# Autoimmune seizures and epilepsy

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The rapid expansion in the number of encephalitis disorders associated with autoantibodies against neuronal proteins has led to an incremental increase in use of the term "autoimmune epilepsy," yet has occurred with limited attention to the physiopathology of each disease and genuine propensity to develop epilepsy. Indeed, most autoimmune encephalitides present with seizures, but the probability of evolving to epilepsy is relatively small. The risk of epilepsy is higher for disorders in which the antigens are intracellular (often T cell–mediated) compared with disorders in which the antigens are on the cell surface (antibody-mediated). Most autoantibodies against neuronal surface antigens show robust effects on the target proteins, resulting in hyperexcitability and impairment of synaptic function and plasticity. Here, we trace the evolution of the concept of autoimmune epilepsy and examine common inflammatory pathways that might lead to epilepsy. Then, we focus on several antibody-mediated encephalitis disorders that associate with seizures and review the synaptic alterations caused by patients' antibodies, with emphasis on those that have been modeled in animals (e.g., antibodies against NMDA, AMPA receptors, LGI1 protein) or in cultured neurons (e.g., antibodies against the GABAb receptor).

## Seizures, epilepsy, and the concept of autoimmune epilepsy

Many disorders can provoke seizures, which are defined as paroxysmal events due to an excessive, hypersynchronous discharge in central nervous system (CNS) neuronal networks (1). These paroxysmal events can manifest with a broad spectrum of symptoms ranging from convulsions and loss of consciousness to barely perceptible behavioral alterations (2). The term "seizures" should be differentiated from epilepsy, which is a chronic brain disorder characterized by an enduring predisposition to generate epileptic seizures (3, 4), and from epileptogenesis, which consists of the formation of a neuronal network where spontaneous seizures occur (5). Fifty million people worldwide are affected by epilepsy, and about one-third have seizures that do not respond to treatment (6).

The idea that some forms of epilepsy could be autoimmune was suggested 119 years ago (7) and reconsidered in the 1960s and 1970s in experiments showing that the infusion of brain-specific antibodies into the ventricles and brain of cats and monkeys resulted in hyperexcitability and epileptiform activity (8). Over the past 20 years, multiple studies have endorsed the hypothesis that inflammatory brain processes involving components of innate immunity play important roles in the pathophysiology of epilepsy (1, 3). Early observations suggesting the involvement of inflammatory and immune processes in epilepsy include the response of some drug-resistant epilepsies to adrenocorticotropic hormone or steroids (9); the presence of T cells and inflammatory molecules in the brains of patients with Rasmussen's encephalitis, temporal lobe epilepsy, or cortical dysplasia–related epilepsy (10–12); and the link between febrile seizures and an increase of levels of proinflammatory markers (13). Moreover, patients with autoimmune diseases have a higher risk of epilepsy than the general population (14).

In the 1980s and 1990s the identification of several antigen-specific CNS immune responses in a rare group of cancer-triggered disorders named paraneoplastic syndromes showed that autoimmunity against neuronal proteins caused severe forms of encephalitis that were often associated with seizures (ref. 15 and Table 1). These immune responses are mediated by cytotoxic T cells accompanied by antibodies against intracellular neuronal proteins (16); although the antibodies are not pathogenic, they are useful biomarkers of the disease. Given that most of these diseases have a poor outcome and require monitoring and treatment of the associated cancer, their study has generated little interest as potential models of autoimmune epilepsy.

The concept of autoimmune epilepsy was reinforced in the mid-1990s by the observation that rabbits immunized with the GluR3 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) developed seizures, GluR3 antibodies, and pathological features resembling those of Rasmussen's encephalitis (ref. 17 and Table 1). Subsequent inconsistencies in the antibody findings (18) and the refractoriness of most patients' symptoms to immune modulation suggested that an antibody-mediated pathogenesis was unlikely (19). Currently, Rasmussen's encephalitis is viewed as an antigen-driven MHC class I T cell–restricted attack against neurons and astrocytes in which the self-protein targets or potential viral antigens are unknown (20–22).

**Table 1. Encephalitis with seizures and autoimmune mechanisms**

| | Antigen features | Immunological mechanism | Main clinical features | Triggers and comorbidities | Seizures | General outcome (GO); Risk of epilepsy (RE) |
|---|---|---|---|---|---|---|
| Encephalitis with antibodies against neuronal intracellular antigens | Onconeuronal proteins: Hu, Ma2, CRMP5, amphiphysin (154) | Cytotoxic T cells | Multifocal encephalitis or encephalomyelitis; limbic encephalitis | Systemic cancer; histological type varies according to the antigen | Variable; frequent if the limbic system is involved; Hu can present with EPC | GO: poor (frequent neurological or cancer-related death); RE: high (>60%) if the limbic system is involved |
| | GAD65 (25, 26) | Probably cytotoxic T cells | Limbic and extralimbic encephalitis; may associate with stiff-person syndrome and cerebellar ataxia | Mostly idiopathic; often associates with diabetes, polyendocrinopathy | Frequent temporal lobe seizures | GO: moderate to poor (residual limbic dysfunction); RE: high (>80%); temporal lobe epilepsy; hippocampal sclerosis, often refractory to antiepileptics |
| Encephalitis with antibodies against neuronal cell-surface antigens | Ion channels, receptors, interacting proteins (see Tables 2–4 and ref. 31) | B cell (pathogenic antibodies) | Vary according to the antigen (see Tables 2, 3, and ref. 27) | Many idiopathic; variable association with tumors depending on the antigen; HSE; in some diseases, HLA association | High frequency: GABAaR, GABAbR, LGI1, NMDAR; moderate-high frequency for the other antigens (Table 2) | GO: good (70%–85% of patients have substantial clinical recovery); RE: low (<5%–10%) for most types; low-moderate for LGI1 and GABAaR |
| Encephalitis possibly autoimmune | Rasmussen's encephalitis (unknown antigen) (19) | T cell | Refractory seizures, hemiparesis, cognitive decline, unilateral brain atrophy | Unknown | Simple motor seizures or EPC in ~70%; less frequently, complex or generalized seizures | GO: poor; patients develop progressive cognitive and focal motor deficits; RE: 100%, refractory to antiepileptics; patients often require functional hemispherectomy |
| | Encephalitis with NORSE presentation (unknown antigen) (133, 134) | Unknown | Acute encephalopathy with new-onset refractory status epilepticus | Unknown; a subset is triggered by fever | Predominant generalized and complex partial seizures | GO: poor in 70% of patients, cognitive deficits; RE: ~90%, often refractory to treatment |
| | Hashimoto encephalopathy (unknown antigen) (149, 150) | Unknown | Confusion, hallucinations, psychosis, seizures, tremor, myoclonus | Thyroid peroxidase antibodies; subclinical hypothyroid function | Frequency ~60%–80%, generalized tonic-clonic, and partial complex | GO: good in 80%–90% of patients; RE: probably low (limited experience) |
| Encephalitis with low frequency of seizures and with antibodies against glial antigens | MOG (cell surface antigen) (140, 142) | B cell (antibody pathogenicity unclear) | ADEM, NMO spectrum disorder, cortical encephalitis | Viral infection in some patients | Frequency ~15%; generalized tonic-clonic more frequent than partial seizures | GO: wide range of neurological deficits and outcomes; worse if there is persistent detection of antibodies; RE: probably low (limited experience) |
| | GFAP (intracellular antigen) (139) | Unknown; CD8+ T cell infiltrates in brain biopsies | Aseptic meningoencephalomyelitis | Prodromal viral infection or tumor association in some cases | Frequency ~10%; isolated seizures uncommon | GO: good, about 80% have improvement of neurological deficits with immunotherapy; RE: unknown, probably low |

