitions and the lack of a standardized "gold standard" for diagnosis (Hanly, 2020). To address this, the American College of Rheumatology (ACR) established a standard nomenclature in 1999, defining 19 neuropsychiatric syndromes categorized into central nervous system (CNS) and peripheral nervous system (PNS) manifestations. While this classification facilitated research, the inclusion of non-specific symptoms such as mild cognitive dysfunction, headache, and mood disorders has complicated the distinction between primary NPSLE (directly attributable to lupus autoimmunity) and secondary causes (Hanly, 2020).

1.2 Genetic Susceptibility and Environmental Triggers

The pathogenesis of NPSLE is underpinned by a complex genetic architecture that likely predisposes the central nervous system to autoimmune attack. Recent genome-wide association studies (GWAS) have identified specific polymorphisms associated with an increased risk of neuropsychiatric involvement, distinct from general SLE susceptibility. For instance, polymorphisms in the *STAT4* gene (signal transducer and activator of transcription 4) have been consistently linked to a higher risk of severe SLE phenotypes, including ischemic stroke and antibody-mediated neuronal damage. Similarly, variants in *TREX1* (three prime repair exonuclease 1) are associated with neurological manifestations, highlighting the critical role of intracellular DNA sensing pathways in driving the aberrant type I interferon production characteristic of SLE.

Epigenetic modifications, particularly DNA hypomethylation in T cells, further contribute to the overexpression of pro-inflammatory genes, lowering the threshold for autoreactivity. These genetic predispositions interact with environmental triggers to breach immune tolerance. Notably, infection with Epstein-Barr Virus (EBV) has been implicated as a potent trigger for lupus autoimmunity. Through mechanisms of molecular mimicry - for example, the EBNA-1 viral antigen cross-reacting with lupus autoantigens like Ro/SSA - EBV may initiate the systemic autoimmune response that eventually targets the blood-brain barrier (BBB), setting the stage for early NPSLE development.

1.3 Socioeconomic Burden and Quality of Life

Beyond the direct clinical symptoms, NPSLE imposes a profound socioeconomic burden that is often underappreciated in clinical assessments. Patients with NPSLE, particularly those suffering from insidious manifestations like cognitive dysfunction or mood disorders, exhibit significantly higher rates of unemployment and work disability compared to SLE patients without neuropsychiatric involvement. A longitudinal study by Hanly et al. (2020) highlighted that cognitive impairment is a stronger independent predictor of poor health-related quality of life (HRQoL) than physical damage accrual or other organ system involvement.

The indirect costs associated with loss of productivity, absenteeism, and early retirement often exceed the direct healthcare costs of managing the disease. Furthermore, the unpredictability of neuropsychiatric flares contributes to high levels of psychological distress and social isolation, creating a vicious cycle where stress exacerbates disease activity. Addressing NPSLE is, therefore, not merely a clinical imperative to prevent organ damage but a societal necessity to preserve the functional autonomy, mental well-being, and economic contribution of young patients afflicted by this chronic condition.

1.4 Research Problem and Rationale

Despite the high burden of disease, the primary challenge in managing NPSLE lies in the difficulty of attribution. Neuropsychiatric symptoms in SLE patients are frequently caused by factors other than the disease itself, including infections, metabolic derangements, adverse effects of medications (e.g., corticosteroid-induced psychosis), or coincidental primary psychiatric disorders (Sarwar et al., 2021). Misattribution is a critical error that can lead to inappropriate therapeutic decisions, such as the unnecessary use of aggressive immunosuppression for non-inflammatory conditions or, conversely, the failure to treat reversible autoimmune brain injury (Hanly, 2020).

Furthermore, the pathogenesis of NPSLE is multifactorial and not fully elucidated. Current evidence suggests two primary pathways: an ischemic/thrombotic mechanism mediated by antiphospholipid antibodies (aPL) and widespread vasculopathy, and an inflammatory/neurotoxic mechanism driven by autoantibodies and cytokines affecting the blood-brain barrier (BBB) and neuronal integrity (Justiz-Vaillant et al., 2024). Despite these insights, specific biomarkers for diagnosis and monitoring remain an unmet need, and therapeutic strategies are often empirical rather than targeted (Kello et al., 2019).

1.5 Objectives

This review aims to synthesize contemporary literature (2019–2025) to provide a comprehensive update on NPSLE. The specific objectives are:

1. To review the key pathogenic mechanisms, with a specific focus on the role of blood-brain barrier disruption, autoantibodies, and neuroinflammation.
2. To describe the clinical spectrum of NPSLE, emphasizing the diagnostic challenges of psychiatric and cognitive manifestations.
3. To discuss current diagnostic challenges and evaluate therapeutic strategies based on the latest EULAR recommendations and emerging research into neuroprotective agents.

2. Methodology

2.1 Study Design and Search Strategy

This review was prepared as a focused narrative synthesis of current knowledge on the pathogenesis, clinical manifestations, diagnostic challenges and therapeutic approaches related to Neuropsychiatric Systemic Lupus Erythematosus (NPSLE). A narrative design was selected because the considerable heterogeneity in definitions, diagnostic criteria and study methodologies across the NPSLE literature limits the applicability and usefulness of formal systematic review frameworks.

