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| ARTICLE REVIEW

Autoantibody-Mediated Synaptopathy: Redefining Neuropsychiatric SLE as a Disorder of Neuroimmune Synapse

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| ABSTRACT

Neuropsychiatric systemic lupus erythematosus (NPSLE) constitutes a severe and often refractory dimension of SLE, manifesting as clinically heterogeneous syndromes—including cognitive impairment, psychosis, and mood disorders—that follow a relapsing–remitting course. Vascular and inflammatory mediator models were developed to explain focal NPSLE and global encephalopathy, respectively. They were never designed to account for the circuit specific, often reversible symptoms of diffuse NPSLE—and they should not be faulted for failing to do so. The fault lies in our continued reliance on them as exclusive frameworks. Converging evidence now positions pathogenic autoantibodies targeting neuronal surface antigens as direct effectors of synaptic dysfunction. This Review synthesizes recent advances to propose a unifying 'synaptopathy' model for diffuse NPSLE pathogenesis. We propose the following four-step pathogenic cascade: (i) autoantibody access to the CNS following blood–brain barrier (BBB) compromise; (ii) acute synaptic dysfunction via receptor binding; (iii) complement-dependent synaptic tagging, amplified by DAMPs such as HMGB1; and (iv) irreversible synaptic loss driven by microglial pruning. These four steps define distinct therapeutic windows: steps (i) and (ii) are potentially fully reversible, step (iii) marks the transition to structural tagging, and step (iv) represents fixed-circuit damage. We aligned these windows with stage-specific biomarker profiles and targeted interventions. We then mapped these cellular events onto specific neural circuit disruptions (hippocampal, prefrontal-limbic, and cortico-thalamo-cortical), directly linking molecular pathology to clinical phenotypes. We operationalize this framework into a precision medicine strategy: three CSF biomarker profiles distinguish reversible synaptic dysfunction from irreversible structural loss, and a stage-matched therapeutic algorithm—B-cell depletion for antibody-driven disease, complement inhibition for synaptic tagging, and neuromodulation for fixed circuit deficits—is aligned with the four-step cascade. This framework reframes diffuse NPSLE as a mechanistically tractable disorder of the neuroimmune synapse—a conceptual advance that opens new avenues for biomarker discovery and targeted intervention.

| KEYWORDS

Systemic Lupus Erythematosus, Neuropsychiatric Lupus, Autoantibodies, NMDA Receptor, Synaptic Pruning, Microglia

| ARTICLE INFORMATION

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1. Introduction

Why do only a subset of SLE patients with circulating anti-NMDAR antibodies develop neuropsychiatric symptoms? Why are those symptoms often reversible, yet current immunosuppression fails to prevent them? This Review argues that the answer lies at the synapse. The American College of Rheumatology defines 19 neuropsychiatric syndromes associated with SLE, broadly categorized into focal (e.g., stroke and seizures) and diffuse (e.g., cognitive dysfunction, acute confusional state, psychosis, and mood disorders) presentations[1]. While focal NPSLE often correlates with vasculopathic or thrombotic events visible on neuroimaging, the pathogenesis of diffuse NPSLE has remained enigmatic, its diagnosis is challenging, and its treatment is frequently empirical and suboptimal.

Historically, two nonexclusive hypotheses have been proposed: the vascular hypothesis, in which antibody-mediated thrombosis, vasculitis, or endothelial dysfunction leads to ischemia[2], and the inflammatory mediator hypothesis, in which circulating cytokines (e.g., type I interferons, IL-6, and TNF-α) breach a compromised blood–brain barrier (BBB) to exert neurotoxic effects[3]. Although these mechanisms are operative, they present a critical paradox: they are systemic processes, yet they produce remarkably specific and often reversible neuropsychiatric syndromes. Furthermore, broad immunosuppressive therapies targeting these pathways show inconsistent efficacy against core diffuse symptoms such as cognitive fog or psychosis [4]. Thus, while vascular and inflammatory mediator hypotheses explain aspects of NPSLE, they fall short of providing a molecular and cellular logic for the circuit specific, often reversible, nature of diffuse symptoms.