ADEM, acute disseminated encephalomyelitis; CRMP, collapsing response mediator protein; EPC, epilepsia partialis continua; GABAaR, γ-aminobutyric acid A receptor; GFAP, glial fibrillary acidic protein; HSE, herpes simplex encephalitis; LGI1, leucine-rich glioma inactivated 1; MOG, myelin-oligodendrocyte glycoprotein; NMDAR, *N*-methyl-ᴅ-aspartate receptor; NMO, neuromyelitis optica; NORSE, new-onset refractory status epilepticus.

Another important step in the field of autoimmune epilepsy (23) was the identification of antibodies against glutamic acid decarboxylase 65 (GAD65; an enzyme involved in the synthesis of GABA) in patients with stiff-person syndrome (ref. 24 and Table 1). This disorder is associated with muscle rigidity with superimposed spasms, and about 10% of patients develop epilepsy. Subsequent studies showed that GAD65 antibodies also occurred in patients with isolated epilepsy, which is often refractory to treatment (25, 26). GAD antibodies are detected at low titers in 1% of healthy people and at high titers in 80% of patients with type 1 diabetes mellitus and other endocrinopathies. Only very high titers of GAD antibodies are associated with neurological disorders (27).

Experience gained from the above studies and from the field of antibody-mediated neuromuscular diseases (e.g., myasthenic syndromes, neuromyotonia) (28) facilitated, in the mid-2000s, the discovery of a group of CNS diseases in which the antibodies alter the structure and function of receptors, ion channels, or interacting proteins (refs. 29, 30, and Table 1). These neuronal antibody–mediated encephalitides or synaptopathies manifest with syndromes that vary according to the antigen (refs. 27, 31, 32, and Table 2). The immunological triggers can be systemic tumors or viral encephalitis (31, 33) but are unknown in many instances; in some diseases, a genetic link to distinct haplotypes has been shown (34–37).

**Table 2. Antibody-mediated encephalitis, general clinical features[A]**

| Antigen (ref.) | Age, median years [range]; male:female | Main presenting symptoms | Main syndrome | Frequency (main types of cancer) | Brain MRI FLAIR/T2 sequences[B] |
|---|---|---|---|---|---|
| NMDAR (42) | 21 [2 months–85 years]; 1:4 | Children: seizures, dyskinesias; adults: behavior changes, psychiatric | Anti-NMDAR encephalitis[C] | Varies with age and sex[D]; 58% of women 18–45 years old have ovarian teratoma | Normal (70%) or nonspecific changes |
| AMPAR (45, 55) | 56 [23–81]; 1:2.3 | Confusion, memory loss, seizures, psychiatric (rare) | Limbic encephalitis | 56% (SCLC thymoma, breast) | Increased signal in medial temporal lobes (67%) |
| GABAbR (47, 48) | 61 [16–77]; 1.5:1 | Seizures, memory loss, and confusion | Limbic encephalitis, prominent seizures | 50% (SCLC) | Increased signal in medial temporal lobes (45%) |
| LGI1 (57, 155, 156) | 64 [31–84]; 2:1 | Memory loss, faciobrachial dystonic seizures; hyponatremia | Limbic encephalitis | <5% (thymoma) | Increased signal in medial temporal lobes (83%) |
| CASPR2 (50, 157, 158) | 66 [25–77]; 9:1 | Memory loss | Limbic encephalitis, Morvan syndrome[E,F] | <5%[G] | Increased signal in medial temporal lobes (67%) |
| GABAaR (58, 59) | 40 [2.5 months–88 years]; 1:1 | Seizures, confusion, behavior changes | Encephalitis, status epilepticus | 27% (thymoma) | Cortical and subcortical FLAIR abnormalities involving two or more brain regions (77%) |
| mGluR5 (49) | 29 [6–75]; 1.5:1 | Confusion, psychiatric | Encephalitis | 6/11 (Hodgkin lymphoma) | Normal in 5 of 11 patients |
| Dopamine 2R (159) | 5.5 [1.6–15]; 1:1 | Parkinsonism, dystonia, and psychiatric | Basal ganglia encephalitis | 0% | Increased signal in basal ganglia (50%) |
| DPPX (160) | 52 [13–76]; 2.3:1 | Confusion, diarrhea, hyperekplexia | Encephalitis[E] | <10% (B cell neoplasms) | Normal or nonspecific changes (100%) |
| GlyR (161) | 50 [1–75]; 1:1 | Muscle spasms, stiffness, rigidity, startle, eye movement disorders; less frequently, cognitive dysfunction, seizures | Progressive encephalomyelitis with rigidity and myoclonus | ~10%–15% (thymoma, B cell lymphoma, breast cancer, melanoma, Hodgkin lymphoma) | Nonspecific changes in 28% |
| Neurexin-3α (162) | 44 [23–57]; 2:4 | Confusion, seizures | Encephalitis | 0% | Normal in 4 of 6 patients |