Relevant publications were identified through targeted searches of PubMed/MEDLINE and Google Scholar. Search terms included combinations of: “Neuropsychiatric Lupus,” “NPSLE,” “Systemic Lupus Erythematosus,” “autoantibodies,” “cognitive dysfunction,” “lupus psychosis,” “blood–brain barrier,” “neuroinflammation,” “microglial activation,” and “neuroimaging.” The search was iterative, incorporating forward and backward citation tracking from key mechanistic, clinical and guideline papers. Foundational earlier studies were included selectively when necessary to provide mechanistic or historical context.

2.2 Evidence Selection

Evidence was selected based on conceptual relevance to NPSLE rather than through formalized inclusion or exclusion criteria. Publications were considered for inclusion if they contributed meaningfully to understanding immunopathogenic mechanisms, clinical neuropsychiatric presentations, biomarker development, neuroimaging findings or therapeutic strategies. Priority was given to peer-reviewed articles, translational studies, high-quality clinical reviews and internationally recognized guideline documents.

Case reports were considered only when they illustrated mechanistically distinctive or diagnostically informative presentations, such as rare instances of psychosis or catatonia clearly attributable to NPSLE. Non–peer-reviewed materials, anecdotal descriptions and studies with minimal relevance or insufficient methodological clarity were not included.

2.3 Analytical Approach

All included sources were reviewed in full text and synthesized narratively. Findings were organized thematically across domains central to NPSLE: immunopathogenesis (including blood–brain barrier disruption, autoantibody-mediated neuronal injury and neuroinflammation), clinical manifestations, diagnostic approaches and therapeutic considerations. This thematic structure was chosen to integrate mechanistic, clinical and translational insights into a coherent interpretative framework suitable for a narrative review format.

3. Review of Current Evidence

The clinical landscape of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) is notoriously heterogeneous, encompassing a wide array of neurological and psychiatric syndromes. Based on the seminal 1999 ACR case definitions and subsequent updates, these manifestations are broadly categorized into those affecting the central nervous system (CNS) and the peripheral nervous system (PNS). This section provides an in-depth synthesis of current evidence regarding the clinical presentation, the intricate underlying immunopathogenic mechanisms, and the diagnostic utility of emerging biomarkers and neuroimaging techniques, drawing heavily on recent high-impact studies.

3.1 Clinical Spectrum: Psychiatric and Neurological Manifestations

While focal neurological events such as cerebrovascular disease, seizures, and myelitis present with distinct clinical signs often attributable to vascular or thrombotic etiologies, diffuse psychiatric and cognitive syndromes represent a greater diagnostic challenge due to their subtle onset and overlap with non-autoimmune conditions.

Cognitive Dysfunction (CD): The "Lupus Fog" and Beyond

Cognitive Dysfunction (CD) is increasingly recognized as the most prevalent NPSLE manifestation, yet estimates of its prevalence vary wildly - from as low as 3% to as high as 80% across different cohorts (Seet et al., 2021). This discrepancy is largely driven by the lack of standardization in assessment tools; studies relying on patient-reported outcomes tend to report higher rates than those utilizing stringent neuropsychological batteries.

Affected Cognitive Domains: Unlike the amnestic deficits typical of Alzheimer's disease, the cognitive profile in SLE is nuanced and multidimensional. Seet et al. (2021), in a comprehensive review, detailed that the most frequently affected domains are complex attention, executive function, working memory, processing speed, and visuospatial processing. Deficits in executive function are particularly debilitating, manifesting as difficulties in multitasking, planning, and organizing. These impairments can severely compromise vocational performance and social functioning, even in patients who have no overt physical disability and whose disease activity is otherwise quiescent. Kello et al. (2019) emphasize that these deficits often occur independently of general disease activity, suggesting a distinct neuropathological process.

Clinical Course and Prognosis: The trajectory of CD is not uniform. Longitudinal data synthesized by Kello et al. (2019) suggest a variable course: while some patients experience fluctuating deficits that mirror systemic disease flares (suggesting an inflammatory component), others demonstrate a stable or slowly progressive decline indicative of cumulative damage. Importantly, progression to severe dementia is rare; however, mild-to-moderate cognitive impairment remains a significant independent predictor of reduced health-related quality of life (HRQoL) and unemployment. A prospective study cited by Seet et al. (2021) found that cognitive impairment was associated with a higher cumulative glucocorticoid dose, highlighting the potential neurotoxic effects of chronic steroid use.

Assessment Challenges and Screening: The "gold standard" for diagnosis remains the comprehensive ACR neuropsychological battery, but its administration requires approximately one hour and specialized personnel, limiting its utility in routine practice. Consequently, shorter screening tools have been evaluated. Seet et al. (2021) reported that the Montreal Cognitive Assessment (MoCA) has a sensitivity of 83% and specificity of 73% for detecting CD in SLE populations, making it a viable bedside tool. Similarly, the Automated Neuropsychological Assessment Metrics (ANAM), a computerized battery, has shown a sensitivity of 78-80% and specificity of 70% compared to the ACR battery. However, clinicians must interpret these results with caution, as these tools may lack sensitivity for subtle, domain-specific deficits (e.g., isolated executive dysfunction). The Hopkins Verbal Learning Test-Revised (HVLT-R) and Controlled Oral Word Association Test (COWAT) are other valuable tools mentioned for assessing specific domains like verbal learning and fluency.