This gap necessitates a paradigm that centres on the primary functional unit of neural computation: the synapse. However, until recently, direct evidence for this paradigm in NPSLE remained fragmentary. transformative insight emerged from parallel research into autoimmune encephalitis. The discovery that antibodies against neuronal surface proteins, most famously the N-methyl-D-aspartate receptor (NMDAR), can directly cause severe neuropsychiatric illness prompted a radical re-evaluation of the NPSLE[5]. Could a subset of the diverse autoantibodies characteristic of SLE similarly act as precise molecular weapons against the central nervous system (CNS)?

Here, we argue that a large subset of diffuse NPSLE cases constitute autoantibody-mediated synaptopathy—a mechanistic reclassification with immediate diagnostic and therapeutic implications. We delineate this cascade in four steps: (i) autoantibody access to the CNS; (ii) synaptic binding and acute dysfunction; (iii) complement-dependent synaptic tagging; and (iv) microglial pruning and irreversible loss. We then explore the translational implications of this model for biomarker-driven diagnosis and mechanism-targeted therapy, arguing for a paradigm shift toward precision neuroimmunology in the management of NPSLE.

2. Pathogenic autoantibodies in NPSLE: Targets and mechanisms

The diverse autoantibody repertoire in systemic lupus erythematosus (SLE) includes a select subset with direct neuropathogenic potential, which can be categorized by their primary targets and mechanisms (Table 1). A central category comprises antibodies that directly bind to and disrupt synaptic receptors. Most importantly, antibodies targeting the GluN2 subunit of the N-methyl-D-aspartate receptor (NMDAR) are detected in the cerebrospinal fluid of a significant proportion of patients with active diffuse neuropsychiatric SLE (NPSLE) and are strongly associated with psychosis, severe memory loss, and refractory seizures[6, 7]. These anti-NMDAR antibodies cause rapid receptor internalization and synaptic silencing[8, 9]. Similarly, antibodies against the GABA A receptor, although less common, are linked to severe presentations such as refractory status epilepticus via receptor antagonism and reduced inhibitory transmission [10].

Beyond direct synaptic targeting, another pathogenic mechanism involves molecular mimicry, whereby classic systemic autoantibodies cross-react with neuronal structures. Anti-ribosomal P antibodies, for instance, cross-react with a neuronal surface P-type ATPase, inducing calcium influx and apoptosis, and correlate clinically with depression and psychosis[11, 12]. Similarly, a subset of anti-dsDNA antibodies has been shown to cross-react with the NR2 subunit of NMDAR, and in experimental models, this can lead to excitotoxic receptor overactivation, suggesting a potential contributing mechanism[13].

Finally, for circulating antibodies to access their central nervous system targets, initial compromise of the BBB is often critical. Antibodies such as those targeting the endothelial protein GRP78 promote BBB dysfunction by activating inflammatory pathways in endothelial cells[14]. Furthermore, antiphospholipid antibodies (e.g., anti-β2-glycoprotein I), in addition to their thrombotic role, activate the brain endothelium and astrocytes, creating a proinflammatory state that disrupts barrier integrity and facilitates neuroinvasion[15].

Table 1. Pathogenic Autoantibodies in NPSLE: Targets, Mechanisms, and Evidence Bases

Autoantibody Specificity	Primary Mechanism	Clinical Associations	Evidence Level
NMDAR (GluN2 subunit)	Receptor cross-linking, internalization, synaptic hypofunction	Psychosis, memory deficits, refractory seizures	Human CSF; passive transfer models; in vitro
GABAA receptor	Receptor antagonism, decreased inhibitory transmission	status epilepticus, rapid cognitive decline	Human CSF; in vitro
Ribosomal P protein (neuronal cross-reactive epitope)	Surface binding, calcium influx, apoptosis	Depression, psychosis	Human CSF; in vitro
dsDNA/NR2 cross-reactive epitope	Direct NMDAR agonism (putative), excitotoxicity	diffuse encephalopathy (contributory)	In vitro; animal models
GRP78	Endothelial NF-κB activation, increased BBB permeability	Biomarker of BBB dysfunction	Human serum; in vitro
β2-glycoprotein Ⅰ	Endothelial/astrocyte activation, proinflammatory state	Focal and diffuse NPSLE	Human serum; in vitro

3. The Four-Step Pathogenic Cascade of Synaptic Injury

3.1 Step 1: Autoantibody Access to the CNS

The initial step in the synaptopathy cascade requires circulating autoantibodies to gain access to the CNS. This is contingent upon compromise of the BBB. Evidence indicates that BBB disruption is a common but not universal feature of NPSLE, with factors such as anti-GRP78 antibodies and anti-phospholipid antibodies contributing to endothelial activation and increased permeability[14,15]. Once they are within the CNS parenchyma, autoantibodies encounter their target synaptic antigens.