[A]Reviewed in refs. 31, 32. [B]Unless indicated, the MRI is normal or with nonspecific changes. [C]Usually presents with psychiatric, behavioral, and cognitive changes followed by abnormal movements, decreased level of consciousness, autonomic dysfunction, or hypoventilation; seizures can occur at any time during the disease. In young children the first symptoms are usually seizures or abnormal movements accompanied by behavioral change. [D]The association with teratoma is sex- and age-dependent. While young adult females frequently have an ovarian teratoma, the presence of a tumor is uncommon in children or young adult males. [E]Most patients have progressive symptoms over more than 3 months. [F]CASPR2 antibodies are frequently associated with Morvan syndrome, a chronic disorder characterized by neuromyotonia, cognitive deterioration, sleep dysfunction (agrypnia excitata), and autonomic features. [G]The frequency of an underlying tumor in patients with CASPR2 antibodies varies according to the syndrome; whereas patients with limbic encephalitis rarely have an underlying tumor (without any histological predominance), 40% of patients with Morvan syndrome have an underlying thymoma. CASPR2, contactin-associated protein–like 2; D2R, dopamine 2 receptor; DPPX, dipeptidyl-peptidase-like protein-6; FLAIR, fluid-attenuated inversion recovery; GlyR, glycine receptor; mGluR5, metabotropic glutamate receptor 5; SCLC, small-cell lung cancer.

In antibody-mediated encephalitis, seizures can be the first, the predominant, or, rarely, the only manifestation of the disease (Table 3), providing a solid foundation for the term "autoimmune epileptic seizures." In these disorders, the extracellular epitopes are accessible to circulating antibodies, and the antibody pathogenicity has been shown in cultured neurons and in vivo models (31). Despite the severity of the symptoms, 70% to 80% of patients with antibody-mediated encephalitis substantially improve or recover with appropriate treatment (32).

The exact frequency of neuronal antibody–mediated encephalitis is unknown. It has been estimated to constitute 10% to 15% of all cases of encephalitis (which have an annual incidence of 5 to 10 cases per 100,000 persons) (38, 39). A study showed that the incidence of the most frequent neuronal antibody–mediated encephalitis, anti–NMDA receptor (anti-NMDAR) encephalitis, surpassed that of herpes simplex

encephalitis (40), and another study showed that the incidence of the second most frequent of these diseases, anti-LGI1 encephalitis, is 0.83 cases per 1 million persons (41).

## Enduring predisposition to seizures varies in neuron-specific autoimmunity

In 2014, the International League Against Epilepsy (ILAE) established a new definition of epilepsy requiring "two unprovoked (or reflex) seizures occurring >24 hours apart, or one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years" (4). In 2017, a new classification of epilepsy by the ILAE introduced the concept of "epilepsy of immune etiology" for patients whose epilepsy "results directly from an immune disorder in which seizures are a core symptom of the disorder" (2). According to these defini-

**Table 3. Antibody-mediated encephalitis, seizures, and estimated risk of epilepsy[A]**

| Antigen | Seizures | Risk of epilepsy | General outcome |
|---|---|---|---|
| NMDAR | ~75% of patients develop seizures, which are often the first symptom in children and young males (53). 11%–30% of adults and 6% of children have a highly characteristic EEG pattern (extreme delta brush) that associates with more severe symptoms (163, 164). Diffuse slowing and focal slowing are the most frequent EEG findings (42). A normal posterior rhythm on the first EEG predicts a favorable clinical outcome, while a severely abnormal EEG associates with poor outcome. In a few patients the EEG can be normal (164). | Low (<5%) | Good. ~80%–85% of patients with substantial or full recovery. Relapses in ~15%–20%. |
| AMPAR | ~30%–40% of patients develop seizures in the context of limbic encephalitis. | Low (~5%) | Depends on the control of the tumor. Otherwise, ~70% partial or full recovery. Relapses in ~16%. |
| GABAbR | 90%–95% of patients have early and prominent seizures in the context of limbic encephalitis. Can present with status epilepticus. | Low (5%) | Depends on the control of the tumor. Otherwise, ~70% partial or full recovery. Relapses can occur (frequency unknown). |
| LGI1 | ~40%–50% of patients present with faciobrachial dystonic seizures (FDS). EEG is often normal in patients with isolated FDS (165); some of these patients have MRI T1 and T2 basal ganglia hyperintensity (166). At the stage of encephalitis, multiple types of seizures (temporal lobe, focal, tonic-clonic, or autonomic) can occur (57, 167, 168). Low chance of seizure control unless immunotherapy is used. | ~15% (some with hippocampal sclerosis) | ~70%–80% partial or complete recovery, but only ~35% able to return to work. Relapses in 27%–34% (57, 155). |
| CASPR2 | 24% of patients present with seizures. Overall, 54% develop seizures during the course of the disease (50). | Exact risk of epilepsy unknown; probably low (<10%) (143) | 48% full response to treatment, 44% partial response, 7% no response. Relapses in 25% (50). |
| GABAaR | Seizures occurred in 88% of patients (48% developed status epilepticus). Compared with adults, children were more likely to have generalized seizures (59). | Exact risk of epilepsy unknown; probably moderate (20%–30%) (58) | 23% complete recovery, 64% partial recovery, 13% death (status epilepticus or sepsis) (59). |
| mGluR5 | 6 of 11 patients presented with seizures. Compared with adults, children were more prone to develop generalized seizures and status epilepticus (49). | Low (5%) | 6 of 11 patients had complete recovery and 5 partial recovery. None developed epilepsy (49). |
| D2R | 2 of 12 patients developed seizures (159). | Low (5%) | 5 of 12 patients had full recovery. None developed epilepsy. Relapses in 3 of 12 cases (159). |
| DPPX | Seizures in 10%–22% of patients (160, 169). | Not available (small number of patients) | 60% substantial or moderate improvement, 23% no improvement (most not treated), 17% died (160, 169). Relapses in 23% (160). |
| GlyR | At disease onset, 13% of patients had seizures. 5 of 45 patients developed only encephalopathy with seizures (161). | Not available | Most patients with substantial or partial improvement; 11% died. Relapses in 14% (161). |

[A]Excludes neurexin-3α, as fewer than 10 patients reported.

tions, the frequent categorization of the seizures occurring in antibody-mediated encephalitis as autoimmune epilepsy would appear to be incorrect. Indeed, seizures are extraordinarily frequent in the acute, inflammatory-provoked phase of many types of antibody-mediated encephalitis, ranging from 33% to 100% depending on the antigen, but in most patients the seizures are not sustained, and resolve after the encephalitis abates (42–50). Young children and toddlers, who are among the most vulnerable patients for epileptogenesis, rarely develop epilepsy after anti-NMDAR encephalitis (51, 52); possible exceptions are patients who develop complications during the course of the disease (e.g., hypoxia, infection). Therefore, the contribution to the development of epilepsy of anti-NMDAR and other antibody-mediated encephalitis is low (refs. 45, 47–49, 53–55, and Table 3).

