

Antibodies in neurological diseases: Established, emerging, explorative

Lucie Y. Li^{1,2}  | Amelya Keles^{1,2}  | Marie A. Homeyer^{1,2}  | Harald Prüss^{1,2} 

¹Department of Neurology and Experimental Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany

²German Center for Neurodegenerative Diseases (DZNE) Berlin, Berlin, Germany

Correspondence

Harald Prüss, Department of Neurology and Experimental Neurology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
Email: harald.pruess@charite.de

Funding information

Helmholtz Association of German Research Centres, Grant/Award Number: HIL-A03 BaoBab; Deutsche Forschungsgemeinschaft, Grant/Award Number: Clinical Research Unit KFO 5023 BECAUSE-Y; project and 504745852; grants FOR3004, PR1274/5-1, and PR1274/9-1; Bundesministerium für Bildung und Forschung, Grant/Award Number: Connect-Generate 01GM1908D

Summary

Within a few years, autoantibodies targeting the nervous system resulted in a novel disease classification. For several of them, which we termed ‘established’, direct pathogenicity has been proven and now guides diagnostic pathways and early immunotherapy. For a rapidly growing number of further anti-neuronal autoantibodies, the role in disease is less clear. Increasing evidence suggests that they could contribute to disease, by playing a modulating role on brain function. We therefore suggest a three-level classification of neurological autoantibodies according to the degree of experimentally proven pathogenicity and strength of clinical association: established, emerging, explorative. This may facilitate focusing on clinical constellations in which autoantibody-mediated mechanisms have not been assumed previously, including autoimmune psychosis and dementia, cognitive impairment in cancer, and neurodegenerative diseases. Based on recent data reviewed here, humoral autoimmunity may represent an additional “super-system” for brain health. The “brain antibody-ome”, that is, the composition of thousands of anti-neuronal autoantibodies, may shape neuronal function not only in disease, but even in healthy aging. Towards this novel concept, extensive research will have to elucidate pathogenicity from the atomic to the clinical level, autoantibody by autoantibody. Such profiling can uncover novel biomarkers, enhance our understanding of underlying mechanisms, and identify selective therapies.

KEYWORDS

autoimmune dementia, autoimmune encephalitis, brain antibody-ome, human monoclonal antibodies, NMDAR, smoldering autoimmunity

1 | INTRODUCTION

Autoantibody-mediated neurological diseases represent a rapidly growing clinical and scientific field. The strong association between certain autoantibodies and distinct clinical phenotypes, underlying tumors or responses to immunotherapy has profoundly changed clinical decision-making. Paradigmatic examples, such as

N-methyl-D-aspartate receptor (NMDAR) encephalitis and further autoimmune encephalitides (AIE), have resulted in re-diagnosis in patients previously assumed to have psychosomatic, viral, idiopathic, or ‘unclear’ disease. For the group of *established* anti-neuronal autoantibodies, it has become clear that they cause disease directly. Here, human clinical phenotypes can be reproduced in animals, for example by use of patient-derived monoclonal autoantibodies (mAbs).

This article is part of a series of reviews covering Effector Functions of Antibodies in Health and Disease appearing in Volume 328 of *Immunological Reviews*.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Author(s). *Immunological Reviews* published by John Wiley & Sons Ltd.

The current focus of the field has been shifting towards the group of *emerging* neurological autoantibodies. In some patients of this group with autoimmune dementia or autoimmune psychosis, autoantibodies were associated with clinical improvement after immunotherapy; however, the detailed mechanisms and underlying antigenic targets await experimental confirmation. Most interestingly, evidence has been emerging that autoantibodies could even play a role in clinical constellations not previously thought to be autoimmune-mediated. Autoantibodies in this third *explorative* group of patients with stroke, neurodegenerative diseases, or cancer-associated cognitive impairment, but also in normal brain aging, may play an important additive, modulating role on brain function.

2 | ESTABLISHED (GROUP I): ANTIBODIES CAUSING THE DISEASE

2.1 | Learnings from antibodies in myasthenia gravis

The presence of autoantibodies in neurological diseases has always been an exciting laboratory finding, but often generates controversy about direct pathogenicity, the usefulness as a diagnostic marker or being a mere immunological bystander. For 'established' autoantibodies (Figure 1), profound evidence has accumulated that they can directly cause the disease and thus serve as the therapeutic target.

Much has been learned from several decades of research in myasthenia gravis (MG), a paradigmatic autoimmune neurological disease. The description of the clinical symptoms as a combination of drooping eyelids and general weakness with fatigue can be traced back to the seventeenth century. The first treatments 200 years later were not disease specific.¹ Antibiotics and mechanical ventilation could decrease the mortality rate in patients with respiratory failure and pneumonia.¹ The first therapeutic breakthrough was the administration of physostigmine by Mary Walker.²

A major discovery was the identification of autoantibodies targeting postsynaptic proteins at the neuromuscular junction, with the acetylcholine receptor (AChR) as the predominant antigen in MG. AChR antibodies disrupt neuromuscular transmission by complement activation,³ antigenic modulation and blockade of

receptor function.^{4,5} Such scientific observations in MG translated into specific treatment options including complement inhibition.^{6–8} Thorough research identified detailed disease mechanisms, including AChR antibody-related blockade preventing the ligand from binding^{9,10} or the combinatory effect of antibodies for receptor cross-linking and internalization,⁵ partially explaining the incomplete correlation between clinical disease and antibody titer.

2.2 | Emergence of disease subgroups defined by specific autoantibodies

2.2.1 | Aquaporin-4 autoantibodies in NMOSD

Long thought to be an optico-spinal disease subgroup of multiple sclerosis, neuromyelitis optica (NMO) became a distinct entity after the discovery of pathogenic IgG autoantibodies against the aquaporin-4 (AQP4) water channel protein on astrocytic endfeet and ependymal surfaces.^{11,12} NMO patients had IgG and IgM deposits along with products of complement activation,¹³ and they improved after plasmapheresis indicating direct autoantibody-mediated effects.¹⁴ Further research confirmed pathogenicity, for example, by intrathecal injection of AQP4 IgG into animals which could recapitulate key disease features with perivascular astrocyte depletion, myelin loss and complement deposition.¹⁵ Interestingly, the discovery of the underlying autoantibody allowed recognition of an extended clinical spectrum and involvement of further brain areas such as the brainstem, resulting in the concept of neuromyelitis optica spectrum disease (NMOSD).¹⁶

In the following years, immunological findings in NMOSD pioneered research in the entire group of well-defined neurological autoantibodies. AQP4 IgG is class-switched and hypermutated,¹⁷ and antibodies reverted to their germline configuration lost detectable binding.¹⁸ Ex vivo stimulated AQP4 IgG-secreting B cells included naive B cells,¹⁹ suggesting impaired early B cell tolerance. Most autoantibodies recognize native conformational epitopes, which are best detected in live cell-based assays (CBA).^{16,20,21} Like MG, experimental evidence guided treatment development and led to the FDA approval of effective drugs such as eculizumab, inebilizumab and satralizumab, which target complement, CD19-positive B cells, and the interleukin (IL)-6 pathway, respectively.^{22,23}

Classification of Antibodies in Neurological Disorders

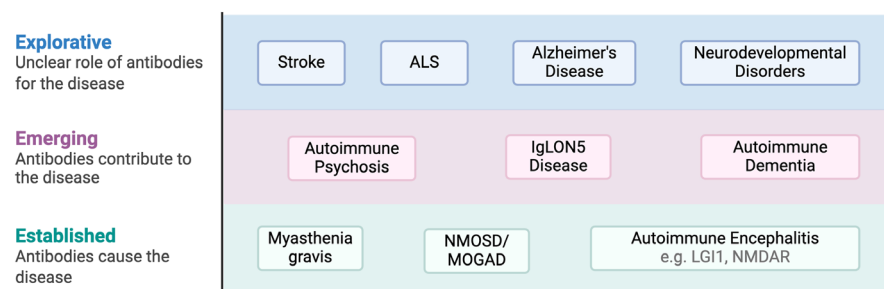


FIGURE 1 Three-level classification of anti-neuronal autoantibodies (*established*, *emerging*, *explorative*) according to the degree of experimentally proven pathogenicity and strength of clinical association. Created with BioRender.com.

2.2.2 | MOG autoantibodies in MOGAD

Roughly 10%–20% of patients with an NMOSD phenotype are seronegative for AQP4 autoantibodies, but instead harbor autoantibodies against myelin oligodendrocyte glycoprotein (MOG).^{24–26} In addition to optic neuritis or transverse myelitis, MOG-associated disease (MOGAD) comprises acute disseminated encephalomyelitis, in particular in children.²⁷ The detection of specific conformation-sensitive autoantibodies paved the way for identifying MOGAD as a separate disorder.^{28–30} MOG IgGs facilitate complement deposition, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis.³¹ B cell-depleting therapies reduce the relapse risk in MOGAD patients.^{32–34} Also, IL-6 inhibition with tocilizumab^{35,36} or satralizumab,³⁷ neonatal Fc receptor (FcRn) inhibition³⁸ or CD19 CAR (chimeric antigen receptor) T cells³⁹ are currently explored in MOGAD cases.

2.3 | Neuronal surface antibodies in autoimmune encephalitis

The discovery of autoantibodies against neuronal surface antigens has significantly advanced the clinical understanding of autoimmune neurological diseases (Figure 2) and now defines the growing group of AIE. Antibodies target ion channels and neuronal surface receptors, such as NMDAR, γ -aminobutyric-acid A-receptor (GABA_AR), or leucine-rich glioma inactivated 1 (LGI1). Patients can have a broad spectrum of neurological symptoms including seizures, altered consciousness, but also cognitive impairment, psychiatric symptoms, and sleep dysfunction.⁴⁰

2.3.1 | NMDAR autoantibodies in NMDAR encephalitis

Anti-NMDAR encephalitis, first described in 2007, is associated with pathogenic autoantibodies targeting the GluN1 subunit of the NMDAR on neuronal surfaces^{41,42} which turned out to be the most

common form of AIE in the Western world. Clinically, it manifests as a complex neuropsychiatric syndrome that typically begins with a flu-like prodromal phase, followed by psychiatric symptoms such as behavioral changes, delusions, or affective disturbances.^{43,44} Cerebrospinal fluid (CSF)-derived autoantibodies strongly bind to brain sections, in particular in the hippocampus (Figure 3). The pathogenic role of these antibodies has been demonstrated in animal studies, where both CSF and recombinant NMDAR mAbs can induce encephalitis symptoms.^{45,46} NMDAR autoantibodies reduce the surface expression of NMDARs by promoting cross-linked receptor internalization, thereby leading to decreased synaptic excitatory neurotransmission.^{47,48} Refined studies using single molecule-based imaging of membrane proteins demonstrated the unexpected finding that extrasynaptic NMDARs are the primary autoantibody target, pointing to the enormous (and largely unexplored) complexity of how autoantibodies can lead to neurological dysfunction.⁴⁹

Given the lack of controlled studies in AIE that directly compare the efficacy of first-line therapies, pragmatic treatment in NMDAR encephalitis builds on findings from retrospective case series,^{42,50,51} meta-analyses⁵² and on lessons learned from MG and NMOSD. One of the most widely accepted therapeutic approaches is the use of plasma exchange or immunoadsorption, which relates to the direct pathogenicity of NMDAR autoantibodies. Generally, immunotherapy must be initiated early, which emphasizes the need for prompt diagnosis and treatment to improve patient prognosis. In the frequent cases of NMDAR encephalitis patients harboring an underlying ovarian teratoma, tumor removal is critical for a good outcome. Second-line therapies include the use of rituximab, and increasingly also other B cell-depleting antibodies, proteasome inhibitors⁵³ or daratumumab.⁵⁴

2.3.2 | LGI1 autoantibodies in LGI1 encephalitis

LGI1 encephalitis occurs in older patients, usually men, and presents with altered consciousness, fever, focal neurological deficits, seizures, cognitive impairment, and confusion. A clinical key

Neuronal Autoantibody Targets

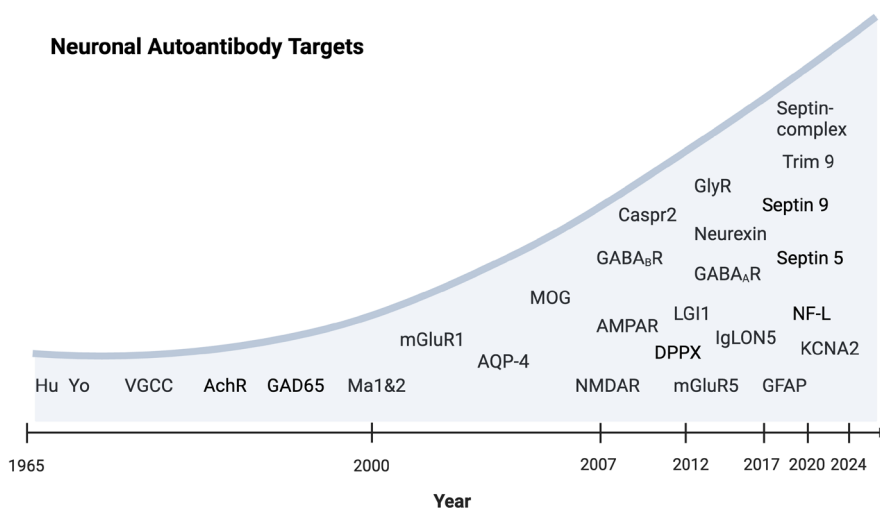


FIGURE 2 The ongoing discovery of neurological autoantibodies suggests an ever-increasing number of associated phenotypes and treatable clinical constellations. Created with BioRender.com.