3.2 Step 2: Acute Synaptic Dysfunction via Receptor Binding

The binding of a pathogenic autoantibody initiates a meticulously orchestrated, multistep attack on the synapse, progressing from acute functional silencing to permanent structural removal. The immediate consequence of this binding is the rapid modulation of synaptic efficacy. Upon engagement, anti-NMDAR antibodies cluster surface receptors and trigger their endocytosis via clathrin-coated pits, leading to a profound and rapid decrease in synaptic NMDAR-mediated currents[16]. This "chemical inactivation" of synapses occurs within hours, providing a plausible mechanism for the acute onset and potential reversibility of symptoms such as psychosis or confusion. Similarly, anti-GABA A receptor antibodies can allosterically inhibit receptor function, tipping the excitatory/inhibitory (E/I) balance toward network hyperexcitability and seizures [10].

3.3 Step 3: Complement-dependent Synaptic Tagging

The resulting antibody–antigen complex is a potent activator of the classical complement pathway, with C1q binding serving as the critical initiating event. Beyond its role in cascade initiation, C1q itself functions as a pattern recognition molecule that directly binds to and opsonizes synapses, particularly during developmental pruning and, maladaptively, in disease [17].

A crucial damage signalling amplifier involved in this process has been identified. Neurons stressed by antibody binding release high-mobility group box 1 (HMGB1), a canonical damage-associated molecular pattern (DAMP). HMGB1 is translocated to synapses and acts as a molecular bridge, with high-affinity binding sites for both synaptic elements and the globular heads of C1q [18]. This HMGB1-C1q tethering creates an exceptionally stable "eat-me" signal on the synapse, dramatically enhancing the efficiency of complement tagging. HMGB1 is a well-established mediator of neuroinflammation and cognitive impairment across multiple neurological disorders, and its antagonism—e.g., via glycyrrhizin or anti-HMGB1 antibodies—confers cognitive protection in preclinical models [19]. In parallel, C1q-dependent synaptic pruning represents a canonical complement-dependent mechanism of synapse loss, initially characterized by developmental refinement and subsequently implicated in neurodegenerative diseases [20]. The convergence of these two independent lines of evidence renders this axis a high-priority target for mechanistic validation in lupus-prone models.

3.4 Step 4: Microglial Pruning and Irreversible Synaptic Loss

The final executioner of this cascade is the resident brain macrophage microglia. Via complement receptor 3 (CR3/CD11b-CD18), microglia recognize and engulf C3b/iC3b-opsonized synaptic structures. In the inflammatory milieu of NPSLE—which is shaped by type I interferons, TNF-α, and other cytokines—microglia adopt a reactive, phagocytically active phenotype. Pioneering

imaging studies in developmental and neurodegenerative contexts have established that microglia actively engulf synapses in a complement-dependent manner, with thin, plastic spines being preferentially eliminated [21]. Crucially, this pruning appears to lose its normal 'activity-dependent' precision in the inflammatory context, leading to indiscriminate removal of synapses regardless of their functional importance.

This process, termed excessive synaptic pruning, represents the conversion of an acute, functional disturbance into a chronic, structural circuit defect. For instance, complement C3 deficiency has been shown to protect against synapse loss and cognitive decline in Alzheimer's disease models [22]. In contrast, sustained microglial depletion in Alzheimer's disease models exacerbates the amyloid plaque load and worsens cognitive deficits, reflecting the essential role of microglia in Aβ clearance and neurotrophic support. This dichotomy—pruning is harmful, but microglia themselves are protective—poses a fundamental challenge for therapeutic microglial modulation in NPSLE. These observations position the microglia–complement axis as a critical effector in complement-dependent neurodegeneration and strongly support the hypothesis that similar mechanisms drive synaptic injury in NPSLE [23].