Two exceptions regarding the risk of epilepsy within the group of antibody-mediated encephalitis disorders are the encephalitis associated with LGI1 antibodies (which is extremely rare in children) (56) and the encephalitis with GABAa receptor (GABAaR) antibodies, which can affect children and adults. A study showed that after a follow-up of 2 years, 14% of patients with anti-LGI1 encephalitis had seizures and an additional 14% were on antiepileptic drugs (57). Early hippocampal lesions and multiple daily seizures favored the development of hippocampal sclerosis.

Experience with anti-GABAaR encephalitis is more limited because of its recent discovery. However, studies indicate that most patients with this disorder present with refractory seizures or status epilepticus (58, 59). In one study, 2 of 21 patients (10%) died of status epilepticus (59), and in another study, 3 of 9 patients (33%) had seizures after 1 year follow-up (58).

The group of antibody-mediated encephalitis disorders should be separated from other types of autoimmune encephalitis in which the antibodies target intracellular proteins, such as the above-mentioned paraneoplastic encephalitis, or GAD65 antibody–associated encephalitis (60). Clinical and laboratory investigations suggest that when the antigens are intracellular, cytotoxic T cells mediate the predominant pathogenic mechanisms (32). The accompanying antibodies against intracellular antigens do not appear to be pathogenic; for example, neurons exposed to GAD65 antibodies do not show surface labeling or antibody internalization (61). Accordingly, the associated syndromes are often refractory to antiepileptic drugs and immuno-
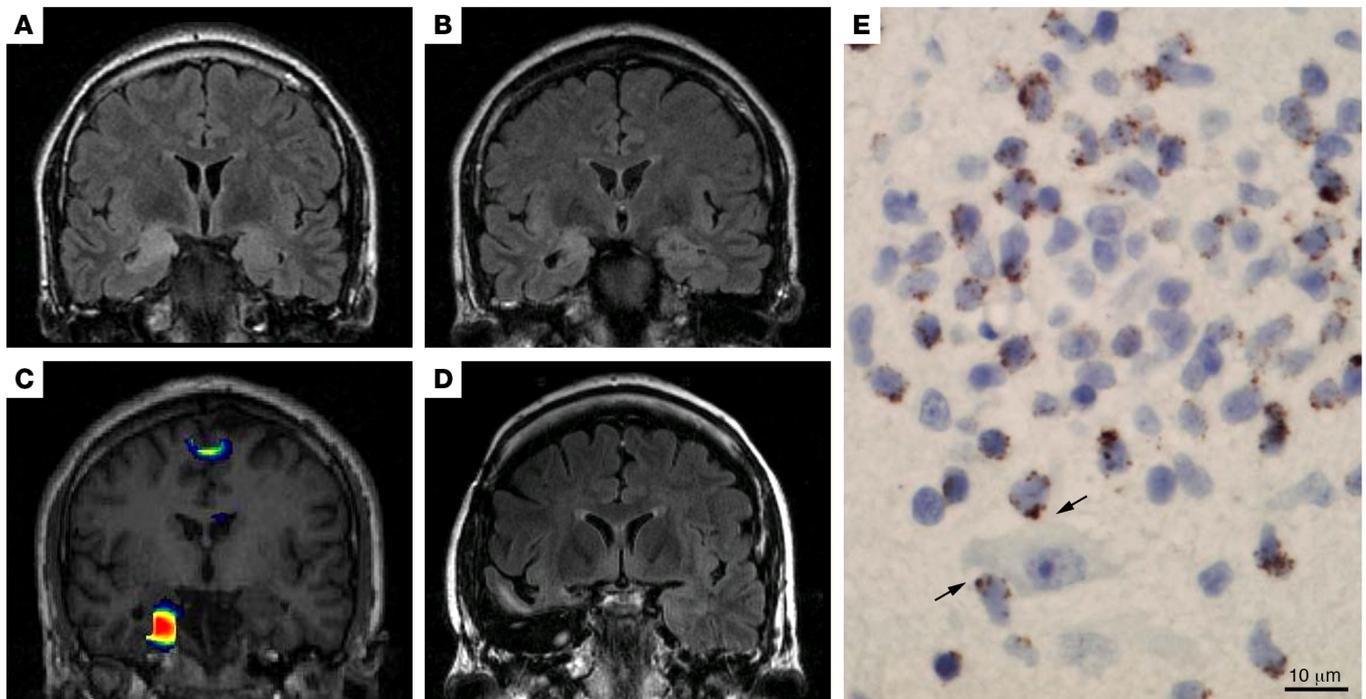
**Figure 1. Paraneoplastic limbic encephalitis and epilepsy mediated by cytotoxic T cell mechanisms.** (**A**) Coronal fluid-attenuated inversion recovery (FLAIR) MRI image showing increased signal and volume of the right amygdala and hippocampus, suggestive of limbic encephalitis, in a patient with a history of seminoma and acute-onset seizures associated with Ma2 paraneoplastic antibodies. (**B**) Coronal FLAIR image 1 year later, showing atrophy of the right hippocampus and medial temporal lobe sclerosis. (**C**) Subtraction ictal SPECT coregistered to MRI (SISCOM) showing increased ictal perfusion over the right hippocampus and parahippocampal gyrus during a right temporal lobe seizure with epigastric aura, piloerection, and loss of awareness. (**D**) Coronal FLAIR image showing resection of the temporal pole and right mesial temporal lobe structures. After surgery, the frequency of the seizures decreased, but they did not resolve (Engel's class III). (**E**) Inflammatory infiltrates in the surgical specimen; the section of the tissue was immunostained with TIA-1 antibody, a marker of cytotoxic T cells (shown as brown granular staining). Some TIA-1–positive cells are in close apposition with neurons (arrows). Scale bars: 10 μm. Images reprinted with permission from Carreño et al. (63).

therapies and markedly contribute to the number of patients with autoimmune epilepsy seen in outpatient clinics (60, 62). For example, among 13 patients who underwent epilepsy surgery for autoimmune epilepsy refractory to treatment, 11 had antibodies against intracellular antigens (eight GAD65, three onconeuronal) and only 2 against surface antigens (one LGI1, one CASPR2) (63). Pathological studies showed chronic lymphocytic infiltrates in 7, gliosis in 5, neuronal loss in 4, and hippocampal sclerosis in 3 (all 3 with GAD65 antibodies).