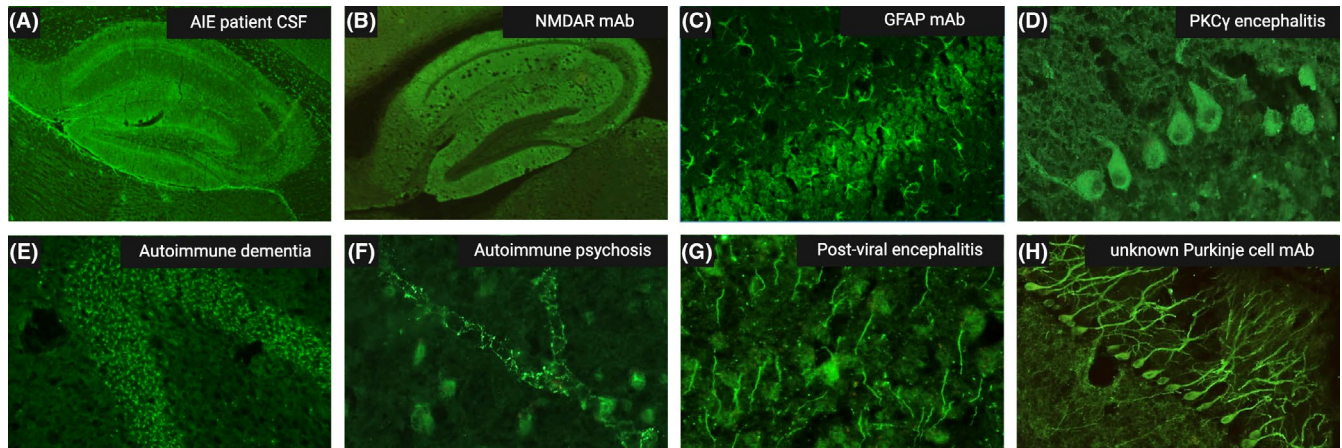


FIGURE 3 Tissue-based assays using unfixed murine brain sections. (A) CSF of a patient with AIE shows neuronal and astrocytic staining in the hippocampus. Monoclonal antibodies (mAbs) generated from this patient reveal that the pattern is an overlap of (B) mAb binding against neuropil NMDARs and (C) against GFAP on astrocytes. (D) Protein kinase-C (PKC) γ antibodies in a patient with paraneoplastic cerebellar degeneration strongly bind to Purkinje cells in the cerebellum. (E) Immunofluorescence staining of the dentate gyrus targeting a not-yet-identified antigen from a patient with autoimmune dementia. (F) Staining of fine fibers around blood vessels in the brain with CSF from a patient with autoimmune psychosis, most likely targeting nervi vasorum. (G) CSF autoantibodies targeting cortical axon initial segments from a patient with encephalitis following severe COVID-19 infection. (H) Strong staining of cerebellar Purkinje cells with a mAb cloned from the CSF of an encephalitis patient, the underlying antigenic target still awaits identification.

characteristic of LGI1 encephalitis are frequent, brief, stereotyped seizures predominantly affecting one arm and the ipsilateral face that are now known as faciobrachial dystonic seizures.⁵⁵ The diagnosis is supported by the typical magnetic resonance imaging (MRI) finding of mesiotemporal T2/ fluid-attenuated inversion recovery (FLAIR) hyperintensities.^{56,57} LGI1 is a neuronal secreted protein which links ADAM22 and ADAM23 across the synaptic cleft⁵⁸ to connect presynaptic Kv1.1 potassium channels with postsynaptic AMPA receptors.^{59–61} The disease-underlying LGI1 autoantibodies can target both the N-terminal leucine-rich repeat (LRR) domain and the C-terminal epitempin (EPTP)-repeat domain.^{60,62} They induce neuronal dysfunction by interrupting the trans-synaptic binding of LGI1 to ADAM22/ADAM23.⁶³ Infusion of monoclonal LGI1 autoantibodies into the brain of rodents mimicked the hyperexcitability phenotype seen in human patients.^{59,64} In line with this molecular concept of humoral autoimmunity, LGI1 encephalitis patients often show poor responses to anti-seizure medication, but generally respond well to immunotherapy. However, faciobrachial dystonic seizures, focal onset seizures, and sleep structure disruptions can persist for several months.

2.4 | GABA_AR encephalitis – proof of pathogenicity from the clinical to the atomic level

GABA_AR encephalitis is caused by autoantibodies targeting the GABA_AR, a pentameric ligand-gated chloride channel that modulates inhibitory synaptic transmission and dampens neuronal excitability. We here retrace the “GABA_AR autoantibody story” (Figure 4), that is, providing a shining autoantibody example within the *established* group of antibody-mediated neurological diseases. For GABA_AR

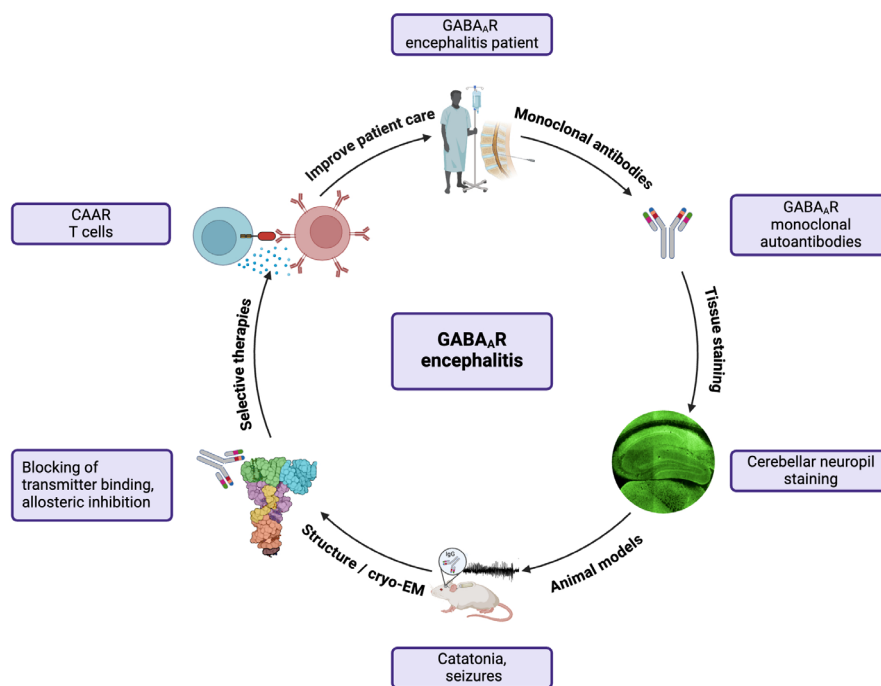
autoantibodies, direct pathogenicity has been proven at multiple levels, and the experimental and clinical approach may serve as a paradigm for future research.

Patients with GABA_AR encephalitis experience rapidly progressive symptoms including refractory seizures and status epilepticus, cognitive impairment, altered levels of consciousness, behavioral changes and movement disorders.^{65,66} Already the first investigations with polyclonal autoantibodies using CSF and serum of patients could demonstrate receptor internalization in cultured neurons and determined the $\alpha 1$, $\beta 3$ and $\gamma 2$ subunits as main epitopes.^{67,68}

2.4.1 | Monoclonal patient-derived autoantibodies

GABA_AR encephalitis patients frequently harbor not only GABA_AR autoantibodies, but also antibodies against NMDAR, LGI1 or contactin-associated protein receptor 2 (CASPR2) in their polyclonal repertoire.⁶⁷ To understand the effects exclusively related to GABA_AR autoantibodies, mAbs were generated from patients by single-cell immunoglobulin cloning using CSF B cells and antibody-producing cells.^{69,70} The staining pattern of the generated mAbs resembled the known pattern of CSF (Figure 4) with prominent neuropil binding in hippocampus and cerebellum.⁶⁹ Four of five GABA_AR-reactive mAbs bound to $\alpha 1\beta 3$ or $\alpha 1\beta 3\gamma 2$, whereas one mAb required the $\alpha 1\beta 3\gamma 2$ configuration.⁶⁹ Interestingly, while some mAbs competed for binding, one GABA_AR-reactive autoantibody resulted in enhanced binding of another GABA_AR mAb. This surprising finding suggests an additional level of complexity, that is, that binding-induced conformational changes may be required for effects of further autoantibodies or receptor ligands.

FIGURE 4 GABA_AR autoantibodies serve as a paradigm for the group of *established* neurological autoantibodies. Patient-derived mAbs bind to brain tissue with the characteristic GABA_AR pattern and recapitulate the clinical phenotypes in rodent models. Direct pathogenicity has been proven at multiple levels, including electrophysiology and structural resolution at the atomic level using cryo-electron microscopy. The detailed understanding of antibody pathogenicity paves the way for personalized and highly selective therapies, such as chimeric autoantibody receptor (CAAR) T cells. Created with [BioRender.com](#).



2.4.2 | Recapitulation of the human disease in animal models

The human GABA_AR mAbs were further evaluated in electrophysiological studies including autaptic neurons, where one mAb directly inhibited GABA-activated currents, thereby reducing postsynaptic inhibitory signaling.⁶⁹ Changes in currents were not accompanied by receptor internalization as protein levels remained unaltered after mAb incubation. Intrathecal administration of one GABA_AR mAb or its respective fragment antigen binding (Fab) induced severe encephalitis with seizures, catatonia and status epilepticus, consistent with impaired GABAergic inhibition and similar to the human disease. Infusion into the brains of EEG-monitored rats led to a significant increase in EEG coastline length and the recording of ictal events. The high excitability of hippocampal neurons persisted in ex vivo brain slices of GABA_AR mAb-infused animals.

2.4.3 | Cryo-electron microscopy reveals antibody mechanisms at atomic resolution

Analyses of GABA_AR autoantibody structures using cryo-electron microscopy (cryo-EM) demonstrated autoantibody-receptor binding at 3.0 Å resolution.⁷¹ GABA_AR proteins were reconstituted into lipid nanodiscs. Binding of one GABA_AR mAb relied on a specific sequence of four key residues, the CD3 region of this mAb penetrated the neurotransmitter binding pocket in a conserved area important for agonist binding. The respective Fab mimicked aspects of GABA chemistry and thereby sterically blocked the ligand-binding site through direct antagonism. Somatic hypermutations contributed to

the affinity of this mAb. Knowledge from autoantibody structure and function not only helps to understand pathogenicity, but also to develop novel targeted immunotherapies aiming for antibody-selective B cell removal (Figure 4).

3 | CLASSIFICATION OF ANTIBODY PATHOPHYSIOLOGY

3.1 | Complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC)

Most of the directly pathogenic autoantibodies against neuronal surface proteins belong to the IgG1 subclass, less frequently to IgG4. An important function of IgG1 is the activation of the complement system. This process is initiated when the C1q component binds to the Fc region of autoantibodies that have engaged their specific antigen, resulting in the lysis of neurons by complement-dependent cytotoxicity (CDC).⁷² The Fc region of the antibody also binds to Fcγ receptors on natural killer (NK) cells, resulting in antibody-dependent cellular cytotoxicity (ADCC) directed against neurons. Both mechanisms have been demonstrated in vivo using human AQP4 mAbs (Figure 5), where CDC and ADCC contributed to the reproduction of disease-specific lesions in rodent models.^{15,73,74} For MOG antibodies previous studies using purified patient IgG in vitro and evidence from patient autopsy studies have suggested MOG antibodies to induce CDC and ADCC.^{75–77} A recent study has highlighted the impact of MOG antibodies in triggering CDC and ADCC and provided evidence for antibody-dependent cellular phagocytosis (ADCP) in vitro.³¹ Notably, the magnitude of CDC and ADCP

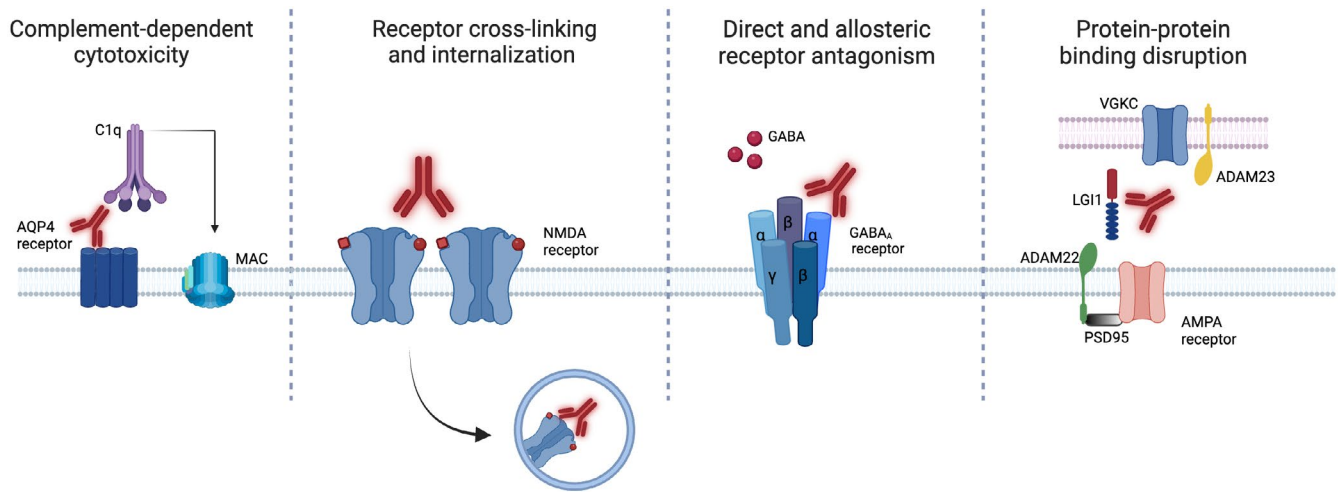


FIGURE 5 Established neurological autoantibodies confer pathology via numerous (often combined) mechanisms, including complement-dependent cytotoxicity, cross-linking and receptor internalization, receptor antagonism, or inhibition of protein–protein interaction. Created with BioRender.com.

increased at time points closer to relapse,³¹ adding an interesting aspect of disease activity-related pathogenicity.