Depression, Anxiety, and Sleep Disturbances

Mood disorders are highly prevalent in SLE, often exceeding rates observed in other chronic inflammatory diseases like rheumatoid arthritis.

Prevalence and Impact: Systematic reviews indicate that depression and anxiety affect between 17% and 75% of SLE patients (Zhang et al., 2017). These conditions are not merely reactive to the burden of chronic illness but may share common inflammatory pathways with NPSLE mechanisms. Studies have shown that anxiety is more strongly associated with active disease than depression, suggesting different underlying mechanisms.

The Sleep-Mood-Pain Triad: A recent comprehensive meta-analysis by Yin et al. (2022), which included data from 514 patients, elucidated the complex relationship between mood and sleep. The authors found a moderate, statistically significant correlation (pooled r = 0.580; 95% CI 0.473–0.670) between depression scores and poor sleep quality. Specifically, depression was strongly associated with subjective sleep quality (r=0.332), sleep latency (r=0.412), sleep disturbances (r=0.405), and daytime dysfunction (r=0.503). This suggests a bidirectional "vicious cycle" where systemic inflammation (e.g., elevated IL-6) disrupts sleep architecture, which in turn lowers the pain threshold and exacerbates depressive symptoms, further impairing the patient's functional status. Pain amplification, commonly observed in SLE, further reinforces this loop by increasing sleep fragmentation and worsening mood symptoms, thereby sustaining the cycle of neuroinflammation and functional decline. The study emphasizes that improving sleep hygiene could be a crucial non-pharmacological intervention for managing depression in SLE.

Lupus Psychosis and Catatonia

Lupus psychosis is a rare but severe manifestation, occurring in approximately 2–5% of patients (Fidan et al., 2025). It represents a medical emergency requiring rapid differentiation from other causes.

Clinical Presentation: Fidan et al. (2025) described a case series highlighting that lupus psychosis typically manifests as paranoid delusions and auditory or visual hallucinations, often occurring in the setting of clear consciousness (distinguishing it from delirium). It is frequently an early manifestation, occurring within the first years of SLE diagnosis or during severe systemic flares involving other organs (e.g., nephritis). The psychosis can be treatment-resistant to standard antipsychotics, necessitating the addition of immunosuppressive therapy.

Catatonia: An extremely rare but distinct presentation is catatonia, documented by Lucas-Hernández et al. (2025) as an initial manifestation of NPSLE in young patients. Symptoms include immobility, stupor, mutism, posturing, and waxy flexibility. This presentation requires a high index of suspicion, as it can be easily misdiagnosed as a primary psychiatric disorder (e.g., schizophrenia or bipolar disorder). In the reported case, the patient responded dramatically to a combination of benzodiazepines and immunosuppression, underscoring the autoimmune etiology.

Differentiation from Steroid Psychosis: A critical clinical dilemma explored in recent literature is distinguishing primary lupus psychosis from glucocorticoid-induced psychosis. Fidan et al. (2025) emphasize that primary NPSLE psychosis typically presents during active serological disease (e.g., low complement, high anti-dsDNA) and responds to intensified immunosuppression (e.g., cyclophosphamide). In contrast, steroid psychosis is dose-dependent (usually >40mg prednisone daily), occurs shortly after dose escalation, and necessitates tapering of glucocorticoids.

3.2 Pathogenic Mechanisms of CNS Injury

The pathogenesis of diffuse NPSLE is multifactorial, involving a complex interplay between the systemic immune system and the brain's local environment. Current evidence strongly supports a "two-hit" model, where the disruption of the Blood-Brain Barrier (BBB) allows the entry of neurotoxic autoantibodies and inflammatory mediators that normally would be excluded from the CNS.

The "Two-Hit" Hypothesis and Blood-Brain Barrier (BBB) Dysfunction

The integrity of the BBB is paramount in maintaining CNS homeostasis. In NPSLE, the BBB is frequently compromised, constituting the necessary "second hit" for pathology to occur.

Mechanisms of Disruption: Systemic inflammation leads to the activation of brain endothelial cells. Shimizu et al. (2024) provided a detailed molecular account of this process, explaining how pro-inflammatory cytokines (e.g., IL-6, IL-1β) and complement activation products (specifically C5a) can disrupt the tight junctions between endothelial cells. This involves the downregulation or degradation of key structural proteins such as claudin-5 and occludin. Furthermore, Shimizu et al. (2024) highlighted a novel mechanism involving anti-GRP78 autoantibodies (Glucose-Regulated Protein 78). These antibodies bind to GRP78 expressed on the

surface of BBB endothelial cells, activating the NF-κB signaling pathway, which further downregulates tight junction proteins and increases paracellular permeability.

Leukocyte Trafficking: In addition to increased permeability, activated endothelial cells upregulate adhesion molecules such as VCAM-1 and ICAM-1. This facilitates the adhesion and trans-endothelial migration of activated T and B lymphocytes into the brain parenchyma, turning a systemic immune response into local neuroinflammation (Shimizu, 2024). This influx of immune cells perpetuates the inflammatory cycle within the CNS.