In paraneoplastic syndromes and probably in anti-GAD65 encephalitis, the infiltrating T cells cause neuronophagia, granzyme B neurotoxicity, neuronal loss, and gliosis, likely favoring epileptogenesis (64, 65) (Figure 1). This is in contrast with findings observed in patients with anti-NMDAR encephalitis that show milder inflammatory infiltrates, limited or absent neuronophagia, more frequent B cell or plasma cell infiltrates, and deposits of antibodies without activation of the complement system (an ancient immune defense system that triggers antigen phagocytosis and membrane attack) (30, 66, 67). For other antibody-mediated encephalitis disorders, pathological studies are limited to anecdotal case reports; a study that included one patient with anti-LGI1 encephalitis and two with antibodies probably directed against LGI1 suggested that complement fixation played a pathogenic role (65).

In summary, the predisposition to cause enduring seizures in autoimmune encephalitis is dependent on the mechanism that drives the immune response, ranging from a high predisposition in cytotoxic T cell–mediated encephalitis (intracellular antigens) to a moderate or absent predisposition in antibody-mediated encephalitis (surface antigens). Among the latter, the severity of the seizures and likelihood to develop epilepsy vary according to the antigen. Additionally, all these disorders occur with a variable degree of inflammation that could have downstream effects on synaptic function, hyperexcitability, and epileptogenesis.

## Downstream synaptic targets of epilepsy-related inflammation

Multiple studies indicate that inflammation, and therefore innate immunity, are involved in epilepsy (refs. 1, 62, 68, and Figure 2). In rodents, induction of seizures or status epilepticus triggers rapid recruitment of inflammatory mediators in the regions of seizure activity and propagation (69, 70). During the process of epileptogenesis, which is ignited in experimental models by acquired brain injuries or by mimicking of infections, proinflammatory cytokines (IL-1β, TNF-α, and IL-6) are first expressed in activated astrocytes and microglia, accompanied by changes in cytokine receptor expression in the same cells and in neurons (71, 72). These events are followed by the induction of COX-2 and prostaglandins (PGE2), with upregulation of components of the complement system in the indicated cells (73). Subsequent changes include the production of chemokines and their receptors in neurons and activated astrocytes (69, 74).
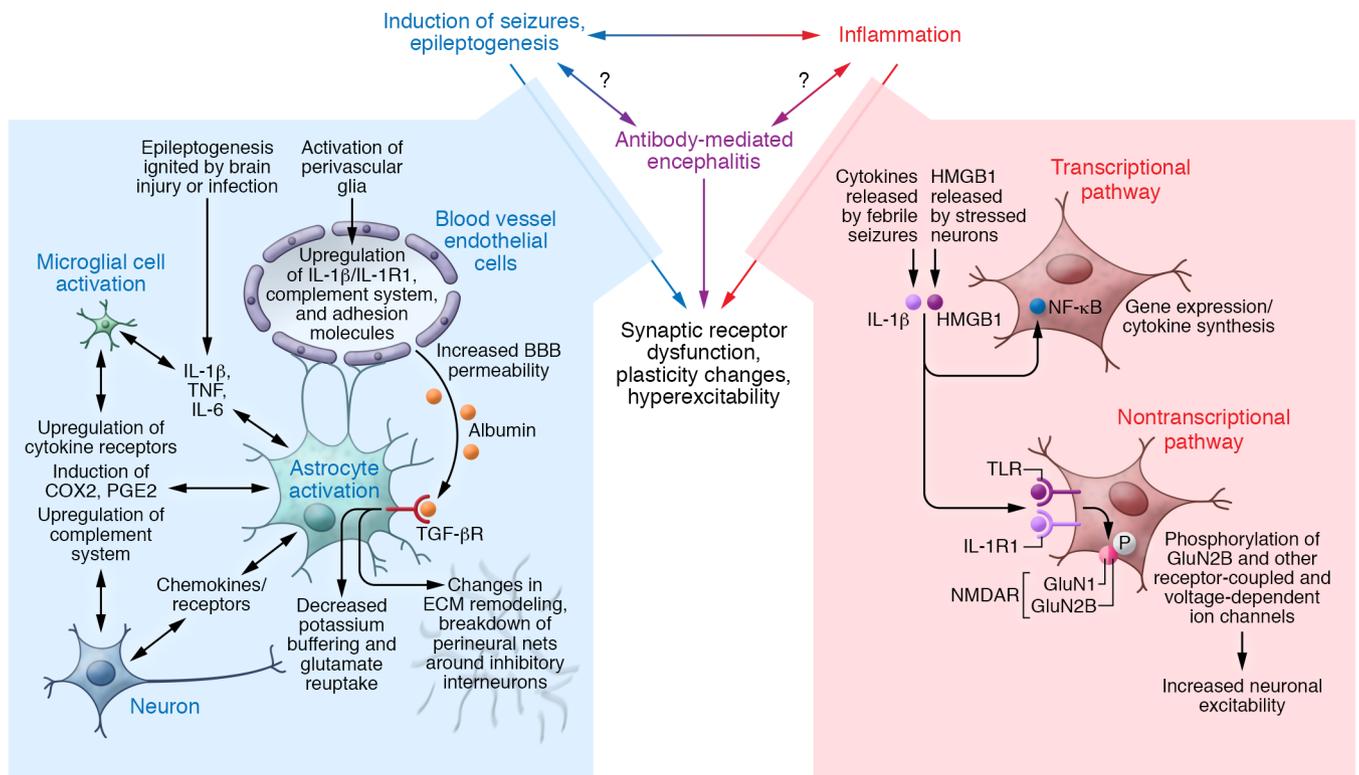
**Figure 2. Synaptic dysfunction and hyperexcitability as a result of seizures, inflammation, and antibody-mediated encephalitis.** Diagram showing multiple inflammatory/innate immunity mechanisms triggered by seizures and epileptogenesis, along with inflammation-related transcriptional and nontranscriptional pathways that lead to synaptic dysfunction, changes in plasticity, and hyperexcitability (corresponding with blue and red arrows). In contrast to these mechanisms, the antibody-mediated encephalitides such as those associated with NMDAR, AMPAR, LGI1, or GABAbR autoantibodies (see others in Tables 3 and 4), represent a direct antibody-mediated alteration of the corresponding targets also leading to synaptic dysfunction, impairment of synaptic plasticity, and hyperexcitability (purple arrow). The degree of involvement of inflammatory/innate immunity molecules and pathways of inflammation in antibody-mediated encephalitis is currently unknown.