3.2 | Cross-linking and receptor internalization

IgG1 consists of two identical arms each binding the same epitope.⁷⁸ Thereby IgG1 antibodies can cross-link target antigens and induce internalization. Cross-linking and receptor internalization are typical mechanisms for antibodies targeting ionotropic receptors including the NMDAR (Figure 5)^{47,79} AMPAR,⁸⁰ or mGluR5.⁸¹ In studies using human recombinant mAbs from NMDAR encephalitis, mAbs alone were sufficient to promote receptor internalization after cerebroventricular infusion.⁴⁵ Furthermore, mAbs induced concentration-dependent reduction of NMDAR-mediated currents in neurons.⁸² For other forms of AIE, validation with mAbs is pending. Studies showed that CSF containing AMPAR antibodies led to a reduction in GluR2-containing AMPA receptor clusters in cultured neurons.⁸³ Also in cultured neurons, incubation with mGluR5 antibodies led to decreased surface density of synaptic and extrasynaptic mGluR5.⁸¹

3.3 | Inhibition of protein–protein interaction

In LGI1 encephalitis, autoantibodies interfere with synaptic function by inhibiting protein–protein interactions (Figure 5).⁸⁴ LGI1 mAbs comprise at least two populations binding to either the LRR or EPTP domain.⁶² An individual patient's serum can typically harbor both specificities.^{60,84} LGI1 mAbs targeting the EPTP domain disrupted the interaction between LGI1 and its pre- and postsynaptic receptors, ADAM23 and ADAM22, respectively. In contrast, mAbs directed against the LRR domain facilitated the internalization of the LGI1 complex bound to ADAM22/23.^{62,84}

3.4 | Autoantibody valency-dependent receptor stimulation and inhibition

Another pathomechanism of neurological autoantibodies is seen in MG patients with muscle-specific kinase (MuSK) antibodies, a rare subgroup of MG in whom AChR autoantibodies are absent.^{85,86} MuSK autoantibodies are predominantly of the IgG4 subclass. MuSK mAbs demonstrated two opposing mechanisms depending on the valency. The bivalent mAb facilitated cross-linking of MuSK receptors, leading to increased phosphorylation, whereas the functionally monovalent mAb disrupted the interaction between MuSK and the agrin-LRP4 complex, thereby blocking MuSK phosphorylation.^{87,88} Both pathways ultimately inhibit AChR clustering.

3.5 | Synergistic effect of antibodies

Recent findings using mAbs against AChR identified synergistic pathogenic effects requiring more than one autoantibody in MG. Only the combination of AChR mAbs induced strong complement activation in vitro, and recapitulated key clinical features in vivo, associated with destruction of the neuromuscular junction and complement activation.⁵ Individual AChR mAbs alone did not show pathogenicity despite clear binding.

4 | EMERGING (GROUP II): ANTIBODIES CONTRIBUTING TO THE DISEASE

For many novel autoantibodies it is not yet clear whether they are directly pathogenic or just immunological bystanders. Although clinical improvement after immunotherapy may suggest a contribution to disease, thorough experimental evaluation is needed to understand autoantibody properties and functions. The group of *emerging*

neurological autoantibodies is particularly exciting, as proof of pathogenicity will open novel treatment options to various patients, for example, with suspected autoimmune dementia, autoimmune psychosis or post-viral neurological autoimmunity.

4.1 | Autoimmune dementia

This new field of *emerging* autoantibodies is often fueled by observations in individual patients. There is growing evidence that autoantibodies may not only cause subacute neurological symptoms but can also contribute to slowly progressing diseases including suspected neurodegenerative dementias. For example, a patient was diagnosed with Alzheimer's disease but turned out later to have LGI1 encephalitis.⁸⁹ Also, patients with IgA/IgM NMDAR autoantibodies and progressive cognitive impairment can have the working diagnosis of Alzheimer's or frontotemporal lobe degeneration.⁹⁰ In a retrospective study analyzing 286 CSF and serum samples of patients with different dementia forms, 16% of the serum samples had NMDAR IgA, IgM or IgG antibodies compared to 4.3% in a healthy control group.⁹¹ Further studies linked neurodegenerative dementias to the same or additional anti-neuronal autoantibodies, such as IgLON5, LGI1, DPPX, or NMDAR.⁹² Although these autoantibodies have been repeatedly suggested to correlate with cognitive decline,^{93–95} their exact pathogenic role remains to be determined.

In the spectrum of autoimmune neurodegeneration, IgLON5 syndrome stands out for its complex relationship with neurodegeneration. First described in 2014, this syndrome is characterized by sleep disorders, bulbar dysfunction, and cognitive impairment.^{96,97} Some patients with IgLON5 disease develop neurodegeneration, marked by tau protein deposition in the tegmentum and hippocampus and disruption of the neuronal cytoskeleton.^{98,99} Recent research demonstrated binding of IgLON5 antibodies to areas prone to tau pathology, suggesting that they may precede pathology and that neurodegeneration is potentially secondary to an autoimmune response.¹⁰⁰ Early diagnosis of IgLON5 disease is crucial, as these patients could benefit from prompt initiation of immunotherapy before neurodegeneration sets in.¹⁰¹

Understanding the role of *emerging* autoantibodies in dementia has immediate clinical significance, as it raises the possibility that some forms of dementia may benefit from immunotherapy. These findings advocate for the expansion of diagnostic criteria and treatment approaches in autoimmune dementia, emphasizing the potential of immunotherapy in cases where traditional dementia treatments fall short. Along these lines, we recently completed an unblinded prospective observational trial (TIP-COG) using immunoadsorption in 20 patients with a variety of high-titer anti-neuronal autoantibodies in the context of cognitive decline (Rössling et al., in prep.). Approximately half of the patients had a previous diagnosis of neurodegenerative dementia. Cognitive performance, as measured with the Mini-Mental State Examination (MMSE), showed a slight mean improvement, paralleled by autoantibody level reduction in

most cases and partially restored functional brain MRI connectivity. The findings suggest that autoantibody removal may be a promising treatment option for selected patients and encouraged us to initiate a larger placebo-controlled interventional trial in patients with suspected autoimmune dementia.

4.2 | Autoimmune psychosis

Likewise in psychiatric disorders, there is recent awareness in cases of schizophreniform or polymorphic psychotic disorders in which clinical features are potentially related to underlying immune-mediated mechanisms. Patients can show improvement with immunotherapy and should be identified according to emerging guidelines.^{102–104} Evidence of immune system dysregulation in a wide range of psychiatric disorders also comes from large-scale genetic, gene expression, and proteomic studies.^{105–107} Autoimmunity and psychiatric diseases are mutually reinforcing, with each condition increasing the risk of developing the other.^{108,109} A large-scale cross-sectional study investigating the IgG repertoire in patients with established psychotic disorder diagnoses found six autoantibodies associated with specific psychopathological symptoms, among them AP3B2 antibodies associated with persecutory delusions and TDO2 antibodies which were detected in patients with hallucinations.¹¹⁰

Several *emerging* autoantibodies detected in primary psychotic presentations already belong to the group of *established* autoantibodies in AIE, such as NMDAR, LGI1, and CASPR2 autoantibodies.^{111–113} Psychiatric symptoms are a well-known part of the symptomatic onset in AIE^{114,115} and can frequently culminate into cognitive dysfunction at later disease stages.¹¹⁶ In animal studies, NMDAR autoantibodies induced and modulated psychiatric behaviors.¹¹⁷ Using single nanoparticle tracking, a recent study demonstrated altered NMDAR distribution in cultured neurons exposed to CSF from patients with schizophrenia, further supporting NMDAR autoantibody-induced dysfunction in psychotic disorders.¹¹⁸ Such detailed experimental analyses are required to support the role of anti-neuronal autoantibodies in autoimmune psychosis, as correlations can rarely be drawn from clinical cohorts alone. In fact, most studies on NMDAR autoantibodies and psychiatric disease have been conducted using serum samples and have varied significantly in terms of disease duration, age distribution, and testing methods, which complicates precise prevalence estimates and pathophysiological links.^{119,120}

4.3 | Post-viral humoral autoimmunity

Viral encephalitides have long been considered as important differential diagnoses of AIE; however, increasing evidence indicates that clinical symptomatology, disease mechanisms and triggers of both entities can broadly overlap in a single patient. The best-characterized example is post-herpes simplex virus type 1 (HSV-1) encephalitis, where approximately 30% of patients develop NMDAR

autoantibodies within 3 months after HSV-1 encephalitis, leading to the full clinical picture of immunotherapy-responsive NMDAR encephalitis.¹²¹⁻¹²³ Patients with NMDAR encephalitis are nearly 2.5 times more likely to harbor HSV-1 antibodies compared with healthy controls, indicating a strong link between past HSV-1 infection and NMDAR encephalitis.¹²⁴

With increased recognition of post-viral autoimmunity, other infections have been linked to the development of NMDAR antibodies, such as varicella zoster virus,¹²⁵⁻¹²⁷ Japanese encephalitis virus,¹²⁸⁻¹³⁰ Epstein Barr virus, human herpesvirus (HHV) 6 and HHV-7, Chikungunya virus,¹³¹ human immunodeficiency virus (HIV),¹³² influenza A virus,¹³³ tick-borne encephalitis virus,¹³⁴ and also bacterial infections like mycobacterium tuberculosis and rarely parasites (*angiostrongylus cantonensis*).¹³⁵ Moreover, other autoantibodies such as GABA_AR after HSV-1 and HHV-6 infection⁶⁶ or dopamine-2 receptor (D2R) antibodies after HSV-1 infection have been reported.¹³⁶

Besides these *established* disease-associated antibodies, viral disease seems to also trigger autoimmunity against yet unknown, *emerging* targets. For example, in the SARS-CoV-2 pandemic, critically ill patients had numerous unidentified anti-neuronal autoantibodies in their serum and CSF detected on unfixed murine brain sections.¹³⁷ A subset of monoclonal patient-derived SARS-CoV-2-neutralizing antibodies showed strong binding to mammalian epitopes expressed in brain, lung, heart, kidney, or gut (Figure 3G).¹³⁸ Interestingly, the presence of anti-neuronal autoantibodies in post-COVID-19 syndrome was associated with cognitive decline,¹³⁹ and passive transfer of human IgG into mice mirrored symptoms reported by patients suffering from long COVID.¹⁴⁰

It is well established that immune reactions to foreign antigens can trigger the production of antibodies against self-antigens.¹⁴¹ With each infection, the immune system must strike a balance between combating the pathogen and preventing autoimmunity. If self-tolerance mechanisms fail, central nervous system infections can precipitate an autoimmune response. The ongoing challenge lies in understanding how slight shifts in an individual's immune tolerance, particularly in response to ever-evolving pathogens, predispose them to post-viral autoimmunity. Some pathogens have been selected to exploit this fine-tuned balance, for example, by closely mimicking human proteins, allowing them to evade the immune response (i.e. gp41 of HIV).¹⁴² In order to detect these pathogens, ~20% of circulating human naive B cells remain autoreactive.¹⁴³ Ideally, as a tolerance mechanism called "clonal redemption", these B cells would in germinal centers acquire somatic hypermutations and lose autoreactivity but retain specificity towards the pathogen.¹⁴⁴ Interestingly, some autoantibodies in NMDAR encephalitis did not exhibit somatic hypermutations,⁴⁸ and a longitudinal analysis of SARS-CoV-2 antibodies showed only a moderate increase.¹⁴⁵ This indicates that clonal redemption can be incomplete in the setting of autoimmunity and infections and is one example of how tolerance mechanisms can be overcome. In the case of post-HSV-1 encephalitis, molecular mimicry, but also neo-antigen presentation in the draining lymph nodes after neuronal damage, with costimulatory

signals stemming from necrotic tissue or from the virus directly, have been suggested. In addition, viral infections might alter protein expression, for example by interfering with the unfolded protein response and thereby rendering the NMDAR immunogenic.¹⁴⁶

Future research around post-viral autoimmunity should focus on the potential consequences of newly generated autoantibodies for acute but also chronic neurological diseases, such as neurodegenerative dementias. Better characterization of post-viral autoimmune responses could lead to the identification of biomarkers, new candidates for immunotherapy and the development of more specific therapeutic interventions.

5 | TOOLBOX FOR ANTIBODY RECLASSIFICATION FROM EMERGING TO ESTABLISHED

It is an obvious approach to generate as much clinical and experimental data as possible to support the pathogenic role of a given anti-neuronal autoantibody. Once pathogenicity has been determined, autoantibodies can be classified as *established*, which has immediate implications for routine diagnostics and administration of immunotherapy. The following two technologies are very helpful in attributing the relevance of novel autoantibodies to clinical symptoms.

5.1 | Generation of patient-derived monoclonal autoantibodies

Early discoveries were made using patient serum, CSF, or purified IgG containing a polyclonal mixture of many different antibodies. Analyzing the contribution of individual autoantibodies to pathology requires mAbs, which can be recombinantly produced in theoretically unlimited amounts.⁴⁸ For this, patient blood or CSF is collected and sorted by fluorescent-activated cell sorting (FACS) to select memory B cells (MBCs) and antibody-secreting cells (ASCs) for single-cell lysis. Single-cell mRNA is then transcribed into cDNA. A nested polymerase chain reaction (PCR) protocol amplifies the genes of the Ig heavy chain (IgH) and both Ig light (IgL) chains (kappa and lambda) resulting in PCR products that are sequenced.¹⁴⁷ The productive rearrangements of the IgH and IgL variable regions are specifically amplified and prepared for subcloning into IgG expression vectors. The plasmids are amplified in bacteria to check for complete overlap with the source sequence. Then, matching IgH and IgL chains of the respective original antibodies are co-transfected into HEK293 cells. The secreted mAbs are harvested from the supernatant and purified.

Resulting recombinant human mAbs are essential for elucidating the pathogenicity of autoantibodies, the structural resolution, epitope binding, affinity, clonal relationships, the origin of pathogenic B cells, and the functional contributions of individual autoantibodies. For example, the application of human NMDAR mAbs could confirm

that they are directly pathogenic. They caused downregulation of neuronal surface receptors and subsequent impairment of NMDAR-mediated currents.⁴⁸ Furthermore, when mAbs were intrathecally administered via an osmotic pump, they induced epileptic seizures in vivo. Other than expected, the reduction of synaptic excitatory neurotransmission, rather than inhibitory neurotransmission, was shown to underlie the ictal events through alterations in the dynamic behavior of microcircuits in brain tissue.⁸² Recent investigations using CASPR2 mAbs revealed that they interfere with the binding between CASPR2 and contactin-2 in an affinity- and concentration-dependent manner, and that mAb affinity correlated with the number of somatic hypermutations, an analysis which has only become possible with the mAb technology.^{148,149} Lastly, achieving a detailed understanding of individual binding sites of antibodies to the GABA_AR was only possible through the use of mAbs in cryo-EM investigations, something that could not have been accomplished with polyclonal material.⁷¹

5.2 | Target identification

Established AIE are defined and characterized through their respective target protein. Routine laboratory assessments for the detection of autoantibodies in patients with a suspected autoimmune neurological disease involve panels of known antigens that can be screened with line blots or cell-based assays. For the screening of novel autoantibodies, tissue-based assays are helpful including staining on unfixed murine brain tissue.^{103,137} As described above, growing evidence suggests that selected patients with immunotherapy-responsive autoimmune dementia and autoimmune psychosis harbor disease-driving autoantibodies, in particular when the immunostainings on unfixed brain tissue suggest a conformational surface epitope (Figure 3).