4. Circuit-Specific Vulnerability and Clinical Phenotypes

These pathogenic antibodies do not cause diffuse, random damage; rather, the resulting synaptic injury converges selectively on neural circuits whose integrity depends on finely tuned excitation/inhibition (E/I) balance and synaptic plasticity. This circuit-specific vulnerability translates into distinct clinical syndromes through several interlinked pathways.

4.1 Hippocampal Circuits: Memory Impairment

With its high density of NMDA receptors (NMDARs) and central role in memory, the hippocampus represents a prime target. Here, anti-NMDAR antibody-mediated internalization directly impaired long-term potentiation (LTP) at critical synapses, such as the Schaffer collateral-CA1 connection, the cellular substrate of learning [24]. Subsequent microglial pruning of these weakened circuits leads to a simplification of dendritic architecture, which is clinically mirrored by deficits in hippocampus-dependent tasks (e.g., verbal recall) and radiologically by progressive hippocampal atrophy, a robust biomarker of chronic cognitive impairment in NPSLE [25].

4.2 Prefrontal-Limbic Circuits: Emotional Dysregulation

Emotional dysregulation arises from the disruption of limbic networks. The ventral prefrontal cortex (vPFC) and anterior cingulate cortex normally exert top-down inhibitory control over the amygdala; synaptic loss in these regions or impaired amygdala inhibition (e.g., via GABA A receptor dysfunction) uncouples this regulatory circuit, leading to unchecked amygdala activity. This neurobiological alteration is strongly correlated with the high prevalence of anxiety, depression, and emotional lability in NPSLE patients, a finding confirmed by functional MRI studies demonstrating altered connectivity within this affective network [26,27].

4.3 Thalamocortical Circuits: Psychosis

Furthermore, the psychotic symptoms shared by NPSLE and anti-NMDAR encephalitis suggest dysfunction in thalamocortical circuits. NMDAR hypofunction on GABAergic interneurons within the thalamus and cortex likely disrupts sensory gating and predictive coding, resulting in a failure to filter irrelevant stimuli and an aberrant assignment of salience to internal representations—the core perceptual disturbances underlying delusions and hallucinations [28]. Given that anti-NMDAR antibodies can induce rapid receptor internalization within hours, the acute onset of psychosis during antibody surges supports this mechanism of rapid synaptic dysregulation.

4.4 Diffuse Network Injury: Brain Fog

In addition to these focal circuitopathies, diffuse injury to widespread networks is common, as evidenced by white matter hyperintensities and microstructural damage on diffusion tensor imaging. This may stem from microvascular ischemia, direct cytokine-mediated toxicity to oligodendrocytes, or Wallerian degeneration secondary to cortical synaptic loss. This extensive network disruption likely underlies the more generalized symptoms of slowed processing speed, attentional deficits, and debilitating "brain fog" reported by patients [29].

5. A Biomarker-Driven Diagnostic Framework

The delineation of these specific synaptic and circuit-based mechanisms provides a compelling rationale for shifting the diagnostic paradigm of NPSLE from reliance on clinical syndromes alone to a biomarker-driven, precise framework. This transition relies on a multimodal toolkit that targets different facets of the disease process.

Direct evidence of autoimmune attack can be obtained through cerebrospinal fluid (CSF) autoantibody profiling, where cell-based assays using live neurons remain the gold standard for detecting pathogenic antibodies such as those targeting the NMDAR. A positive finding, especially when paired with evidence of intrathecal synthesis (indicated by a CSF/serum antibody index >1), is highly specific and has immediate therapeutic implications [30, 31].

To assess the resulting neuronal injury, biomarkers such as neurofilament light chain (NfL), a cytoskeletal protein released from damaged axons, serve as dynamic indicators. Serum NfL levels, which can be measured via ultrasensitive techniques, are correlated with clinical disease activity, MRI lesion load, and cognitive performance and offer a potential tool for monitoring treatment response [32]. Concurrently, the direct loss of synaptic structures may be reflected in the CSF levels of proteins such as neurogranin (postsynaptic) and SNAP-25 (presynaptic), which are emerging as specific markers of synaptic turnover, although their validation in NPSLE is ongoing.