Autoantibody-Mediated Neurotoxicity

Once the BBB is breached, specific autoantibodies can enter the brain and exert direct neurotoxic effects. Two antibody specificities have the strongest evidence base for pathogenicity in diffuse NPSLE.

A. Anti-N-methyl-D-aspartate Receptor (Anti-NR2) Antibodies (DNRAb) A subset of anti-dsDNA antibodies cross-reacts with the NR2A and NR2B subunits of the N-methyl-D-aspartate receptor (NMDAR) on neurons.

Mechanism of Injury: As described by Su et al. (2025) and extensively reviewed by Kello et al. (2019), these antibodies (termed DNRAb) bind to NMDARs, which are particularly abundant in the hippocampus. Unlike the antibodies in anti-NMDAR encephalitis (which cause receptor internalization and hypofunction), anti-NR2 antibodies in SLE act as positive allosteric modulators. They prolong the opening time of the receptor ion channel, leading to massive, unregulated calcium influx.

Excitotoxicity and Apoptosis: This calcium overload triggers excitotoxicity, activating apoptotic pathways that lead to the immediate death of post-synaptic neurons (acute phase). This mechanism is thought to underlie acute confusional states and severe cognitive decline.

Synaptic Dysfunction: In surviving neurons, chronic exposure to lower levels of these antibodies leads to a structural remodelling of the neuron. Kello et al. (2019) described how this results in dendritic retraction and a significant loss of spine density. This synaptic loss, rather than frank neuronal death, provides the structural basis for the subtle, chronic cognitive dysfunction and spatial memory deficits observed in murine models and human patients.

B. Anti-Ribosomal P (Anti-P) Antibodies Anti-P antibodies target the P0, P1, and P2 phosphoproteins of the 60S ribosomal subunit.

Clinical Association: Justiz-Vaillant et al. (2024) reaffirmed the high specificity of these antibodies for SLE and their consistent association with lupus psychosis and, to a lesser extent, severe depression. A meta-analysis cited by the authors found a significant odds ratio for the association between anti-P antibodies and psychosis.

Mechanism: The pathogenic mechanism is believed to involve molecular mimicry. It is hypothesized that anti-P antibodies cross-react with a novel Neuronal Surface P Antigen (NSPA) distributed in limbic areas involved in emotion and memory. Binding to NSPA may interfere with glutamatergic transmission and intracellular calcium signaling, leading to neuronal dysfunction and aberrant electrical activity without necessarily causing cell death (Justiz-Vaillant et al., 2024).

C. Other Autoantibodies

Anti-Ganglioside M1: In the pediatric population, Sapountzi et al. (2025) highlighted the high specificity of anti-ganglioside M1 antibodies. Their systematic review noted a remarkable predictive value of 100% for NPSLE when these antibodies were combined with anti-RibP, suggesting they may serve as a potent biomarker for neuronal membrane injury.

Antiphospholipid Antibodies (aPL): While primarily associated with focal thrombotic events (stroke, TIA), Sarwar et al. (2021) noted that aPLs may also exert direct neurotoxic effects by binding to neuronal or glial membranes, potentially contributing to cognitive decline independent of infarction. Direct binding to hippocampal neurons has been shown to alter synaptic transmission in animal models.

Major autoantibodies implicated in NPSLE and their pathogenic mechanisms are summarized in Table 1.

Table 1. Autoantibodies Implicated in NPSLE and Their Mechanisms of CNS Injury

Autoantibody	Target	Mechanism	Associated clinical features
Anti-NR2	NMDA receptor subunit	Calcium influx → excitotoxicity, dendritic loss	Cognitive dysfunction, acute confusional state
Anti-Ribosomal P	Ribosomal P proteins / NSPA	Disrupted limbic signaling	Psychosis, mood disorders
Anti-Ganglioside M1	Neuronal membrane gangliosides	Membrane dysfunction	Pediatric NPSLE
Antiphospholipid antibodies	Phospholipid-binding proteins	Thrombosis + direct neuronal binding	Stroke, cognitive decline

Neuroinflammation: The Role of Microglia and Cytokines

Recent translational research has shifted focus from purely antibody-mediated damage to the role of the innate immune system within the brain.

Microglial Activation: Microglia, the resident macrophages of the CNS, are key effectors of damage. In a groundbreaking study using the NZB/W-F1 murine model, Nikolopoulos et al. (2023) demonstrated that microglia can become activated even in the presence of an intact BBB, likely via soluble factors like Interferon-alpha (IFN-α) crossing from the periphery or produced locally. This challenges the traditional view that BBB disruption is always the primary event.

Synaptic Pruning: Activated microglia shift to a pro-inflammatory phenotype (M1-like) and engage in aberrant synaptic pruning. This process involves the excessive engulfment of healthy synaptic terminals via the complement cascade (specifically the C1q-C3 pathway). Kello et al. (2019) argue that this synaptic loss, rather than frank neuronal death, is the primary driver of cognitive dysfunction in many patients. Importantly, this offers a potential therapeutic target: agents that suppress microglial activation (e.g., ACE inhibitors) could theoretically halt this process.