To identify the underlying antigens of such novel autoantibodies, various methods are available, including phage immunoprecipitation sequencing (PhIP-seq) and printed proteome arrays.¹⁵⁰ Our approach focuses on immunoprecipitation combined with mass spectrometry (IP/MS). For this, mAbs or autoreactive IgG in patient serum or CSF are bound to protein-G-coupled beads. Antibody-bead complexes are then exposed to nervous system tissue lysates containing the antigenic epitopes and are allowed to bind their respective target antigen. Proteins digested from the antibody-bead complexes can then be separated by liquid chromatography and analyzed via MS. The subsequent comparison to negative controls reveals highly abundant target candidates. IP/MS can identify complex targets, for example in patients with neurological post-COVID-19-vaccination syndrome.¹⁵¹ The next step is the broad expansion of emerging autoantibodies found in autoimmune dementia, autoimmune psychosis, stroke, cancer, and neurodegenerative disorders. The strength of the IP/MS approach is the use of nervous tissue lysates where antigens are in their native conformation, closely mirroring the in vivo situation. This seems to be required, as anti-neuronal autoantibodies can bind to highly complex epitopes,⁷¹ which are lost when using

arrays of linearized proteins. Identified targets have to be validated in cell-based assays, where HEK cells overexpress the respective protein. Novel autoantibodies can then be screened in clinical cohorts to understand their frequencies and expanding phenotypes.

6 | EXPLORATORY (GROUP III): UNCLEAR ROLES OF ANTIBODIES IN DISEASES

With broader availability of diagnostic testing, anti-neuronal autoantibodies are increasingly found also in clinical constellations not previously thought to be autoimmune-mediated. It is therefore important to focus on the identification of the underlying antigens, the generation of patient-derived mAbs for determining pathogenicity, and the confirmation in clinical cohorts to understand which of these *explorative* autoantibodies can affect brain function. This approach contains enormous therapeutic potential in many neurological diseases, ranging from stroke and neurodegeneration to cancer-associated cognitive impairment, nervous system development, and normal brain aging.

6.1 | Autoantibodies in stroke

Emerging evidence suggests that NMDAR autoantibodies, especially of the IgA and IgM isotype, are present in a significant subset of stroke patients, with prevalence rates varying between 11% and 22%.^{152,153} Interestingly, the prevalence is comparable to healthy controls,^{91,154-156} raising questions about their clinical relevance. It may be possible, however, that they exert a pathogenic role only in a certain disease context, for example related to stroke-induced blood-brain barrier breakdown. While one study found no significant association between these autoantibodies and stroke outcomes,¹⁵² other research suggested that high antibody titers or the presence of a leaky blood-brain barrier (e.g., in ApoE4 carriers) correlate with worse functional outcomes, larger MRI diffusion weighted imaging lesion volumes, and increased vascular risk 3 years post-stroke.^{157,158} Furthermore, neuropsychiatric symptoms were more common in seropositive patients one to 3 years after stroke.¹⁵⁹ Thus, whether removal of autoantibodies can be protective in selected stroke patients warrants further investigation.

6.2 | Neuronal autoantibodies and cognitive impairment in cancer

Autoantibodies targeting intracellular antigens are commonly associated with paraneoplastic neurological syndromes, however, autoantibodies against neuronal cell surface proteins are increasingly recognized in cancer patients. Earlier work reported the high prevalence of anti-neuronal autoantibodies, predominantly NMDAR autoantibodies of the IgA and IgM isotype, in multiple patients with cancer.¹⁶⁰ The patients exhibited significantly higher rates of

cognitive deficits compared to those without autoantibodies. In further support of these initial findings, another study of 157 patients with malignant melanoma found that 22.3% had anti-neuronal autoantibodies, again most frequently IgA/IgM NMDAR autoantibodies. In this cohort, autoantibodies were an independent risk factor for cognitive impairment, which also correlated with the NMDAR antibody titer arguing for a dose–response relationship.¹⁶¹ A follow-up study specifically investigated the association between neuronal autoantibodies and cognitive deficits in 167 patients with small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC).¹⁶² Remarkably, this study found that SCLC patients with any type of neuronal autoantibodies had an 11-fold increased risk of cognitive impairment compared to seronegative patients, and patients with NSCLC and NMDAR IgA autoantibodies even a 20-fold increased risk. Importantly, also the presence of antibodies against yet unknown antigens—which belong to the *explorative* group of neurological autoantibodies—was associated with cognitive decline. It is tempting to speculate whether antibody-depleting immunotherapy could be a therapeutic option if cognitive impairment occurs in cancer patients, and whether it may account for some forms of “brain fog”, which is traditionally attributed to chemotherapy. It will therefore be worthwhile to analyze the role of unknown autoantibodies, including the generation of mAbs and the identification of the underlying antigens.

6.3 | Autoantibodies during neurodevelopment

Maternal health influences the fetal brain development through many different factors, one of them could be anti-neuronal autoantibodies. During normal pregnancy, antibodies, including potentially pathogenic autoantibodies, are continuously transferred from the maternal circulation into the fetal bloodstream.¹⁶³ Due to the incomplete development of the fetal blood–brain barrier, these autoantibodies can accumulate in the fetus and potentially enter the brain, posing risks to fetal neurological development.¹⁶⁴ The concept of materno-fetal autoantibody transfer is known, for example, from in utero exposure to maternal autoantibodies targeting the fetal acetylcholine receptor (fAChR) isoform, which can result in fAChR antibody-related disorders (FARAD)¹⁶⁵ including arthrogryposis multiplex congenita (AMC), a condition characterized by severe congenital joint contractures.¹⁶⁶ Notably, some mothers have no clinical signs of MG themselves,¹⁶⁷ thus a link to fetal abnormalities can be difficult to establish.

Similarly, mothers can also harbor antibodies against brain antigens. Exposure to several maternal brain-reactive antibodies was associated with increased risk of having a child with autism spectrum disorder (ASD).^{168–170} Studies involving the administration of serum or purified IgG from mothers of children with ASD to dams have shown anxiety and deficits in social behavior.¹⁷¹ Likewise, when ASD-IgG was administered to non-human primates atypical social behavior was observed.¹⁷² A recent study using active immunization to induce the production of ASD-associated antibodies, including antibodies

against LDHA, LDHB, CRMP1, and STIP1, reported alterations in behavior and brain structure, reminiscent of ASD.¹⁷³ The precise mechanisms underlying the pathological effects of these autoantibodies await clarification and are likely influenced by various factors, such as antibody isotype and affinity, the sex of the offspring,¹⁷⁴ and post-translational modifications like antigen glycosylation.¹⁷⁵

Further examples include autoantibodies against CASPR2, synapsin and NMDAR. In utero exposure to CASPR2 antibodies induced by active immunization led to ASD-like behavioral changes in rodents.¹⁷⁶ Antibodies against synapsin-1, a neuronal protein crucial for synaptic vesicle release, were detected in ~10% of mothers having children with neurologic abnormalities.¹⁷⁷ A subsequent confirmation cohort of pregnant women detected synapsin-1 autoantibodies with similar frequency and found a correlation of seropositivity with multiple abnormalities of fetal development.¹⁷⁸ A materno-fetal transfer model using human recombinant NMDAR mAbs resulted in NMDAR reduction and decreased amplitudes of spontaneous excitatory postsynaptic currents in the offspring.¹⁷⁹ Since NMDAR IgG autoantibodies are found in ~1% of the healthy population,^{180,181} a large number of asymptomatic mothers may diaplacentally transfer low-level pathogenic autoantibodies and inadvertently affect neonatal development.

6.4 | A role of autoantibodies in brain homeostasis and normal aging?

The rapidly increasing number of novel pathogenic autoantibodies in neurological diseases together with their detection also in a certain percentage of healthy controls suggests that anti-neuronal autoantibodies are not always a diagnostic “yes or no” finding. In AIE patients, established autoantibodies can prove the diagnosis and explain disease symptoms. However, can the same autoantibodies also contribute to brain function if they occur in healthy subjects?

We hypothesize that the detailed experimental proof of pathogenicity, involving patient-derived mAbs and their use in animal models, electrophysiology and structural analyses (for example, as discussed for GABA_AR autoantibodies), (Figure 4), categorizes autoantibodies as “relevant”, irrespective of a person's clinical constellation. Not having full-blown AIE may then be related to lower autoantibody levels, compartmentalization of the immune response, autoantibody affinity, epitope specificity, and duration of the autoantibody exposure, among other factors. Autoantibodies may rather play an important additive, modulating role on brain function, a concept which we recently termed “smoldering humoral autoimmunity”.⁴⁰

This concept may be particularly relevant for neurodegenerative diseases by linking them to triggers of humoral autoimmunity. As described above, the generation of anti-neuronal autoantibodies following viral disease is largely accidental and unpredictable. Depending on the properties of such autoantibodies, they may continuously interfere with brain targets, cause chronic neuroinflammation and predispose individuals to cognitive impairment after stroke and cancer, but also to neurodegenerative diseases such as

Alzheimer's disease. Indeed, a large body of evidence suggests that infections, especially with HSV-1 are associated with and accelerate the pathogenesis of Alzheimer's dementia.^{182,183} In turn, prevention of viral infection using vaccination with recombinant shingles vaccine was able to reduce the risk of developing dementia.¹⁸⁴ It is tempting to speculate whether the viral effects on neurodegeneration are mediated in part via down-stream anti-neuronal autoantibodies.

Bringing these different lines of evidence together, anti-neuronal autoantibodies may collectively constitute the "brain antibody-ome" and thus represent an additional, not previously acknowledged "super-system" for brain health and disease. For example, in neurodegenerative dementias such as Alzheimer's disease, the composition of many thousands of autoantibodies could modulate the disease risk, similar to other "super-systems" such as genetics, metabolism, lifestyle, vascular or environmental factors, among others (Figures 6).

Confirmation of the concept of smoldering humoral autoimmunity will require extensive research. We envision remarkable similarities to the identification of polygenic disease risks over the last three decades, where function and significance were analyzed gene by gene. Likewise, the community will have to identify autoantibody by autoantibody, experimentally confirm their pathogenicity and classify them from pathogenic to uncertain significance to beneficial. Such autoantibody profiling has massive potential to uncover novel biomarkers, enhance our understanding of underlying mechanisms, and identify novel therapeutic targets.

7 | SELECTIVE THERAPIES

The ongoing discovery of pathogenic neurological autoantibodies paved the way for personalized and increasingly selective therapies. For example, in MG, unselective immunosuppression has been used for decades, but now switches more and more to targeted approaches. This includes cellular therapies against B cells from pro-B

cells to plasma blasts (i.e., CD19 CAR T cells) or against plasma cells (i.e., BCMA CAR T cells), even in combination in a patient with MG.¹⁸⁵ Cell therapies now rapidly expand to other neurological disorders, such as MOGAD and NMOSD.^{39,186}

Aside from CAR T cells, most recent developments in cell therapy focus on highly selected depletion of only autoantibody-producing B cells. One such innovative approach involves the use of chimeric autoantibody receptor (CAAR) T cells. It leverages the fact that autoantibody-producing B cells express the specific antibody they produce on their surface as the B cell receptor (BCR). In this approach, T cells are extracted from the patient and genetically engineered to express the autoantigen (such as the NMDAR) on their surface together with intracellular activating domains from the T cell receptor.¹⁸⁷ Once reintroduced into the patient, these CAAR T cells circulate throughout the body. When they encounter B cells that express the NMDAR antibody on their surface, they selectively destroy these pathogenic B cells. Crucially, other B cells are ignored, such as those producing protective antibodies following an infection or vaccination.

In preclinical mouse models, this approach has demonstrated both efficacy and specificity in autoantibody induced neurological diseases for NMDAR encephalitis¹⁸⁷ and MG.¹⁸⁸ If these findings are replicated in clinical trials, there is a well-founded hope that pathogenic autoantibodies could be depleted highly selectively without the extensive side effects commonly associated with immunotherapies. This could accelerate clinical remission, improve prognosis and potentially lead to cure. Moreover, this technology may not only be useful for NMDAR encephalitis, but could also be applied to other encephalitides, MG, and autoantibody-mediated diseases beyond neurology.

8 | CONCLUSIONS

The massive advancement in the understanding of diseases caused by well-established anti-neuronal autoantibodies has expanded the

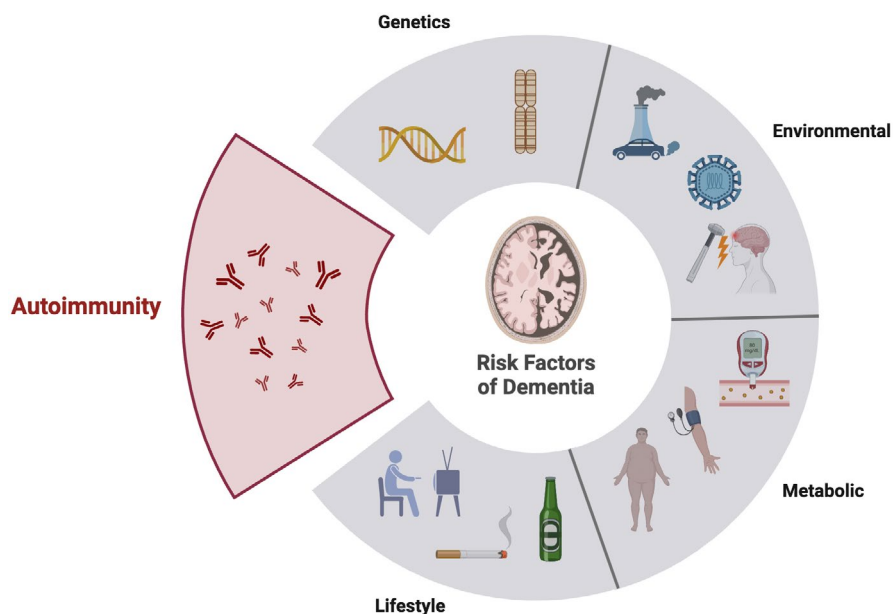


FIGURE 6 Thousands (or millions) of autoantibodies may collectively constitute the "brain antibody-ome" and represent a novel "super-system" for modulating nervous system function in health and disease. In case of Alzheimer's disease, it may act in concert with established super-systems including genetics (e.g., ApoE4 carrier status), metabolism (e.g., diabetes, hypertension), lifestyle (e.g., smoking), vascular (e.g., atherosclerosis) or environmental factors (e.g., infections). Created with [BioRender.com](https://www.biorender.com).

attention also to clinical constellations where a contribution of autoantibodies has not been assumed previously. Based on recent data reviewed here, we envision that humoral autoimmunity represents an additional “super-system” for brain health and disease, together with genetics, metabolism, lifestyle or environmental factors, among others. Future concepts will likely shift the focus from individual autoantibodies to the “brain antibody-ome”, where the composition of thousands of anti-neuronal autoantibodies shapes neuronal function and homeostasis, neurodegeneration, but also healthy aging. To fully understand the contribution of this humoral “super-system”, we first need to recognize its pieces, that is, thousands of individual autoantibodies and their functions from the atomic to the clinical level.