Seizures activate the perivascular glia and a cascade of cytokine-mediated events that lead to involvement of endothelial cells, with upregulation of IL-1β, IL-1R1, complement system, and multiple adhesion molecules (75, 76) that may direct blood leukocytes into the brain and associate with blood-brain barrier (BBB) leakage (75, 77). An increase of vascular permeability to serum albumin affects astrocyte function via TGF-β1 receptor (TGF-βR), altering potassium buffering and the ability of astrocytes to reuptake glutamate, which in turn results in NMDAR-mediated hyperexcitability (78, 79). TGF-β1 signaling in astrocytes induces upregulation of molecules related to extracellular matrix (ECM) remodeling and a persistent breakdown of perineuronal nets around fast-spiking inhibitory interneurons, predisposing to chronic deficits in inhibitory neurotransmission (80).

Conversely, CNS and systemic inflammation predispose to seizure precipitation (81). Two typical examples include febrile seizures, which involve the release of endogenous cytokines, mainly IL-1β within the brain (82), and the experimental model of increase of release of an endogenous "danger signal" molecule named high-mobility group box-1 (HMGB1), which is produced by stressed neurons (83). The interaction of HMGB1 with Toll-like receptor 4 (TLR4), a receptor of innate immunity, constitutes an important proconvulsant pathway and is a key initiator of neuroinflammation following brain injuries leading to epilepsy (84,

85). Indeed, the expression of HMGB1 and TLR4 is increased in human epileptogenic tissue, and clinical and experimental data suggest that HMGB1 isoforms may serve as biomarkers for epileptogenesis and drug-resistant epilepsy (84, 85).

IL-1β, HMGB1, and the corresponding receptors IL-1R1 and TLR4 have downstream effects that converge with the TNF pathway at the transcription factor NF-κB, which regulates the synthesis of cytokines and modulates the expression of genes involved in cell death and survival, neurogenesis, and synaptic plasticity (86, 87). A separate nontranscriptional pathway related to IL-1R1 and TLR activation involves Src and other kinase systems that result in phosphorylation of the NMDAR GluN2B subunit and other receptor-coupled or voltage-dependent ion channels, affecting neuronal excitability (88, 89). Genetic and pharmacological animal models have shown that elevated expression of IL-1β and IL-1R1 also increases neuronal excitability by altering GABAergic and glutamatergic neurotransmission (refs. 72, 89–91, and Figure 2).

Antibody-mediated encephalitis disorders also occur with inflammation and seizures, but compared with other diseases and experimental models, they provide a direct mechanism of synaptic dysfunction and hyperexcitability via specific antibody binding to synaptic receptors and proteins (ref. 92 and Figure 2). Although there are no studies available on the above-described
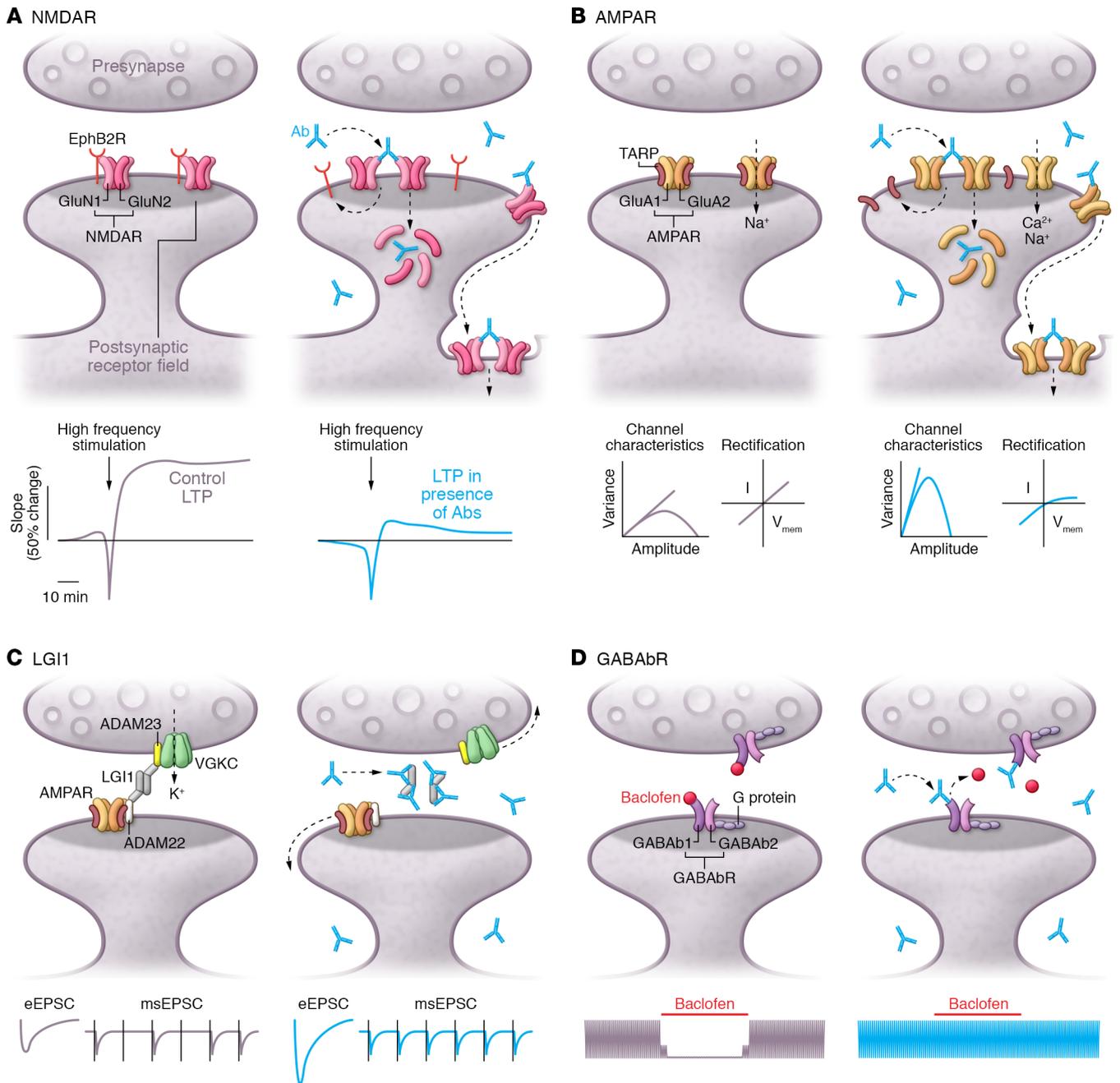
**Figure 3. Synaptic alterations and changes in neuronal excitability induced by autoantibodies against neuronal surface antigens.** (**A**) Top: Patients' antibodies (blue) against NMDARs bind to GluN1 subunits, inducing NMDAR clustering and dissociation from Ephrin-B2 receptor (EphB2R), followed by NMDAR internalization. Below: Reduction of synaptic NMDARs affects synaptic plasticity, revealed by decreased long-term potentiation (LTP). In each panel, blue traces depict effects of patients' antibodies, and gray traces show effects of normal human IgG. (**B**) Top: Antibodies against AMPAR GluA2 subunit induce internalization of GluA2-containing heterodimers after dissociation from TARPs. AMPAR loss is followed by homeostatic compensation with insertion of $Ca^{2+}$-permeable inward-rectifying AMPARs (e.g., GluA1 monomeric AMPAR), which have higher channel permeability. Below: Nonstationary fluctuation analysis shows an increase in AMPAR channel conductance (steeper hyperbola slope) along with reduced channel number (reduced hyperbola width). Current-voltage relationship of excitatory postsynaptic currents (EPSCs) in neurons preincubated with patients' GluA2 antibodies reveals incorporation of inward-rectifying AMPARs in the synapse. (**C**) Top: Anti-LGI1 antibodies react with epitopes in leucine-rich repeat (LRR) and EPTP domains of LGI1, disrupting LGI1's interaction with presynaptic ADAM23 and postsynaptic ADAM22, and reducing presynaptic voltage-gated Kv1.1 channels and postsynaptic AMPARs. Below: Downregulation of presynaptic Kv1.1 channels increases presynaptic release probability and enhances glutamatergic transmission, resulting in increased evoked EPSCs (eEPSCs) and reduced failure rate of synaptic transmission after minimal stimulation (msEPSCs). (**D**) Top: Anti-GABAbR antibodies bind to the GABAb1 subunit, which localizes at pre- and postsynaptic membranes and contains the GABA-binding site. Antibody binding does not cause GABAbR internalization but interferes with baclofen-induced GABAbR activation. Below: Baclofen blocks spontaneous network activity of cultured neurons (gray). Anti-GABAbR antibodies interrupt its inhibitory effect (blue).