Cytokine Milieu: The inflammatory milieu in the CNS of NPSLE patients is distinct. Elevated levels of IL-6, IL-1, TNF-α, and IFN-α are frequently found in the cerebrospinal fluid (CSF). Nikolopoulos et al. (2023) specifically linked elevated IL-6 and IL-18 in the hippocampus to direct apoptosis of neural stem cells and defective neurogenesis, providing a novel mechanism for cognitive and mood disturbances in early disease stages. IL-6 specifically has been linked to disruption of hippocampal neurogenesis and BBB integrity.

3.3 Diagnosis, Biomarkers, and Neuroimaging

Diagnosing NPSLE remains a complex process of exclusion ("diagnosis by attribution"). No single test confirms the disease, but a combination of biomarkers and imaging can support the diagnosis.

Fluid Biomarkers (Serum and CSF)

The search for reliable biomarkers has identified several promising candidates, particularly in pediatric cohorts where diagnosis is critical.

CSF Neopterin: Sapountzi et al. (2025) identified CSF neopterin as one of the most robust biomarkers, with a sensitivity of 95% and specificity of 85% for active NPSLE. Neopterin is a byproduct of guanosine triphosphate (GTP) metabolism and serves as a marker of macrophage/microglia activation. Its levels have been shown to decrease following successful treatment, suggesting utility as a marker of treatment response.

Multi-Biomarker Panels: Single markers often lack sufficient power. Brunner et al. (cited in Sapountzi et al., 2025) validated a panel of five serum biomarkers - anti-RibP, anti-NR2, S100A8/9, S100B, and NGAL—which showed a sensitivity of 100% and specificity of 76% for detecting neurocognitive dysfunction. This combinatorial approach represents a significant step forward in diagnostic precision.

Autoantibodies: The presence of anti-RibP is highly specific for psychosis but has low sensitivity. Anti-neuronal antibodies combined with anti-RibP and aPLs significantly increase diagnostic predictive value (Sapountzi et al., 2025).

Key fluid biomarkers relevant for the diagnosis of NPSLE are summarized in Table 2.

Table 2. Biomarkers in NPSLE: Diagnostic Utility and Clinical Significance.

Biomarker	Type	Clinical relevance	Sensitivity/Specificity	Notes
CSF Neopterin	Neuroinflammatory marker	Active NPSLE, microglial activation	95% / 85%	Decreases with treatment
Anti-NR2 antibodies	Autoantibody	Cognitive dysfunction, acute confusional state	Moderate / High	Excitotoxic neuronal injury
Anti-Ribosomal P	Autoantibody	Psychosis, severe depression	High specificity	Low sensitivity
S100B	Neuronal injury	Cognitive impairment	Variable	Included in multimarker panels
S100A8/9	Inflammatory marker	Neuroinflammation	Part of 5-marker panel	Combined predictive value
NGAL	Neuroinflammatory marker	Cognitive dysfunction	Part of 5-marker panel	Best in combination

Neuroimaging Modalities

Neuroimaging is essential to exclude other causes (e.g., infection, malignancy) and to document SLE-related pathology.

Structural MRI: Conventional MRI is the first-line modality. It may reveal focal lesions (infarcts), white matter hyperintensities (WMH), or cerebral atrophy (Fanouriakis et al., 2019). However, up to 40% of NPSLE patients may have a normal MRI, limiting its sensitivity for diffuse syndromes. Atrophy, particularly of the hippocampus and corpus callosum, has been correlated with cognitive impairment in some studies.

Diffusion Tensor Imaging (DTI): Seet et al. (2021) highlight the utility of DTI in assessing white matter microstructural integrity. Reduced fractional anisotropy (FA) values in tracts such as the corpus callosum and internal capsule have been correlated with cognitive deficits, even in patients with normal conventional MRI. This technique detects subtle damage to white matter tracts that is invisible on standard sequences.

Functional MRI (fMRI): fMRI studies have demonstrated altered functional connectivity in the default mode network and executive control networks in SLE patients. These functional changes often correlate with the severity of cognitive impairment and may precede structural damage (Fanouriakis et al., 2019). Abnormal activation patterns during working memory tasks have been observed, suggesting compensatory neural recruitment.

Magnetic Resonance Spectroscopy (MRS): MRS allows for the non-invasive assessment of brain metabolism. Reduced ratios of N-acetylaspartate (NAA) to creatine (a marker of neuronal viability) and elevated **choline** peaks (marker of membrane turnover/inflammation) in normal-appearing white matter are indicative of diffuse neuronal injury and metabolic dysfunction (Fanouriakis et al., 2019; Sapountzi et al., 2025). These metabolic changes can occur in the absence of structural lesions.

Positron Emission Tomography (PET): PET imaging using tracers for the translocator protein (TSPO) can visualize activated microglia in vivo, offering a direct window into neuroinflammation, although its use remains primarily research-based (Fanouriakis et al., 2019). Increased uptake in the hippocampus has been linked to memory deficits.

The main neuroimaging techniques used in NPSLE and their diagnostic contributions are summarized in Table 3.

Table 3. Neuroimaging modalities in NPSLE and their diagnostic contributions.