ACKNOWLEDGMENTS

This work was supported by grants from the German Research Foundation (DFG); Clinical Research Unit KFO 5023 BECAUSE-Y; project number 504745852; grants FOR3004, PR1274/5-1, and PR1274/9-1; the Helmholtz Association of German Research Centres (HIL-A03 BaoBab); and the German Federal Ministry of Education and Research (Connect-Generate 01GM1908D) to HP. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Lucie Y. Li  <https://orcid.org/0000-0001-8098-1977>

Amelya Keles  <https://orcid.org/0000-0001-5328-2740>

Marie A. Homeyer  <https://orcid.org/0000-0003-0630-3857>

Harald Prüss  <https://orcid.org/0000-0002-8283-7976>

REFERENCES

1. Keesey JC. A history of treatments for myasthenia gravis. *Semin Neurol.* 2004;24(1):5-16. doi:[10.1055/s-2004-829584](https://doi.org/10.1055/s-2004-829584)
2. Walker MB. Treatment of myasthenia gravis with physostigmine. *Lancet.* 1934;223(5779):1200-1201. doi:[10.1016/S0140-6736\(00\)94294-6](https://doi.org/10.1016/S0140-6736(00)94294-6)
3. Albazli K, Kaminski HJ, Howard JF. Complement inhibitor therapy for myasthenia gravis. *Front Immunol.* 2020;11:917. doi:[10.3389/fimmu.2020.00917](https://doi.org/10.3389/fimmu.2020.00917)
4. Obaid AH, Zografou C, Vadysirisack DD, et al. Heterogeneity of acetylcholine receptor autoantibody-mediated complement activity in patients with myasthenia gravis. *Neurol Neuroimmunol Neuroinflamm.* 2022;9(4):e1169. doi:[10.1212/NXI.0000000000001169](https://doi.org/10.1212/NXI.0000000000001169)
5. Rose N, Holdermann S, Callegari I, et al. Receptor clustering and pathogenic complement activation in myasthenia gravis depend on synergy between antibodies with multiple subunit specificities. *Acta Neuropathol.* 2022;144(5):1005-1025. doi:[10.1007/s00401-022-02493-6](https://doi.org/10.1007/s00401-022-02493-6)
6. Vu T, Meisel A, Mantegazza R, et al. Terminal complement inhibitor Ravulizumab in generalized myasthenia gravis. *NEJM Evid.* 2022;1(5):EVID0a2100066. doi:[10.1056/EVID0a2100066](https://doi.org/10.1056/EVID0a2100066)
7. Howard JF, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol.* 2017;16(12):976-986. doi:[10.1016/S1474-4422\(17\)30369-1](https://doi.org/10.1016/S1474-4422(17)30369-1)
8. Howard JF, Bresch S, Genge A, et al. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Neurol.* 2023;22(5):395-406. doi:[10.1016/S1474-4422\(23\)00080-7](https://doi.org/10.1016/S1474-4422(23)00080-7)
9. Gomez CM, Richman DP. Anti-acetylcholine receptor antibodies directed against the alpha-bungarotoxin binding site induce a unique form of experimental myasthenia. *Proc Natl Acad Sci USA.* 1983;80(13):4089-4093. doi:[10.1073/pnas.80.13.4089](https://doi.org/10.1073/pnas.80.13.4089)
10. Cetin H, Webster R, Liu WW, et al. Myasthenia gravis AChR antibodies inhibit function of rapsyn-clustered AChRs. *J Neurol Neurosurg Psychiatry.* 2020;91(5):526-532. doi:[10.1136/jnnp-2019-322640](https://doi.org/10.1136/jnnp-2019-322640)
11. Jarius S, Franciotta D, Paul F, et al. Cerebrospinal fluid antibodies to aquaporin-4 in neuromyelitis optica and related disorders: frequency, origin, and diagnostic relevance. *J Neuroinflammation.* 2010;7:52. doi:[10.1186/1742-2094-7-52](https://doi.org/10.1186/1742-2094-7-52)
12. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med.* 2005;202(4):473-477. doi:[10.1084/jem.20050304](https://doi.org/10.1084/jem.20050304)
13. Lucchinetti CF, Mandler RN, McGavern D, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain J Neurol.* 2002;125(Pt 7):1450-1461. doi:[10.1093/brain/awf151](https://doi.org/10.1093/brain/awf151)
14. Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M, Weinshenker BG. Plasma exchange for severe attacks of CNS demyelination: predictors of response. *Neurology.* 2002;58(1):143-146. doi:[10.1212/wnl.58.1.143](https://doi.org/10.1212/wnl.58.1.143)
15. Bennett JL, Lam C, Kalluri SR, et al. Intrathecal pathogenic anti-aquaporin-4 antibodies in early neuromyelitis optica. *Ann Neurol.* 2009;66(5):617-629. doi:[10.1002/ana.21802](https://doi.org/10.1002/ana.21802)
16. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015;85(2):177-189. doi:[10.1212/WNL.0000000000001729](https://doi.org/10.1212/WNL.0000000000001729)
17. Damato V, Theorell J, Al-Diwani A, et al. Rituximab abrogates aquaporin-4-specific germinal center activity in patients with neuromyelitis optica spectrum disorders. *Proc Natl Acad Sci USA.* 2022;119(24):e2121804119. doi:[10.1073/pnas.2121804119](https://doi.org/10.1073/pnas.2121804119)
18. Cotzomi E, Stathopoulos P, Lee CS, et al. Early B cell tolerance defects in neuromyelitis optica favour anti-AQP4 autoantibody production. *Brain J Neurol.* 2019;142(6):1598-1615. doi:[10.1093/brain/awz106](https://doi.org/10.1093/brain/awz106)
19. Binks SNM, Irani SR. Autoantibody-mediated central nervous system channelopathies. *Handb Clin Neurol.* 2024;203:235-269. doi:[10.1016/B978-0-323-90820-7.00005-7](https://doi.org/10.1016/B978-0-323-90820-7.00005-7)
20. Waters PJ, McKeon A, Leite MI, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. *Neurology.* 2012;78(9):665-671. doi:[10.1212/WNL.0b013e318248dec1](https://doi.org/10.1212/WNL.0b013e318248dec1)
21. Iorio R, Fryer JP, Hinson SR, et al. Astrocytic autoantibody of neuromyelitis optica (NMO-IgG) binds to aquaporin-4 extracellular loops, monomers, tetramers and high order arrays. *J Autoimmun.* 2013;40:21-27. doi:[10.1016/j.jaut.2012.07.008](https://doi.org/10.1016/j.jaut.2012.07.008)
22. Kaminski HJ, Sikorski P, Coronel SI, Kusner LL. Myasthenia gravis: the future is here. *J Clin Invest.* 2024;134(12):e179742. doi:[10.1172/JCI179742](https://doi.org/10.1172/JCI179742)

23. Kümpef T, Giglhuber K, Aktas O, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD)-revised recommendations of the Neuromyelitis Optica study group (NEMOS). Part II: attack therapy and long-term management. *J Neurol*. 2024;271(1):141-176. doi:[10.1007/s00415-023-11910-z](https://doi.org/10.1007/s00415-023-11910-z)
24. Kitley J, Leite MI, Küker W, et al. Longitudinally extensive transverse myelitis with and without aquaporin 4 antibodies. *JAMA Neurol*. 2013;70(11):1375-1381. doi:[10.1001/jamaneurol.2013.3890](https://doi.org/10.1001/jamaneurol.2013.3890)
25. Kitley J, Woodhall M, Waters P, et al. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. *Neurology*. 2012;79(12):1273-1277. doi:[10.1212/WNL.0b013e31826aac4e](https://doi.org/10.1212/WNL.0b013e31826aac4e)
26. Hamid SHM, Whittam D, Mutch K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. *J Neurol*. 2017;264(10):2088-2094. doi:[10.1007/s00415-017-8596-7](https://doi.org/10.1007/s00415-017-8596-7)
27. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: international MOGAD panel proposed criteria. *Lancet Neurol*. 2023;22(3):268-282. doi:[10.1016/S1474-4422\(22\)00431-8](https://doi.org/10.1016/S1474-4422(22)00431-8)
28. O'Connor KC, McLaughlin KA, De Jager PL, et al. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. *Nat Med*. 2007;13(2):211-217. doi:[10.1038/nm1488](https://doi.org/10.1038/nm1488)
29. Waters P, Woodhall M, O'Connor KC, et al. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(3):e89. doi:[10.1212/NXI.0000000000000089](https://doi.org/10.1212/NXI.0000000000000089)
30. Waters PJ, Komorowski L, Woodhall M, et al. A multicenter comparison of MOG-IgG cell-based assays. *Neurology*. 2019;92(11):e1250-e1255. doi:[10.1212/WNL.0000000000007096](https://doi.org/10.1212/WNL.0000000000007096)
31. Yandamuri SS, Filipek B, Obaid AH, et al. MOGAD patient autoantibodies induce complement, phagocytosis, and cellular cytotoxicity. *JCI Insight*. 2023;8(11):e165373. doi:[10.1172/jci.insight.165373](https://doi.org/10.1172/jci.insight.165373)
32. Durozard P, Rico A, Boutiere C, et al. Comparison of the response to rituximab between myelin oligodendrocyte glycoprotein and Aquaporin-4 antibody diseases. *Ann Neurol*. 2020;87(2):256-266. doi:[10.1002/ana.25648](https://doi.org/10.1002/ana.25648)
33. Whittam DH, Cobo-Calvo A, Lopez-Chiriboga AS, et al. Treatment of MOG-IgG-associated disorder with rituximab: An international study of 121 patients. *Mult Scler Relat Disord*. 2020;44:102251. doi:[10.1016/j.msard.2020.102251](https://doi.org/10.1016/j.msard.2020.102251)
34. Barreras P, Vasileiou ES, Filippatou AG, et al. Long-term effectiveness and safety of rituximab in neuromyelitis optica spectrum disorder and MOG antibody disease. *Neurology*. 2022;99(22):e2504-e2516. doi:[10.1212/WNL.0000000000001260](https://doi.org/10.1212/WNL.0000000000001260)
35. Ringelstein M, Ayzenberg I, Lindenblatt G, et al. Interleukin-6 receptor blockade in treatment-refractory MOG-IgG-associated disease and Neuromyelitis Optica Spectrum disorders. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(1):e1100. doi:[10.1212/NXI.0000000000001100](https://doi.org/10.1212/NXI.0000000000001100)
36. Schirò G, Iacono S, Andolina M, Bianchi A, Ragonese P, Salemi G. Tocilizumab treatment in MOGAD: a case report and literature review. *Neurol Sci*. 2024;45(4):1429-1436. doi:[10.1007/s10072-023-07189-7](https://doi.org/10.1007/s10072-023-07189-7)
37. ClinicalTrials.gov. Study Details: A Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Satralizumab in Patients With Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. 2024. <https://www.clinicaltrials.gov/study/NCT05271409>
38. ClinicalTrials.gov. Study Details: A Study to Evaluate the Efficacy and Safety of Rozanolizumab in Adult Participants With Myelin Oligodendrocyte Glycoprotein (MOG) Antibody-associated Disease (MOG-AD). 2024. <https://www.clinicaltrials.gov/study/NCT05063162>
39. Cabrera-Maqueda JM, Sepulveda M, García RR, et al. CD19-directed CAR T-cells in a patient with refractory MOGAD: clinical and immunologic follow-up for 1 year. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(5):e200292. doi:[10.1212/NXI.000000000000200292](https://doi.org/10.1212/NXI.000000000000200292)
40. Prüss H. Autoantibodies in neurological disease. *Nat Rev Immunol*. 2021;21(12):798-813. doi:[10.1038/s41577-021-00543-w](https://doi.org/10.1038/s41577-021-00543-w)
41. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61(1):25-36. doi:[10.1002/ana.21050](https://doi.org/10.1002/ana.21050)
42. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7(12):1091-1098. doi:[10.1016/S1474-4422\(08\)70224-2](https://doi.org/10.1016/S1474-4422(08)70224-2)
43. Dalmau J, Armangué T, Planagumà J, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. *Lancet Neurol*. 2019;18(11):1045-1057. doi:[10.1016/S1474-4422\(19\)30244-3](https://doi.org/10.1016/S1474-4422(19)30244-3)
44. Bien CG, Vincent A, Barnett MH, et al. Immunopathology of autoantibody-associated encephalitis: clues for pathogenesis. *Brain J Neurol*. 2012;135(Pt 5):1622-1638. doi:[10.1093/brain/aww082](https://doi.org/10.1093/brain/aww082)
45. Malviya M, Barman S, Golombek KS, et al. NMDAR encephalitis: passive transfer from man to mouse by a recombinant antibody. *Ann Clin Transl Neurol*. 2017;4(11):768-783. doi:[10.1002/acn3.444](https://doi.org/10.1002/acn3.444)
46. Planagumà J, Leypoldt F, Mannara F, et al. Human N-methyl D-aspartate receptor antibodies alter memory and behaviour in mice. *Brain*. 2015;138(Pt 1):94-109. doi:[10.1093/brain/awu310](https://doi.org/10.1093/brain/awu310)
47. Moscato EH, Peng X, Jain A, Parsons TD, Dalmau J, Balice-Gordon RJ. Acute mechanisms underlying antibody effects in anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014;76(1):108-119. doi:[10.1002/ana.24195](https://doi.org/10.1002/ana.24195)
48. Kreye J, Wenke NK, Chayka M, et al. Human cerebrospinal fluid monoclonal N-methyl-D-aspartate receptor autoantibodies are sufficient for encephalitis pathogenesis. *Brain*. 2016;139(Pt 10):2641-2652. doi:[10.1093/brain/aww208](https://doi.org/10.1093/brain/aww208)
49. Jamet Z, Mergaux C, Meras M, et al. NMDA receptor autoantibodies primarily impair the extrasynaptic compartment. *Brain*. 2024;147(8):2745-2760. doi:[10.1093/brain/awae163](https://doi.org/10.1093/brain/awae163)
50. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013;12(2):157-165. doi:[10.1016/S1474-4422\(12\)70310-1](https://doi.org/10.1016/S1474-4422(12)70310-1)
51. Viacoz A, Desestret V, Ducray F, et al. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. *Neurology*. 2014;82(7):556-563. doi:[10.1212/WNL.0000000000000126](https://doi.org/10.1212/WNL.0000000000000126)
52. Nosadini M, Eyre M, Molteni E, et al. Use and safety of immunotherapeutic management of N-methyl-d-aspartate receptor antibody encephalitis: A meta-analysis. *JAMA Neurol*. 2021;78(11):1333-1344. doi:[10.1001/jamaneurol.2021.3188](https://doi.org/10.1001/jamaneurol.2021.3188)
53. Scheibe F, Prüss H, Mengel AM, et al. Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis. *Neurology*. 2017;88(4):366-370. doi:[10.1212/WNL.0000000000003536](https://doi.org/10.1212/WNL.0000000000003536)
54. Scheibe F, Ostendorf L, Reincke SM, et al. Daratumumab treatment for therapy-refractory anti-CASPR2 encephalitis. *J Neurol*. 2020;267(2):317-323. doi:[10.1007/s00415-019-09585-6](https://doi.org/10.1007/s00415-019-09585-6)
55. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lg1 antibody limbic encephalitis. *Ann Neurol*. 2011;69(5):892-900. doi:[10.1002/ana.22307](https://doi.org/10.1002/ana.22307)
56. Navarro V, Kas A, Apartis E, et al. Motor cortex and hippocampus are the two main cortical targets in LGI1-antibody encephalitis. *Brain*. 2016;139(Pt 4):1079-1093. doi:[10.1093/brain/aww012](https://doi.org/10.1093/brain/aww012)
57. Heine J, Prüss H, Kopp UA, et al. Beyond the limbic system: disruption and functional compensation of large-scale brain networks in patients with anti-LGI1 encephalitis. *J Neurol*