**Table 4. Comparison of the pathogenic effects of autoantibodies with genetic models of target antigen dysfunction**

| Antigen | Antibody pathogenicity | Genetic model |
|---|---|---|
| NMDAR | Internalization of NMDAR, disruption of the interaction of NMDAR with EphB2R. Decreased memory and learning, depressive-like behavior; decreased long-term potentiation (LTP); lowered threshold for seizures (92, 101, 103, 105, 107). | Neonatal death in homozygous NR1$^{-/-}$ mice (170). Defects in memory and abolished LTP after specific deletion of NR1 in CA1 and CA3 pyramidal neurons (171, 172); impaired hippocampal synchrony after NMDAR deletion in parvalbumin-positive interneurons (173). |
| AMPAR | Internalization of AMPARs; replacement of GluA2- containing receptors for GluA1 homomeric receptors. Decreased memory and learning; anxiety-like behavior (95, 111, 112). | Increased synaptic excitability and decreased learning and memory in mice of forebrain-deleted GluA2 subunits; incorporation of inwardly rectifying Ca$^{2+}$ permeable AMPA receptors (174–176). |
| LGI1 | Inhibition of LGI1 interaction with ADAM22 and ADAM23. Decrease of levels of Kv1.1 and AMPAR along with neuronal hyperexcitability and severe impairment of memory and synaptic plasticity (120, 121). | Epileptic seizures in LGI1$^{-/-}$ mice and in mice with LGI1 mutation (117, 177). Reduction of postsynaptic AMPAR transmission by disturbed ADAM22 interaction (178); altered presynaptic function of Kv1.1 and increase of excitatory synaptic transmission (177, 179, 180). |
| GABAbR | In vitro: Antagonism of the agonist effect of baclofen on GABAbR (31). | Epileptic seizures and memory impairment in GABAb1R$^{-/-}$ mice (181, 182); loss of pre- and postsynaptic inhibitory function and GABAb hetero- and autoreceptor function (181–183). |
| CASPR2 | In vitro: Alteration of gephyrin clusters in inhibitory synapses (184). | No gross phenotypic abnormalities in CASPR2$^{-/-}$ mice; reduction in the accumulation of Kv1.1 and Kv1.2 channels at the juxtaparanodes in PNS and CNS axons (185, 186). |
| mGluR5 | In vitro: Decreased density of surface mGluR5 (49). | Defective NMDAR-dependent LTP and impaired learning and memory in mGluR5$^{-/-}$ mice (187, 188); hyperexcitability and seizures in mice with an mGluR5 knock-in mutation, but no increased seizure susceptibility in mGluR5$^{-/-}$ mice (189, 190). |
| DPPX | In vitro: Decreased density of surface DPPX and Kv4.2 (160). | Defective dendritic A-type K$^+$ currents with enhanced excitability, lower threshold for LTP, and reduced synaptic and extrasynaptic Kv4.2 expression in DPP6 (DPPX)$^{-/-}$ mice (191). Impaired synaptic development, and learning and memory deficits in DPP6$^{-/-}$ mice (192). |
| GABAaR | In vitro: Selective reduction of GABAaR at synapses (58, 193). | Increased central excitability and spontaneous seizures in transgenic mice with deletions of several GABAaR subunits similar to human genetically encoded epilepsy (194). |
| Neurexin-3α | In vitro: Decreased density of surface neurexin-3α and total number of synapses in neurons undergoing development (162). | Postnatal death, reduced Ca$^{2+}$-dependent presynaptic release, and decreased GABAergic inhibition in pan-neurexin and neurexin-3$^{-/-}$ mice (195, 196); ataxia, hyperactivity, and disturbed regulation of AMPAR and presynaptic GABA release in conditional neurexin-3$^{-/-}$ mice (196). |

inflammatory pathways in antibody-mediated encephalitis, two reports suggest a role of the accompanying inflammatory mechanisms in anti-NMDAR encephalitis. In one study, the level of the B cell–attracting chemokine CXCL13, which is produced in response to activation of several TLRs, was found to be elevated in the cerebrospinal fluid (CSF) of 70% of patients at early-stage disease (93). The authors postulated that the prodromal viral-like process frequently observed in this disorder could be involved in initiating the production of CXCL13; the same study showed that prolonged or secondary elevation of CXCL13 in CSF was associated with limited response to treatment and relapses (93).