Modality	What it detects	Strengths	Limitations
MRI	Focal lesions, WMH, atrophy	Widely available	Normal in up to 40% of patients
DTI	White matter microstructural damage	Detects subtle injury	Requires technical expertise
fMRI	Functional connectivity	Early changes before structural damage	Not routine in clinics
MRS	Metabolic abnormalities (NAA↓, choline↑)	Detects diffuse neuronal injury	Limited availability
TSPO-PET	Microglial activation	Direct measure of neuroinflammation	Research use only

4. Discussion

The management of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) remains one of the most enigmatic challenges in modern rheumatology. Despite the elucidation of key pathogenic pathways - specifically the interplay between blood-brain barrier (BBB) dysfunction and autoantibody-mediated neurotoxicity- the translation of these findings into standardized clinical practice has been slow. While international standards like EULAR exist, efforts are also underway to adapt these to national healthcare systems, as evidenced by the recently published protocol for Polish clinical guidelines (Makowska et al., 2025).

This discussion critically evaluates the current diagnostic dilemmas, the limitations of existing therapeutic strategies, and the potential for novel neuroprotective interventions, while also addressing specific challenges in pediatric populations and methodological hurdles in research.

4.1 The Conundrum of Attribution: "Lupus or Not?"

The foremost clinical challenge in NPSLE is not the identification of a neuropsychiatric symptom, but its attribution to SLE. As highlighted by Hanly (2020), approximately 40–50% of neuropsychiatric events in lupus patients are attributable to causes other than the disease itself, such as infections, metabolic abnormalities, or adverse drug reactions. The distinction between "primary" NPSLE (mediated by immune mechanisms) and "secondary" neuropsychiatric events is critical because the therapeutic approaches are diametrically opposed: primary events require immunosuppression, whereas secondary events often require antimicrobial therapy or medication adjustment.

The Steroid Dilemma: A classic example of this diagnostic difficulty is distinguishing lupus psychosis from glucocorticoid-induced psychosis. As noted by Fidan et al. (2025), both conditions can present with similar hallucinations and delusions. However, lupus psychosis typically occurs during periods of high systemic disease activity and responds to increased immunosuppression, while steroid psychosis is dose-dependent (usually >40mg prednisone daily) and necessitates dose reduction. Misdiagnosis in either direction carries the risk of severe morbidity.

Attribution Models: To mitigate subjectivity, several attribution models have been proposed, such as the Italian algorithm, which integrates clinical, serological, and neuroimaging data (Sarwar et al., 2021). While these models provide a structured framework, they often lack sensitivity for diffuse manifestations like cognitive dysfunction (CD) and mood disorders, which do not always correlate with systemic inflammatory markers like anti-dsDNA or complement levels (Fanouriakis et al., 2019). Consequently, physician judgment, supported by a multidisciplinary team including rheumatologists, neurologists, and psychiatrists, remains the gold standard.

4.2 Therapeutic Strategies: Current Standards and Unmet Needs

Current treatment strategies for NPSLE are largely empirical and extrapolated from evidence for other severe lupus manifestations (e.g., nephritis), rather than being derived from randomized controlled trials specific to neuropsychiatric outcomes.

Immunosuppressive Therapy: The EULAR Recommendations

For severe, acute, inflammatory NPSLE manifestations (e.g., aseptic meningitis, myelitis, severe psychosis, acute confusional state), the 2023 EULAR recommendations advocate for aggressive induction therapy (Fanouriakis et al., 2024).

Induction: This typically involves high-dose intravenous glucocorticoids ("pulse" therapy) combined with intravenous cyclophosphamide. This approach targets the rapid suppression of systemic inflammation and the closure of the BBB to prevent further influx of neurotoxic antibodies.

Maintenance and Refractory Disease: For maintenance, or in less life-threatening cases, azathioprine or mycophenolate mofetil are used. Rituximab (anti-CD20 monoclonal antibody) has shown efficacy in refractory cases, particularly those driven by B-cell mediated autoantibody production, although high-quality trial data remains scarce (Fanouriakis et al., 2024).

4.3 The Role of Biologics and Neuroprotective Treatments

Recent years have seen the approval of biological agents for SLE, but their role in NPSLE is still being defined.

Belimumab: Post-hoc analyses of the BLISS trials suggest efficacy in reducing severe flares, but patients with active, severe CNS lupus were generally excluded from these trials. Nevertheless, observational data support its use as a steroid-sparing agent in maintenance therapy (Fanouriakis et al., 2024).

Anifrolumab: The type I interferon receptor antagonist, anifrolumab, showed promise in the TULIP trials. Given the strong implication of the interferon signature in the pathogenesis of diffuse NPSLE (e.g., microglial activation), anifrolumab represents a theoretically attractive option for manifestations driven by neuroinflammation, although dedicated trials for NPSLE are needed (Fanouriakis et al., 2024).

The Treatment Gap: Cognitive Dysfunction and Mood Disorders

In stark contrast to acute focal syndromes, there is no established pharmacological treatment for the most common manifestation of NPSLE: Cognitive Dysfunction.

Inefficacy of Immunosuppression: Conventional immunosuppression has not consistently shown benefit for chronic CD or mood disorders, likely because these symptoms may result from permanent synaptic loss ("pruning") rather than active inflammation (Kello et al., 2019). The "watchful waiting" approach is widely regarded as insufficient given the profound impact of CD on patient quality of life and employment (Seet et al., 2021).