- Neurosurg Psychiatry*. 2018;89(11):1191-1199. doi:[10.1136/jnnp-2017-317780](#)
58. Fukata Y, Adesnik H, Iwanaga T, Bredt DS, Nicoll RA, Fukata M. Epilepsy-related ligand/receptor complex LGI1 and ADAM22 regulate synaptic transmission. *Science*. 2006;313(5794):1792-1795. doi:[10.1126/science.1129947](#)
 59. Petit-Pedrol M, Sell J, Planagumà J, et al. LGI1 antibodies alter Kv1.1 and AMPA receptors changing synaptic excitability, plasticity and memory. *Brain*. 2018;141(11):3144-3159. doi:[10.1093/brain/awy253](#)
 60. Ohkawa T, Fukata Y, Yamasaki M, et al. Autoantibodies to epilepsy-related LGI1 in limbic encephalitis neutralize LGI1-ADAM22 interaction and reduce synaptic AMPA receptors. *J Neurosci*. 2013;33(46):18161-18174. doi:[10.1523/JNEUROSCI.3506-13.2013](#)
 61. Yamagata A, Miyazaki Y, Yokoi N, et al. Structural basis of epilepsy-related ligand-receptor complex LGI1-ADAM22. *Nat Commun*. 2018;9(1):1546. doi:[10.1038/s41467-018-03947-w](#)
 62. Kornau HC, Kreye J, Stumpf A, et al. Human cerebrospinal fluid monoclonal LGI1 autoantibodies increase neuronal excitability. *Ann Neurol*. 2020;87(3):405-418. doi:[10.1002/ana.25666](#)
 63. Fukata Y, Chen X, Chiken S, et al. LGI1-ADAM22-MAGUK configures transsynaptic nanoalignment for synaptic transmission and epilepsy prevention. *Proc Natl Acad Sci USA*. 2021;118(3):e2022580118. doi:[10.1073/pnas.2022580118](#)
 64. Upadhyay M, Kirmann T, Wilson MA, et al. Peripherally-derived LGI1-reactive monoclonal antibodies cause epileptic seizures in vivo. *Brain*. 2024;147(8):2636-2642. doi:[10.1093/brain/awae129](#)
 65. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol*. 2014;13(3):276-286. doi:[10.1016/S1474-4422\(13\)70299-0](#)
 66. Spatola M, Petit-Pedrol M, Simabukuro MM, et al. Investigations in GABAA receptor antibody-associated encephalitis. *Neurology*. 2017;88(11):1012-1020. doi:[10.1212/WNL.0000000000003713](#)
 67. Pettingill P, Kramer HB, Coebergh JA, et al. Antibodies to GABAA receptor $\alpha 1$ and $\gamma 2$ subunits: clinical and serologic characterization. *Neurology*. 2015;84(12):1233-1241. doi:[10.1212/WNL.0000000000001326](#)
 68. Ohkawa T, Satake S, Yokoi N, et al. Identification and characterization of GABA(A) receptor autoantibodies in autoimmune encephalitis. *J Neurosci*. 2014;34(24):8151-8163. doi:[10.1523/JNEUROSCI.4415-13.2014](#)
 69. Kreye J, Wright SK, van Casteren A, et al. Encephalitis patient-derived monoclonal GABAA receptor antibodies cause epileptic seizures. *J Exp Med*. 2021;218(11):e20210012. doi:[10.1084/jem.20210012](#)
 70. Brändle SM, Cerina M, Weber S, et al. Cross-reactivity of a pathogenic autoantibody to a tumor antigen in GABAA receptor encephalitis. *Proc Natl Acad Sci USA*. 2021;118(9):e1916337118. doi:[10.1073/pnas.1916337118](#)
 71. Noviello CM, Kreye J, Teng J, Prüss H, Hibbs RE. Structural mechanisms of GABAA receptor autoimmune encephalitis. *Cell*. 2022;185(14):2469-2477.e13. doi:[10.1016/j.cell.2022.06.025](#)
 72. Duan T, Smith AJ, Verkman AS. Complement-dependent bystander injury to neurons in AQP4-IgG seropositive neuromyelitis optica. *J Neuroinflammation*. 2018;15(1):294. doi:[10.1186/s12974-018-1333-z](#)
 73. Ratelade J, Bennett JL, Verkman AS. Intravenous neuromyelitis optica autoantibody in mice targets aquaporin-4 in peripheral organs and area postrema. *PLoS One*. 2011;6(11):e27412. doi:[10.1371/journal.pone.0027412](#)
 74. Asavapanumas N, Ratelade J, Verkman AS. Unique neuromyelitis optica pathology produced in naïve rats by intracerebral administration of NMO-IgG. *Acta Neuropathol*. 2014;127(4):539-551. doi:[10.1007/s00401-013-1204-8](#)
 75. Höftberger R, Guo Y, Flanagan EP, et al. The pathology of central nervous system inflammatory demyelinating disease accompanying myelin oligodendrocyte glycoprotein autoantibody. *Acta Neuropathol*. 2020;139(5):875-892. doi:[10.1007/s00401-020-02132-y](#)
 76. Brilot F, Dale RC, Selter RC, et al. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. *Ann Neurol*. 2009;66(6):833-842. doi:[10.1002/ana.21916](#)
 77. Peschl P, Schanda K, Zeka B, et al. Human antibodies against the myelin oligodendrocyte glycoprotein can cause complement-dependent demyelination. *J Neuroinflammation*. 2017;14(1):208. doi:[10.1186/s12974-017-0984-5](#)
 78. Vidarsson G, Dekkers G, Rispen T. IgG subclasses and allotypes: from structure to effector functions. *Front Immunol*. 2014;5:520. doi:[10.3389/fimmu.2014.00520](#)
 79. Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci*. 2010;30(17):5866-5875. doi:[10.1523/JNEUROSCI.0167-10.2010](#)
 80. Haselmann H, Mannara F, Werner C, et al. Human autoantibodies against the AMPA receptor subunit GluA2 induce receptor reorganization and memory dysfunction. *Neuron*. 2018;100(1):91-105. doi:[10.1016/j.neuron.2018.07.048](#)
 81. Spatola M, Sabater L, Planagumà J, et al. Encephalitis with mGluR5 antibodies: symptoms and antibody effects. *Neurology*. 2018;90(22):e1964-e1972. doi:[10.1212/WNL.0000000000005614](#)
 82. Sk W, Re R, Ma W, et al. Multimodal electrophysiological analyses reveal that reduced synaptic excitatory neurotransmission underlies seizures in a model of NMDAR antibody-mediated encephalitis. *Commun Biol*. 2021;4(1):1106. doi:[10.1038/s42003-021-02635-8](#)
 83. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol*. 2009;65(4):424-434. doi:[10.1002/ana.21589](#)
 84. Ramberger M, Berretta A, Tan JMM, et al. Distinctive binding properties of human monoclonal LGI1 autoantibodies determine pathogenic mechanisms. *Brain*. 2020;143(6):1731-1745. doi:[10.1093/brain/awaa104](#)
 85. Chan KH, Lachance DH, Harper CM, Lennon VA. Frequency of seronegativity in adult-acquired generalized myasthenia gravis. *Muscle Nerve*. 2007;36(5):651-658. doi:[10.1002/mus.20854](#)
 86. McConville J, Farrugia ME, Beeson D, et al. Detection and characterization of MuSK antibodies in seronegative myasthenia gravis. *Ann Neurol*. 2004;55(4):580-584. doi:[10.1002/ana.20061](#)
 87. Huijbers MG, Vergoossen DL, Fillié-Grijpma YE, et al. MuSK myasthenia gravis monoclonal antibodies: Valency dictates pathogenicity. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(3):e547. doi:[10.1212/NXI.0000000000000547](#)
 88. Takata K, Stathopoulos P, Cao M, et al. Characterization of pathogenic monoclonal autoantibodies derived from muscle-specific kinase myasthenia gravis patients. *JCI Insight*. 2019;4:127167. doi:[10.1172/jci.insight.127167](#)
 89. Marquetand J, van Lessen M, Bender B, et al. Slowly progressive LGI1 encephalitis with isolated late-onset cognitive dysfunction: a treatable mimic of Alzheimer's disease. *Eur J Neurol*. 2016;23(5):e28-e29. doi:[10.1111/ene.12939](#)
 90. Prüss H, Hölte M, Maier N, et al. IgA NMDA receptor antibodies are markers of synaptic immunity in slow cognitive impairment. *Neurology*. 2012;78(22):1743-1753. doi:[10.1212/WNL.0b013e318258300d](#)
 91. Doss S, Wandinger KP, Hyman BT, et al. High prevalence of NMDA receptor IgA/IgM antibodies in different dementia types. *Ann Clin Transl Neurol*. 2014;1(10):822-832. doi:[10.1002/acn3.120](#)
 92. Bastiaans AEM, van Steenhoven RW, Te Vaarwerk ES, et al. Antibodies associated with autoimmune encephalitis in