The accompanying neuroinflammatory milieu is captured by glial activation markers, including soluble TREM2 (microglia) and glial fibrillary acidic protein (GFAP, astrocytic), in the CSF. Complementing these fluid biomarkers, advanced neuroimaging provides structural and functional correlations. Quantitative MRI techniques, from automated hippocampal volumetry to diffusion tensor imaging for assessing white matter integrity, deliver objective anatomical measures. Positron emission tomography (PET) adds a molecular dimension: FDG-PET can identify region-specific hypometabolism, whereas tracers for translocator protein (TSPO), such as PK11195, can quantify activated microglia in vivo, offering a direct window into the neuroinflammation that sustains synaptopathy [33].

Collectively, these biomarkers move us from syndromic guesswork to pathogenic phenotyping. To translate this multimodal framework into clinical practice, we propose a stratified diagnostic algorithm for suspected diffuse NPSLE (Table 2).

Table 2. A Stratified Diagnostic Approach to Suspected Diffuse NPSLE

Tier	Assessment	Key Objectives
Clinical & Basic	Detailed neuropsychiatric history, standardized rating scales, routine brain MRI, serum autoantibodies (ANA, anti-dsDNA, etc.)	Exclusion of mimics; initial assessment.
Advanced CSF Analysis	Cell count, protein, IgG index, comprehensive neuronal antibody panel (CBA), NfL, albumin quotient (Qalb)	Identify antibody-mediated etiology; assess BBB integrity and axonal injury.
Advanced Imaging	Volumetric MRI (hippocampus), DTI, FDG-PET/TSPO-PET (if available)	Quantify structural/functional circuit injury and neuroinflammation
Multidisciplinary Synthesis	Integration of all data by rheumatologist, neurologist, and psychiatrist	Final diagnosis, phenotyping, and personalized treatment planning

6. Towards Mechanism-Targeted Therapy

Building on the stratified diagnostic framework, the treatment of neuropsychiatric systemic lupus erythematosus (NPSLE) must evolve from broad empirical immunosuppression to a precise strategy informed by its underlying synaptopathic and neuroinflammatory mechanisms.

For severe, antibody-positive diffuse disease, acute management hinges on rapidly reducing the pathogenic antibody burden. High-dose intravenous corticosteroids provide immediate anti-inflammatory action, while therapeutic plasma exchange or immunoadsorption offers the most direct means of lowering antibody titres, a critical intervention for life-threatening presentations such as status epilepticus or severe psychosis [34]. To achieve sustained remission, long-term immunomodulation is essential. B-cell depletion with rituximab (anti-CD20) is supported by strong observational evidence for preventing antibody rebound in refractory patients, although formal trial data are awaited [35]. For patients with life-threatening or rapidly progressive diffuse NPSLE, aggressive combination immunotherapy—typically high-dose glucocorticoids, cyclophosphamide, and intravenous immunoglobulin—remains the standard of care. Whether biologic agents such as rituximab can match or exceed the efficacy of this regimen is the subject of ongoing investigation.

Looking forward, the therapeutic frontier is being reshaped by agents that target specific nodes within the disease pathway. Complement inhibition represents a prime example: anti-C1q monoclonal antibodies (e.g., ANX005) can prevent initial synaptic tagging, whereas anti-C5 agents (eculizumab and ravulizumab) block the terminal lytic pathway and subsequent

neuroinflammation [36]. Cytokine blockade with agents such as anifrolumab (anti-IFNAR) or sirukumab (anti-IL-6) aims to dampen the inflammatory milieu that potentiates microglial reactivity. Direct microglial modulation remains an active area of investigation, while CSF1R inhibitors (e.g., PLX3397) effectively deplete microglia in models, their long-term CNS safety is a concern. Exploratory strategies involving the use of Safer include the use of TREM2 agonists and cannabidiol (CBD), which may promote a homeostatic microglial phenotype [37, 38].