Symptomatic Management: Current management relies on symptomatic relief. This includes the use of antidepressants and anxiolytics for mood disorders, although interactions with lupus medications must be carefully monitored. For CD, cognitive rehabilitation and aerobic exercise have demonstrated modest benefits in improving processing speed and executive function, highlighting the importance of non-pharmacological interventions (Seet et al., 2021).

The Frontier of Neuroprotection

The realization that neuronal damage in NPSLE involves specific molecular mechanisms, such as excitotoxicity and microglial activation, has opened avenues for neuroprotective therapies that go beyond broad immunosuppression. Kello et al. (2019) propose several promising targets based on murine models:

1. ACE Inhibitors: Angiotensin-Converting Enzyme (ACE) inhibitors, capable of crossing the BBB, have been shown to suppress microglial activation and preserve dendritic complexity in lupus-prone mice. This suggests a potential dual benefit of ACE inhibitors in SLE patients: cardiovascular protection and neuroprotection.

2. Memantine: As an NMDAR antagonist used in Alzheimer's disease, memantine theoretically blocks the excitotoxic effects of anti-NR2 antibodies. However, a small clinical trial in SLE failed to show significant cognitive improvement, possibly due to study design limitations, suggesting that patient selection based on biomarker positivity (e.g., anti-NR2 presence) may be necessary for future trials.

3. C5a Receptor Blockade: Targeting the complement cascade to maintain BBB integrity represents another viable strategy to prevent the "second hit" required for antibody entry into the CNS.

Beyond traditional biologics and small molecules, the most radical frontier involves advanced cellular therapies. The pioneering work of Müller et al. (2024) demonstrated the potent efficacy of CD19 CAR T-cell therapy in inducing profound and durable remission in small cohorts of patients with refractory systemic lupus

erythematosus (SLE). This approach, which involves the transient ablation of autoreactive B cells, achieved drug-free remission and a normalization of serological markers, representing a potential paradigm shift for treating severe autoimmune diseases. While these initial studies did not specifically focus on NPSLE, the therapy's ability to "reset" the underlying immune dysregulation and autoantibody production positions it as a highly promising, albeit experimental, strategy for future investigation into severe, refractory neuroinflammatory manifestations. Further translational research, while closely monitoring the safety profile (particularly the risk of ICANS, or Immune Effector Cell-Associated Neurotoxicity Syndrome), is essential to assess the feasibility and efficacy of this modality in severe, refractory NPSLE.

4.4 Impact on Health-Related Quality of Life (HRQoL)

The burden of NPSLE extends far beyond clinical symptoms. Yin et al. (2022) emphasized the bidirectional relationship between sleep disturbances and depression, creating a cycle that severely impacts HRQoL. Poor sleep quality exacerbates fatigue, a hallmark symptom of SLE, which in turn worsens cognitive performance ("brain fog") and mood. Addressing these "soft" endpoints is crucial for holistic patient care. Interventions targeting sleep hygiene and cognitive behavioural therapy for insomnia (CBT-I) should be considered integral parts of the management plan for diffuse NPSLE.

5. Clinical Management Challenges in Special Populations

5.1 Pediatric NPSLE (pNPSLE)

Neuropsychiatric involvement in pediatric-onset SLE (pSLE) presents unique challenges compared to adult-onset disease. As reviewed by Sapountzi et al. (2025), pNPSLE tends to be more severe and occurs earlier in the disease course.

Prevalence and Severity: Approximately 20-45% of children with SLE develop NP manifestations, often within the first year of diagnosis. Severe manifestations like psychosis, chorea, and cerebrovascular accidents are more common in children than in adults.

Diagnostic Biomarkers: Sapountzi et al. (2025) highlighted that biomarkers such as anti-ganglioside M1 and CSF neopterin show high specificity (up to 100% predictive value when combined with anti-RibP) in pediatric cohorts. This suggests that children may have a distinct immunopathogenic profile that could be leveraged for earlier diagnosis.

Impact on Development: The impact of NPSLE on the developing brain is profound. Cognitive dysfunction in children can derail academic progress and social development, necessitating early and aggressive intervention, often involving pediatric neurologists and psychologists (Sapountzi et al., 2025).

5.2 Early vs. Late Onset NPSLE

The timing of NP events provides clues to their etiology.

Early Onset: Inflammatory manifestations (e.g., aseptic meningitis, psychosis, acute confusional state) typically occur early in the disease course, often coinciding with generalized systemic activity (high SLEDAI scores). These events are generally responsive to immunosuppression (Hanly, 2020).

Late Onset: Events occurring late in the disease course are more likely to be thrombotic (e.g., stroke) or degenerative (e.g., cognitive decline due to cumulative damage). These manifestations are less responsive to immunosuppression and require management of vascular risk factors and damage limitation strategies (Sarwar et al., 2021).

6. Methodological Limitations of Current Studies

Research on neuropsychiatric systemic lupus erythematosus (NPSLE) remains constrained by several methodological limitations that hinder the ability to draw definitive mechanistic or clinical conclusions. Despite the adoption of the 1999 ACR nomenclature, substantial heterogeneity persists in how neuropsychiatric syndromes are defined and assessed across studies. This is particularly evident in domains such as cognitive dysfunction and mood disorders, where investigators employ different neuropsychological batteries, attribution models, and disease activity indices. As a result, comparisons between studies are difficult, and the reproducibility of findings is limited.