- patients with presumed neurodegenerative dementia. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(5):e200137. doi:[10.1212/NXI.000000000200137](https://doi.org/10.1212/NXI.000000000200137)
93. Busse S, Brix B, Kunschmann R, Bogerts B, Stoecker W, Busse M. N-methyl-D-aspartate glutamate receptor (NMDA-R) antibodies in mild cognitive impairment and dementias. *Neurosci Res*. 2014;85:58-64. doi:[10.1016/j.neures.2014.06.002](https://doi.org/10.1016/j.neures.2014.06.002)
 94. Westman G, Sohrabian A, Aurelius E, et al. Clinical significance of IgM and IgA class anti-NMDAR antibodies in herpes simplex encephalitis. *J Clin Virol*. 2018;103:75-80. doi:[10.1016/j.jcv.2018.04.007](https://doi.org/10.1016/j.jcv.2018.04.007)
 95. Wallukat G, Prüss H, Müller J, Schimke I. Functional autoantibodies in patients with different forms of dementia. *PLoS One*. 2018;13(3):e0192778. doi:[10.1371/journal.pone.0192778](https://doi.org/10.1371/journal.pone.0192778)
 96. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol*. 2014;13(6):575-586. doi:[10.1016/S1474-4422\(14\)70051-1](https://doi.org/10.1016/S1474-4422(14)70051-1)
 97. Gaig C, Graus F, Compta Y, et al. Clinical manifestations of the anti-IgLON5 disease. *Neurology*. 2017;88(18):1736-1743. doi:[10.1212/WNL.0000000000003887](https://doi.org/10.1212/WNL.0000000000003887)
 98. Landa J, Gaig C, Plagumà J, et al. Effects of IgLON5 antibodies on neuronal cytoskeleton: A link between autoimmunity and neurodegeneration. *Ann Neurol*. 2020;88(5):1023-1027. doi:[10.1002/ana.25857](https://doi.org/10.1002/ana.25857)
 99. Gelpi E, Höftberger R, Graus F, et al. Neuropathological criteria of anti-IgLON5-related tauopathy. *Acta Neuropathol*. 2016;132(4):531-543. doi:[10.1007/s00401-016-1591-8](https://doi.org/10.1007/s00401-016-1591-8)
 100. Berger-Sieczkowski E, Endmayr V, Haider C, et al. Analysis of inflammatory markers and tau deposits in an autopsy series of nine patients with anti-IgLON5 disease. *Acta Neuropathol*. 2023;146(4):631-645. doi:[10.1007/s00401-023-02625-6](https://doi.org/10.1007/s00401-023-02625-6)
 101. Grüter T, Möllers FE, Tietz A, et al. Clinical, serological and genetic predictors of response to immunotherapy in anti-IgLON5 disease. *Brain*. 2023;146(2):600-611. doi:[10.1093/brain/awac090](https://doi.org/10.1093/brain/awac090)
 102. Lennox BR, Palmer-Cooper EC, Pollak T, et al. Prevalence and clinical characteristics of serum neuronal cell surface antibodies in first-episode psychosis: a case-control study. *Lancet Psychiatry*. 2017;4(1):42-48. doi:[10.1016/S2215-0366\(16\)30375-3](https://doi.org/10.1016/S2215-0366(16)30375-3)
 103. Endres D, Pankratz B, Robinson T, et al. Autoimmune obsessive-compulsive disorder with novel anti-CNS autoantibodies in cerebrospinal fluid. *Mol Psychiatry*. 2022;27:3926-3928. doi:[10.1038/s41380-022-01688-3](https://doi.org/10.1038/s41380-022-01688-3)
 104. Pollak TA, Lennox BR, Müller S, et al. Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. *Lancet Psychiatry*. 2020;7(1):93-108. doi:[10.1016/S2215-0366\(19\)30290-1](https://doi.org/10.1016/S2215-0366(19)30290-1)
 105. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat Neurosci*. 2015;18(2):199-209. doi:[10.1038/nn.3922](https://doi.org/10.1038/nn.3922)
 106. Gandal MJ, Haney JR, Parikshak NN, et al. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *Science*. 2018;359(6376):693-697. doi:[10.1126/science.aad6469](https://doi.org/10.1126/science.aad6469)
 107. Mongan D, Föcking M, Healy C, et al. Development of proteomic prediction models for transition to psychotic disorder in the clinical high-risk State and psychotic experiences in adolescence. *JAMA Psychiatry*. 2021;78(1):77-90. doi:[10.1001/jamapsychiatry.2020.2459](https://doi.org/10.1001/jamapsychiatry.2020.2459)
 108. Benros ME, Eaton WW, Mortensen PB. The epidemiologic evidence linking autoimmune diseases and psychosis. *Biol Psychiatry*. 2014;75(4):300-306. doi:[10.1016/j.biopsych.2013.09.023](https://doi.org/10.1016/j.biopsych.2013.09.023)
 109. Cullen AE, Holmes S, Pollak TA, et al. Associations between non-neurological autoimmune disorders and psychosis: A meta-analysis. *Biol Psychiatry*. 2019;85(1):35-48. doi:[10.1016/j.biopsych.2018.06.016](https://doi.org/10.1016/j.biopsych.2018.06.016)
 110. Jernbom Falk A, Galletly C, Just D, et al. Autoantibody profiles associated with clinical features in psychotic disorders. *Transl Psychiatry*. 2021;11(1):474. doi:[10.1038/s41398-021-01596-0](https://doi.org/10.1038/s41398-021-01596-0)
 111. Pollak TA, Beck K, Irani SR, Howes OD, David AS, McGuire PK. Autoantibodies to central nervous system neuronal surface antigens: psychiatric symptoms and psychopharmacological implications. *Psychopharmacology*. 2016;233(9):1605-1621. doi:[10.1007/s00213-015-4156-y](https://doi.org/10.1007/s00213-015-4156-y)
 112. Endres D, Meixensberger S, Dersch R, et al. Cerebrospinal fluid, antineuronal autoantibody, EEG, and MRI findings from 992 patients with schizophreniform and affective psychosis. *Transl Psychiatry*. 2020;10(1):279. doi:[10.1038/s41398-020-00967-3](https://doi.org/10.1038/s41398-020-00967-3)
 113. Endres D, Prüss H, Dressing A, et al. Psychiatric manifestation of anti-LG11 encephalitis. *Brain Sci*. 2020;10(6):375. doi:[10.3390/brainsci10060375](https://doi.org/10.3390/brainsci10060375)
 114. Al-Diwani A, Handel A, Townsend L, et al. The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data. *Lancet Psychiatry*. 2019;6(3):235-246. doi:[10.1016/S2215-0366\(19\)30001-X](https://doi.org/10.1016/S2215-0366(19)30001-X)
 115. Ariño H, Coutinho E, Pollak TA, Stewart R. Real-world experience of assessing antibodies against the N-methyl-D-aspartate receptor (NMDAR-IgG) in psychiatric patients. A retrospective single-centre study. *Brain Behav Immun*. 2021;98:330-336. doi:[10.1016/j.bbi.2021.08.233](https://doi.org/10.1016/j.bbi.2021.08.233)
 116. Finke C, Kopp UA, Prüss H, Dalmau J, Wandinger KP, Ploner CJ. Cognitive deficits following anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry*. 2012;83(2):195-198. doi:[10.1136/jnnp-2011-300411](https://doi.org/10.1136/jnnp-2011-300411)
 117. Arinrad S, Wilke JBH, Seelbach A, et al. NMDAR1 autoantibodies amplify behavioral phenotypes of genetic white matter inflammation: a mild encephalitis model with neuropsychiatric relevance. *Mol Psychiatry*. 2022;27(12):4974-4983. doi:[10.1038/s41380-021-01392-8](https://doi.org/10.1038/s41380-021-01392-8)
 118. Espana A, Seth H, Jézéquel J, et al. Alteration of NMDA receptor trafficking as a cellular hallmark of psychosis. *Transl Psychiatry*. 2021;11(1):444. doi:[10.1038/s41398-021-01549-7](https://doi.org/10.1038/s41398-021-01549-7)
 119. Pollak TA, McCormack R, Peakman M, Nicholson TR, David AS. Prevalence of anti-N-methyl-D-aspartate (NMDA) receptor [corrected] antibodies in patients with schizophrenia and related psychoses: a systematic review and meta-analysis. *Psychol Med*. 2014;44(12):2475-2487. doi:[10.1017/S003329171300295X](https://doi.org/10.1017/S003329171300295X)
 120. Gaughan F, Lally J, Beck K, et al. Brain-relevant antibodies in first-episode psychosis: a matched case-control study. *Psychol Med*. 2018;48(8):1257-1263. doi:[10.1017/S0033291717002689](https://doi.org/10.1017/S0033291717002689)
 121. Prüss H, Finke C, Hölting M, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol*. 2012;72(6):902-911. doi:[10.1002/ana.23689](https://doi.org/10.1002/ana.23689)
 122. Armangue T, Spatola M, Vlagea A, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol*. 2018;17(9):760-772. doi:[10.1016/S1474-4422\(18\)30244-8](https://doi.org/10.1016/S1474-4422(18)30244-8)
 123. Nosadini M, Mohammad SS, Corazza F, et al. Herpes simplex virus-induced anti-N-methyl-D-aspartate receptor encephalitis: a systematic literature review with analysis of 43 cases. *Dev Med Child Neurol*. 2017;59(8):796-805. doi:[10.1111/dmcn.13448](https://doi.org/10.1111/dmcn.13448)
 124. Salovin A, Glanzman J, Roslin K, Armangue T, Lynch DR, Panzer JA. Anti-NMDA receptor encephalitis and nonencephalitic HSV-1 infection. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(4):e458. doi:[10.1212/NXI.0000000000000458](https://doi.org/10.1212/NXI.0000000000000458)
 125. Pa P, Jin J, Matharu K, et al. Anti-NMDAR encephalitis with concomitant varicella zoster virus detection and nonteratoma malignancy. *Neurol Neuroimmunol Neuroinflamm*. 2018;6(2):e537. doi:[10.1212/NXI.0000000000000537](https://doi.org/10.1212/NXI.0000000000000537)

126. Schäbitz WR, Rogalewski A, Hagemeister C, Bien CG. VZV brainstem encephalitis triggers NMDA receptor immunoreaction. *Neurology*. 2014;83(24):2309-2311. doi:[10.1212/WNL.0000000000001072](https://doi.org/10.1212/WNL.0000000000001072)
127. Solís N, Salazar L, Hasbun R. Anti-NMDA receptor antibody encephalitis with concomitant detection of varicella zoster virus. *J Clin Virol*. 2016;83:26-28. doi:[10.1016/j.jcv.2016.08.292](https://doi.org/10.1016/j.jcv.2016.08.292)
128. Ma J, Zhang T, Jiang L. Japanese encephalitis can trigger anti-N-methyl-D-aspartate receptor encephalitis. *J Neurol*. 2017;264(6):1127-1131. doi:[10.1007/s00415-017-8501-4](https://doi.org/10.1007/s00415-017-8501-4)
129. Frank JC, Song BH, Lee YM. Japanese encephalitis virus-induced anti-N-methyl-D-aspartate receptor encephalitis: A case report and review of literature. *Neuropediatrics*. 2019;50(2):111-115. doi:[10.1055/s-0038-1675607](https://doi.org/10.1055/s-0038-1675607)
130. Pastel H, Chakrabarty B, Saini L, Kumar A, Gulati S. A case of anti-N-methyl-D-aspartate (NMDA) receptor encephalitis possibly triggered by an episode of Japanese B encephalitis. *Neurol India*. 2017;65(4):895-897. doi:[10.4103/neuroindia.NI_340_16](https://doi.org/10.4103/neuroindia.NI_340_16)
131. Herrera-Mora P, Munive-Baez L, Ruiz García M, et al. Anti-N-methyl-D-aspartate receptor encephalitis: An observational and comparative study in Mexican children and adults. *Clin Neurol Neurosurg*. 2021;210:106986. doi:[10.1016/j.clineuro.2021.106986](https://doi.org/10.1016/j.clineuro.2021.106986)
132. Haneche F, Demeret S, Psimaras D, Katlama C, Pourcher V. An anti-NMDA receptor encephalitis mimicking an HIV encephalitis. *Clin Immunol*. 2018;193:10-11. doi:[10.1016/j.clim.2018.05.003](https://doi.org/10.1016/j.clim.2018.05.003)
133. Goenka A, Jain V, Nariai H, Spiro A, Steinschneider M. Extended clinical Spectrum of anti-N-methyl-d-aspartate receptor encephalitis in children: A Case series. *Pediatr Neurol*. 2017;72:51-55. doi:[10.1016/j.pediatrneurol.2017.03.010](https://doi.org/10.1016/j.pediatrneurol.2017.03.010)
134. Cavaliere E, Nosadini M, Pelizza MF, Ventura G, Toldo I, Sartori S. Anti-NMDAR encephalitis preceded by non-herpetic central nervous system infection: systematic literature review and first case of tick-borne encephalitis triggering anti-NMDAR encephalitis. *J Neuroimmunol*. 2019;332:1-7. doi:[10.1016/j.jneuroim.2019.03.011](https://doi.org/10.1016/j.jneuroim.2019.03.011)
135. Peng Y, Liu X, Pan S, Xie Z, Wang H. Anti-N-methyl-D-aspartate receptor encephalitis associated with intracranial *Angiostrongylus cantonensis* infection: a case report. *Neurol Sci*. 2017;38(4):703-706. doi:[10.1007/s10072-016-2718-3](https://doi.org/10.1007/s10072-016-2718-3)
136. Mohammad SS, Sinclair K, Pillai S, et al. Herpes simplex encephalitis relapse with chorea is associated with autoantibodies to N-methyl-D-aspartate receptor or dopamine-2 receptor. *Mov Disord*. 2014;29(1):117-122. doi:[10.1002/mds.25623](https://doi.org/10.1002/mds.25623)
137. Franke C, Ferse C, Kreye J, et al. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. *Brain Behav Immun*. 2021;93:415-419. doi:[10.1016/j.bbi.2020.12.022](https://doi.org/10.1016/j.bbi.2020.12.022)
138. Kreye J, Reincke SM, Kornau HC, et al. A therapeutic non-self-reactive SARS-CoV-2 antibody protects from lung pathology in a COVID-19 hamster model. *Cell*. 2020;183(4):1058-1069. doi:[10.1016/j.cell.2020.09.049](https://doi.org/10.1016/j.cell.2020.09.049)
139. Franke C, Boesl F, Goeraci Y, et al. Association of cerebrospinal fluid brain-binding autoantibodies with cognitive impairment in post-COVID-19 syndrome. *Brain Behav Immun*. 2023;109:139-143. doi:[10.1016/j.bbi.2023.01.006](https://doi.org/10.1016/j.bbi.2023.01.006)
140. Santos Guedes de Sa K, Silva J, Bayarri-Olmos R, et al. A causal link between autoantibodies and neurological symptoms in long COVID. *medRxiv*. 2024. doi:[10.1101/2024.06.18.24309100](https://doi.org/10.1101/2024.06.18.24309100)
141. Ray SK, Putterman C, Diamond B. Pathogenic autoantibodies are routinely generated during the response to foreign antigen: a paradigm for autoimmune disease. *Proc Natl Acad Sci USA*. 1996;93(5):2019-2024. doi:[10.1073/pnas.93.5.2019](https://doi.org/10.1073/pnas.93.5.2019)
142. Yang G, Holl TM, Liu Y, et al. Identification of autoantigens recognized by the 2F5 and 4E10 broadly neutralizing HIV-1 antibodies. *J Exp Med*. 2013;210(2):241-256. doi:[10.1084/jem.20121977](https://doi.org/10.1084/jem.20121977)
143. Wardemann H, Yurasov S, Schaefer A, Young JW, Meffre E, Nussenzweig MC. Predominant autoantibody production by early human B cell precursors. *Science*. 2003;301(5638):1374-1377. doi:[10.1126/science.1086907](https://doi.org/10.1126/science.1086907)
144. Reed JH, Jackson J, Christ D, Goodnow CC. Clonal redemption of autoantibodies by somatic hypermutation away from self-reactivity during human immunization. *J Exp Med*. 2016;213(7):1255-1265. doi:[10.1084/jem.20151978](https://doi.org/10.1084/jem.20151978)
145. Kreer C, Zehner M, Weber T, et al. Longitudinal isolation of potent near-germline SARS-CoV-2-neutralizing antibodies from COVID-19 patients. *Cell*. 2020;182(4):843-854.e12. doi:[10.1016/j.cell.2020.06.044](https://doi.org/10.1016/j.cell.2020.06.044)
146. Johnston BP, McCormick C. Herpesviruses and the unfolded protein response. *Viruses*. 2019;12(1):17. doi:[10.3390/v12010017](https://doi.org/10.3390/v12010017)
147. Reincke SM, Prüss H, Kreye J. Brain antibody sequence evaluation (BASE): an easy-to-use software for complete data analysis in single cell immunoglobulin cloning. *BMC Bioinformatics*. 2020;21(1):446. doi:[10.1186/s12859-020-03741-w](https://doi.org/10.1186/s12859-020-03741-w)
148. van Hoof S, Kreye J, Cordero-Gómez C, et al. Human cerebrospinal fluid monoclonal CASPR2 autoantibodies induce changes in electrophysiology, functional MRI, and behavior in rodent models. *Brain Behav Immun*. 2024;122:266-278. doi:[10.1016/j.bbi.2024.08.027](https://doi.org/10.1016/j.bbi.2024.08.027)
149. Theorell J, Harrison R, Williams R, et al. Ultrahigh frequencies of peripherally matured LGI1- and CASPR2-reactive B cells characterize the cerebrospinal fluid in autoimmune encephalitis. *Proc Natl Acad Sci USA*. 2024;121(7):e2311049121. doi:[10.1073/pnas.2311049121](https://doi.org/10.1073/pnas.2311049121)
150. Vazquez SE, Mann SA, Bodansky A, et al. Autoantibody discovery across monogenic, acquired, and COVID-19-associated autoimmunity with scalable PhIP-seq. *elife*. 2022;11:e78550. doi:[10.7554/eLife.78550](https://doi.org/10.7554/eLife.78550)
151. Arlt FA, Breuer A, Trampenau E, et al. High serum prevalence of autoreactive IgG antibodies against peripheral nerve structures in patients with neurological post-COVID-19 vaccination syndrome. *Front Immunol*. 2024;15:1404800. doi:[10.3389/fimmu.2024.1404800](https://doi.org/10.3389/fimmu.2024.1404800)
152. Royle G, Fokou TJ, Chunder R, et al. Antibodies against neural antigens in patients with acute stroke: joint results of three independent cohort studies. *J Neurol*. 2019;266(11):2772-2779. doi:[10.1007/s00415-019-09470-2](https://doi.org/10.1007/s00415-019-09470-2)
153. Zerche M, Weissenborn K, Ott C, et al. Preexisting serum autoantibodies against the NMDAR subunit NR1 modulate evolution of lesion size in acute ischemic stroke. *Stroke*. 2015;46(5):1180-1186. doi:[10.1161/STROKEAHA.114.008323](https://doi.org/10.1161/STROKEAHA.114.008323)
154. Castillo-Gomez E, Kästner A, Steiner J, et al. The brain as immunoprecipitator of serum autoantibodies against N-methyl-D-aspartate receptor subunit NR1. *Ann Neurol*. 2016;79(1):144-151. doi:[10.1002/ana.24545](https://doi.org/10.1002/ana.24545)
155. Dahm L, Ott C, Steiner J, et al. Seroprevalence of autoantibodies against brain antigens in health and disease. *Ann Neurol*. 2014;76(1):82-94. doi:[10.1002/ana.24189](https://doi.org/10.1002/ana.24189)
156. Steiner J, Teegen B, Schiltz K, Bernstein HG, Stoecker W, Bogerts B. Prevalence of N-methyl-D-aspartate receptor autoantibodies in the peripheral blood: healthy control samples revisited. *JAMA Psychiatry*. 2014;71(7):838-839. doi:[10.1001/jamapsychiatry.2014.469](https://doi.org/10.1001/jamapsychiatry.2014.469)
157. Sperber PS, Siegerink B, Huo S, et al. Serum anti-NMDA (N-methyl-D-aspartate)-receptor antibodies and long-term clinical outcome after stroke (PROSCIS-B). *Stroke*. 2019;50(11):3213-3219. doi:[10.1161/STROKEAHA.119.026100](https://doi.org/10.1161/STROKEAHA.119.026100)
158. Sperber PS, Gebert P, Broersen LHA, et al. Serum anti-NMDA-receptor antibodies and cognitive function after ischemic stroke (PROSCIS-B). *J Neurol*. 2022;269(10):5521-5530. doi:[10.1007/s00415-022-11203-x](https://doi.org/10.1007/s00415-022-11203-x)