At the synaptic level, neuroprotective strategies are emerging. The NMDAR modulator memantine, for example, may paradoxically upregulate synaptic receptor trafficking in states of hypofunction and has shown promise in pilot studies for SLE-related cognitive dysfunction [39]. Furthermore, the active promotion of inflammation resolution—via specialized proresolving mediators (SPMs) such as Resolvin D1—or their omega-3 fatty acid precursors—offers a paradigm shift from suppression to active repair [40, 41]. Beyond purely pharmacological approaches, circuit-based neuromodulation, such as repetitive transcranial magnetic stimulation (rTMS) targeting the dorsolateral prefrontal cortex, provides a nonpharmacological, circuit-specific intervention for mood and cognitive symptoms, with a strong evidence base in major depression [42].

In terms of strategies for promoting inflammation resolution, nutritional and metabolic adjuncts offer complementary support. Omega-3 polyunsaturated fatty acids serve as precursors for SPMs, while correcting prevalent vitamin D deficiency may help stabilize the neuroimmune environment via effects on T-cell balance and cytokine production [43, 44].

The future of NPSLE therapy will probably involve mechanism-guided stratification rather than uniform polypharmacy. For instance, patients with high-titre pathogenic antibodies may benefit from B-cell depletion plus complement inhibition, whereas those with predominant microglial activation signatures may be candidates for TREM2 agonists or CSF1R inhibitors—a hypothesis that must be tested in biomarker-stratified trials. Network pharmacology—exemplified by multitarget natural products such as triptolide and ginsenoside compound K—has demonstrated immunomodulatory and neuroprotective effects in preclinical models. However, significant barriers to clinical translation remain, including narrow therapeutic windows and a lack of high-quality randomized trials. Whether these agents offer an advantage over well-tolerated adjuncts is currently unknown [45-51].

7. Conclusions

Despite its integrative strength, the synaptopathy framework remains a working model that requires further empirical validation. Several limitations should be acknowledged. First, direct in vivo evidence linking specific autoantibodies to complement-mediated synaptic pruning in human NPSLE is still limited, and much of the mechanistic inference is derived from autoimmune encephalitis and neurodegenerative models. Whether these processes occur with the same temporal dynamics and regional specificity in patients with lupus remains to be established. Second, not all patients with circulating or even intrathecal neuronal autoantibodies develop neuropsychiatric symptoms, suggesting the presence of additional modifiers, such as genetic susceptibility, BBB resilience, or microglial priming states. Third, the proposed biomarker framework, while mechanistically grounded, lacks large-scale prospective validation, and the thresholds distinguishing reversible synaptic dysfunction from irreversible structural loss remain to be defined. Addressing these gaps is essential for translating this conceptual model into a clinically actionable standard. The synaptopathy model transforms our understanding of diffuse NPSLE—from an enigmatic complication of systemic autoimmunity to a mechanistically definable disorder of the neuroimmune interface. This framework coherently explains long-standing clinical conundrums: the remarkable specificity of neuropsychiatric symptomatology, its frequent temporal dissociation from peripheral disease activity, and the inconsistent efficacy of blanket immunosuppressive regimens. It moves beyond the view of the brain as a passive bystander in systemic autoimmunity, revealing it instead as an active, synaptic-level battlefield where precise immunologic attacks disrupt defined neural circuits. This refined pathophysiological understanding demands a decisive translation into clinical practice. Diagnostic precision must evolve to incorporate CSF analysis for pathogenic neuronal autoantibodies and biomarkers of neuro-axonal injury as standard components of the workup for diffuse NPSLE. Therapeutic strategies require strict stratification, moving from empiric “one-size-fits-all” immunosuppression to mechanism-informed, algorithmic approaches. Clinical trial paradigms need fundamental redesign, adopting pathogenic stratification as a core enrollment criterion. Despite this progress, profound questions remain. What determinants govern CNS tropism? What are the full genetic, epigenetic, and environmental modifications that establish an individual’s synaptic vulnerability? How do we rationally sequence, combine, and personalize the expanding arsenal of immunomodulatory and neuromodulatory therapies? Answering these questions will require deliberate integration of rheumatology, neuroimmunology, and systems neuroscience—a convergence that the synaptopathy framework now makes both necessary and possible. The journey from this theoretical framework to improved patient outcomes is urgent, and its immediate adoption into diagnostic guidelines and clinical trial design is the next critical step. Importantly, by aligning discrete pathogenic stages with defined therapeutic windows, this framework provides not only a conceptual advance but also a clinically actionable roadmap for precision intervention in diffuse NPSLE.

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