A fundamental challenge is the absence of a true diagnostic gold standard. Because NPSLE is diagnosed primarily by attribution and exclusion, most biomarker and neuroimaging studies rely on clinician judgment as the reference. This creates circularity in validation efforts, with the risk of overestimating diagnostic performance and complicating attempts to externally validate multimarker approaches. At the same time, many

investigations rely on small, highly selected patient cohorts. The low incidence of individual neuropsychiatric manifestations reduces statistical power, restricts subgroup analyses, and increases the likelihood of both type I and type II errors.

The predominance of cross-sectional study designs further limits the field. Few longitudinal studies are available to assess the temporal dynamics of autoantibodies, cytokines, blood–brain barrier integrity, microglial activation, or structural brain changes. Consequently, causal inferences remain speculative, and the relationship between immunological fluctuations and clinical outcomes is often unclear. Limitations of animal models compound these challenges. Although murine lupus strains offer critical insight into BBB dysfunction, excitotoxic injury, and microglial behaviour, they do not fully replicate the complexity of human cognitive impairment, psychiatric symptoms, or treatment responsiveness, which restricts translational relevance.

Neuroimaging studies face additional methodological barriers. Differences in MRI field strengths, acquisition protocols, post-processing pipelines for diffusion tensor imaging, spectroscopy techniques, and PET tracers impede the development of harmonized, reproducible imaging biomarkers. Moreover, the NPSLE literature remains vulnerable to publication bias, with positive results - particularly those involving novel biomarkers or imaging signatures - more likely to be published than negative or inconclusive findings. Finally, most studies still classify patients by clinical phenotype rather than underlying biological mechanism. Insufficient stratification by endotype blurs distinctions between inflammatory, vascular, and autoantibody-mediated processes, limiting the precision of diagnostic tools and hindering progress toward personalized therapeutic strategies.

7. Future Directions

Future research in NPSLE should prioritize the development of validated, mechanism-based diagnostic tools capable of distinguishing inflammatory, antibody-mediated syndromes from non-inflammatory neuropsychiatric events. A key objective is the creation and external validation of integrated biomarker panels that combine autoantibody profiles, markers of blood–brain barrier integrity, neuroinflammatory mediators and indicators of neuronal injury, thereby reducing attribution bias and supporting individualized clinical decision-making.

Advances in neuroimaging require harmonized acquisition protocols and prospective multicenter validation. Techniques such as diffusion tensor imaging, functional connectivity mapping, quantitative MRI and TSPO-PET hold promise for identifying reproducible signatures of microglial activation, synaptic dysfunction and subclinical white-matter pathology. Establishing their clinical utility will require large, standardized cohorts and longitudinal follow-up.

Therapeutically, future studies must move beyond broad immunosuppression and evaluate neuroprotective strategies targeting the core mechanisms of CNS injury in NPSLE, including complement-mediated endothelial damage, microglial synaptic pruning and antibody-driven excitotoxicity. Clinical trials stratified by biomarker-defined endotypes—rather than broad clinical syndromes—represent a critical path toward identifying patients most likely to respond to emerging targeted interventions. Incorporating longitudinal cognitive testing and patient-reported outcomes will be essential for capturing the true burden of NPSLE and advancing precision-based management.

8. Conclusions

Neuropsychiatric systemic lupus erythematosus remains one of the most complex and clinically consequential manifestations of SLE, arising from a convergence of autoantibody-mediated neuronal injury, chronic neuroinflammation, microglial dysregulation, and blood-brain barrier dysfunction. Although acute inflammatory presentations frequently respond to high-dose corticosteroids and cyclophosphamide, the more prevalent diffuse manifestations -particularly cognitive dysfunction - continue to impose substantial long-term morbidity. Their persistence reflects both diagnostic uncertainty and the absence of interventions capable of modifying the underlying neurobiological processes. Despite substantial mechanistic progress over the past decade, including refined characterizations of cytokine networks, excitotoxicity, complement-mediated synaptic loss, and microglial activation states, translation of these insights into durable therapeutic benefit remains limited.

Taken together, the available evidence delineates several unifying principles that define current understanding and future priorities in NPSLE (Hanly, 2020; Seet et al., 2021; Fanouriakis et al., 2024; Su et al., 2025). Foremost is the recognition that NPSLE reflects the interplay of blood–brain barrier disruption, pathogenic autoantibodies, and sustained microglial activation rather than a single dominant pathway. The central unmet challenge remains the lack of validated, mechanism-specific biomarkers capable of distinguishing inflammatory NPSLE from non-inflammatory neuropsychiatric events, a limitation that continues to constrain diagnostic accuracy and hinder individualized treatment. Emerging multimodal

strategies integrating molecular biomarkers, autoantibody profiling, signatures of neuroinflammation, and standardized advanced neuroimaging offer the most realistic pathway toward precision diagnosis. Future progress will depend on biomarker-guided patient stratification, targeted immunomodulatory and neuroprotective interventions, and harmonized international research frameworks capable of capturing the full clinical and mechanistic heterogeneity of NPSLE.

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