159. Deutsch NR, Worthmann H, Steixner-Kumar AA, et al. Autoantibodies against the NMDAR subunit NR1 are associated with neuropsychiatric outcome after ischemic stroke. *Brain Behav Immun*. 2021;96:73-79. doi:[10.1016/j.bbi.2021.05.011](https://doi.org/10.1016/j.bbi.2021.05.011)
160. Finke C, Bartels F, Lütt A, Prüss H, Harms L. High prevalence of neuronal surface autoantibodies associated with cognitive deficits in cancer patients. *J Neurol*. 2017;264(9):1968-1977. doi:[10.1007/s00415-017-8582-0](https://doi.org/10.1007/s00415-017-8582-0)
161. Bartels F, Strönisch T, Farmer K, Rentzsch K, Kiecker F, Finke C. Neuronal autoantibodies associated with cognitive impairment in melanoma patients. *Ann Oncol*. 2019;30(5):823-829. doi:[10.1093/annonc/mdz083](https://doi.org/10.1093/annonc/mdz083)
162. Bartels F, Wandrey MM, Aigner A, et al. Association between neuronal autoantibodies and cognitive impairment in patients with lung cancer. *JAMA Oncol*. 2021;7(9):1302-1310. doi:[10.1001/jamaoncol.2021.2049](https://doi.org/10.1001/jamaoncol.2021.2049)
163. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol*. 2012;2012:985646. doi:[10.1155/2012/985646](https://doi.org/10.1155/2012/985646)
164. Kowal C, Athanassiou A, Chen H, Diamond B. Maternal antibodies and developing blood-brain barrier. *Immunol Res*. 2015;63:18-25. doi:[10.1007/s12026-015-8714-5](https://doi.org/10.1007/s12026-015-8714-5)
165. Allen NM, O'Rahelly M, Eymard B, et al. The emerging spectrum of fetal acetylcholine receptor antibody-related disorders (FARAD). *Brain*. 2023;146(10):4233-4246. doi:[10.1093/brain/awad153](https://doi.org/10.1093/brain/awad153)
166. Barnes PR, Kanabar DJ, Brueton L, et al. Recurrent congenital arthrogryposis leading to a diagnosis of myasthenia gravis in an initially asymptomatic mother. *Neuromuscul Disord*. 1995;5(1):59-65. doi:[10.1016/0960-8966\(94\)e0029-8](https://doi.org/10.1016/0960-8966(94)e0029-8)
167. Hacohen Y, Jacobson LW, Byrne S, et al. Fetal acetylcholine receptor inactivation syndrome: a myopathy due to maternal antibodies. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(1):e57. doi:[10.1212/NXI.0000000000000057](https://doi.org/10.1212/NXI.0000000000000057)
168. Bagnall-Moreau C, Spielman B, Brimberg L. Maternal brain reactive antibodies profile in autism spectrum disorder: an update. *Transl Psychiatry*. 2023;13(1):37. doi:[10.1038/s41398-023-02335-3](https://doi.org/10.1038/s41398-023-02335-3)
169. Brimberg L, Sadiq A, Gregersen PK, Diamond B. Brain-reactive IgG correlates with autoimmunity in mothers of a child with an autism spectrum disorder. *Mol Psychiatry*. 2013;18(11):1171-1177. doi:[10.1038/mp.2013.101](https://doi.org/10.1038/mp.2013.101)
170. Ramirez-Celis A, Becker M, Nuño M, Schauer J, Aghaeepour N, Van de Water J. Risk assessment analysis for maternal autoantibody-related autism (MAR-ASD): a subtype of autism. *Mol Psychiatry*. 2021;26(5):1551-1560. doi:[10.1038/s41380-020-00998-8](https://doi.org/10.1038/s41380-020-00998-8)
171. Braunschweig D, Golub MS, Koenig CM, et al. Maternal autism-associated IgG antibodies delay development and produce anxiety in a mouse gestational transfer model. *J Neuroimmunol*. 2012;252(1-2):56-65. doi:[10.1016/j.jneuroim.2012.08.002](https://doi.org/10.1016/j.jneuroim.2012.08.002)
172. Bauman MD, Iosif AM, Ashwood P, et al. Maternal antibodies from mothers of children with autism alter brain growth and social behavior development in the rhesus monkey. *Transl Psychiatry*. 2013;3(7):e278. doi:[10.1038/tp.2013.47](https://doi.org/10.1038/tp.2013.47)
173. Bruce MR, Couch ACM, Grant S, et al. Altered behavior, brain structure, and neurometabolites in a rat model of autism-specific maternal autoantibody exposure. *Mol Psychiatry*. 2023;28(5):2136-2147. doi:[10.1038/s41380-023-02020-3](https://doi.org/10.1038/s41380-023-02020-3)
174. Lee JY, Huerta PT, Zhang J, et al. Neurotoxic autoantibodies mediate congenital cortical impairment of offspring in maternal lupus. *Nat Med*. 2009;15(1):91-96. doi:[10.1038/nm.1892](https://doi.org/10.1038/nm.1892)
175. Mader S, Brimberg L, Vo A, et al. In utero exposure to maternal anti-aquaporin-4 antibodies alters brain vasculature and neural dynamics in male mouse offspring. *Sci Transl Med*. 2022;14:eabe9726. doi:[10.1126/scitranslmed.abe9726](https://doi.org/10.1126/scitranslmed.abe9726)
176. Bagnall-Moreau C, Huerta PT, Comoletti D, et al. In utero exposure to endogenous maternal polyclonal anti-Caspr2 antibody leads to behavioral abnormalities resembling autism spectrum disorder in male mice. *Sci Rep*. 2020;10(1):14446. doi:[10.1038/s41598-020-71201-9](https://doi.org/10.1038/s41598-020-71201-9)
177. Büniger I, Makridis KL, Kreye J, et al. Maternal synapsin autoantibodies are associated with neurodevelopmental delay. *Front Immunol*. 2023;14:1101087. doi:[10.3389/fimmu.2023.1101087](https://doi.org/10.3389/fimmu.2023.1101087)
178. Büniger I, Talucci I, Kreye J, et al. Synapsin autoantibodies during pregnancy are associated with fetal abnormalities. *Brain Behav Immun Health*. 2023;33:100678. doi:[10.1016/j.bbih.2023.100678](https://doi.org/10.1016/j.bbih.2023.100678)
179. Jurek B, Chayka M, Kreye J, et al. Human gestational N-methyl-D-aspartate receptor autoantibodies impair neonatal murine brain function. *Ann Neurol*. 2019;86(5):656-670. doi:[10.1002/ana.25552](https://doi.org/10.1002/ana.25552)
180. Lang K, Prüss H. Frequencies of neuronal autoantibodies in healthy controls: estimation of disease specificity. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(5):e386. doi:[10.1212/NXI.0000000000000386](https://doi.org/10.1212/NXI.0000000000000386)
181. Daguano Gastaldi V, Bh Wilke J, Weidinger CA, et al. Factors predisposing to humoral autoimmunity against brain-antigens in health and disease: analysis of 49 autoantibodies in over 7000 subjects. *Brain Behav Immun*. 2023;108:135-147. doi:[10.1016/j.bbi.2022.10.016](https://doi.org/10.1016/j.bbi.2022.10.016)
182. Lövheim H, Norman T, Weidung B, et al. Herpes simplex virus, APOE4, and cognitive decline in old age: results from the Betula cohort study. *J Alzheimers Dis*. 2019;67(1):211-220. doi:[10.3233/JAD-171162](https://doi.org/10.3233/JAD-171162)
183. Athanasiou E, Gargalionis AN, Anastassopoulou C, Tsakris A, Boufidou F. New insights into the molecular interplay between human herpesviruses and Alzheimer's disease-A Narrative Review. *Brain Sci*. 2022;12(8):1010. doi:[10.3390/brainsci12081010](https://doi.org/10.3390/brainsci12081010)
184. Taquet M, Dercon Q, Todd JA, Harrison PJ. The recombinant shingles vaccine is associated with lower risk of dementia. *Nat Med*. 2024;30(10):2777-2781. doi:[10.1038/s41591-024-03201-5](https://doi.org/10.1038/s41591-024-03201-5)
185. Zhang Y, Liu D, Zhang Z, et al. Bispecific BCMA/CD19 targeted CAR-T cell therapy forces sustained disappearance of symptoms and anti-acetylcholine receptor antibodies in refractory myasthenia gravis: a case report. *J Neurol*. 2024;271:2655-4659. doi:[10.1007/s00415-024-12367-4](https://doi.org/10.1007/s00415-024-12367-4)
186. Qin C, Tian DS, Zhou LQ, et al. Anti-BCMA CAR T-cell therapy CT103A in relapsed or refractory AQP4-IgG seropositive neuromyelitis optica spectrum disorders: phase 1 trial interim results. *Signal Transduct Target Ther*. 2023;8(1):5. doi:[10.1038/s41392-022-01278-3](https://doi.org/10.1038/s41392-022-01278-3)
187. Reincke SM, von Wardenburg N, Homeyer MA, et al. Chimeric autoantibody receptor T cells deplete NMDA receptor-specific B cells. *Cell*. 2023;186:5084-5097. doi:[10.1016/j.cell.2023.10.001](https://doi.org/10.1016/j.cell.2023.10.001)
188. Oh S, Mao X, Manfredo-Vieira S, et al. Precision targeting of autoantigen-specific B cells in muscle-specific tyrosine kinase myasthenia gravis with chimeric autoantibody receptor T cells. *Nat Biotechnol*. 2023;41:1229-1238. doi:[10.1038/s41587-022-01637-z](https://doi.org/10.1038/s41587-022-01637-z)

How to cite this article: Li LY, Keles A, Homeyer MA, Prüss H. Antibodies in neurological diseases: Established, emerging, explorative. *Immunol Rev*. 2024;328:283-299. doi:[10.1111/imr.13405](https://doi.org/10.1111/imr.13405)