The other study focused on patients who after herpes simplex encephalitis developed anti-NMDAR and other autoimmune encephalitis. This complication occurred in 27% of the patients within 2 months after the viral infection had resolved, and the outcome was substantially worse than that reported in classical (not viral-related) anti-NMDAR encephalitis (33). Indeed, 63% of patients aged 4 years or younger and 13% of those older than 4 years had seizures at 1 year follow-up; moreover, 22% of the younger group developed early infantile spasms (33). Brain MRI showed that 82% of the patients had extensive areas of contrast enhancement, which is rare among cases with classical antibody-mediated encephalitis (49, 53, 57, 59). These findings suggested that entry of complement and other proinflammatory molecules through a disrupted BBB could have contributed to epileptogenesis and worse outcome.

## Pathogenic models of antibody-mediated encephalitis

In antibody-mediated encephalitis, the coexistence of antigen-specific antibodies with a variable background of inflammation brings into consideration to what extent the antibodies contribute to patients' symptoms. Findings that suggest a role of the antibodies include (a) the preferential association with distinct clinical syndromes according to antigen specificity (Table 2), sometimes accompanied by different types of seizures, paraclinical findings (EEG, MRI), speed of recovery, and propensity to epilepsy (Table 3); (b) the pathogenic effects of the antibodies in in vitro and in vivo models (Table 4); (c) the resemblance of the antibody-mediated syndromes or mechanisms to those caused by pharmacological or genetic alteration of the same antigens (Table 4); and (d) the frequent clinical response to treatments focused on removing the antibodies or B cells (Table 3).

Target antigens can be subdivided according to structure and function into ionotropic receptors (e.g., NMDAR, AMPAR, GABAaR), metabotropic receptors (e.g., GABAbR), and synaptic linker proteins (e.g., LGI1).

*Autoantibodies against NMDAR and AMPAR change neuronal excitability.* Antibodies against NMDAR, AMPAR, or GABAaR have been shown to cross-link and reduce surface expression of the respective receptor in a dose-dependent manner when applied to cultures of neurons (42, 45, 58). This effect was not observed

**Table 5. Differential diagnosis of seizures and epilepsy of suspected autoimmune etiology in children and adults**

| Disorder | Children | Adults |
|---|---|---|
| Antibody-mediated encephalitis (synaptic and neuronal cell-surface antigens) | Anti-NMDAR and anti-MOG are the main antibody-mediated encephalitis in children (53, 54, 140). Epileptic seizures are often the first symptom of anti-NMDAR encephalitis. Anti-GABAaR encephalitis is much less frequent but strongly associates with seizures and status epilepticus (59). | Anti-LGI1, -GABAaR, and -GABAbR are the most frequent antibody-mediated encephalitis presenting with seizures (48, 57, 59). Anti-NMDAR encephalitis associates with seizures in 75% of patients (predominantly at early disease stages) (43, 53). |
| Acute disseminated encephalomyelitis (ADEM) | ADEM is the most frequent autoimmune encephalitis in children (~50% harbor MOG antibodies) (140). The clinical presentation can mimic autoimmune encephalitis. The MRI findings usually lead to the diagnosis (27). | Infrequent in adults. MOG antibodies occur less frequently than in children (197). |
| Autoimmune encephalitis with GAD65 antibodies | Rare in children (146, 198). GAD65 antibodies often accompany other more disease-relevant neuronal surface antibodies (58). | The most frequent type of neuronal antibody–associated encephalitis in outpatient epilepsy clinics (60, 62, 63). |
| Viral encephalitis | Most viral encephalitis occurs with seizures; at disease onset the clinical picture is very similar to autoimmune encephalitis (135, 199). | Same comments as in children. |
| Antibody-associated encephalitis following herpes simplex encephalitis (HSE) | Occurs in 27% of patients with HSE, often with NMDAR or other neuronal surface antibodies (33). At 1 year follow-up, 63% of children ≤4 years old had seizures compared with 13% of older patients (33). | Same comments as in children. |
| Hashimoto encephalopathy | Ill-defined syndrome. Less frequent in children than in adults. About 80% of children have seizures compared with ~65% of adults (149, 150). | Given that thyroid peroxidase antibodies occur in 13% of healthy subjects, the diagnosis is by exclusion of other causes of encephalitis (27). |
| New-onset refractory status epilepticus (NORSE); febrile infection–related epilepsy syndrome (FIRES) | FIRES: Because of the preceding febrile (or infectious) process and lacking evidence of infectious encephalitis, FIRES is suspected to be immune mediated. Poor response to treatment (200). | NORSE: Probably represents multiple diseases and mechanisms. Some antibody-mediated encephalitis can present as treatment-responsive NORSE (133). Cryptogenic NORSE is often refractory to treatment (134). |
| Paraneoplastic encephalitis | Classical paraneoplastic encephalitis causing seizures is extremely rare in children. | Considered in patients with cancer or risk for cancer who develop acute-onset seizures and encephalitis. Diagnostic criteria reported in ref. 148. |
| Genetic disorders predisposing to brain inflammation or infection | Acute necrotizing encephalopathy; acute encephalopathy with biphasic seizures and reduced diffusion; predisposition to HSE in people with inborn errors of interferon immunity; predisposition to macrophage activation in response to environmental triggers (reviewed in ref. 135). | Presentation of these disorders occurs during childhood. |

when antibody Fab fragments were used (94). Antibody-mediated receptor internalization starts after 30–120 minutes (92, 95) with maximal internalization at 12 hours of incubation time in vitro, and is reversible upon removal of antibodies (96).

In anti-NMDAR encephalitis, IgG antibodies are selectively directed against the N-terminal domain of the obligate GluN1 subunit of the receptor (97). In cultured neurons, antibody-mediated internalization leads to a reduction of NMDARs and selectively diminishes NMDAR-mediated currents (ref. 94 and Figure 3A). These effects are specific for GluN1 antibodies, and experiments using human monoclonal GluN1 antibodies revealed similar results (98). Studies with super-resolution stochastic reconstruction microscopy (STORM) revealed that NMDAR antibodies induce clustering of NMDAR in nanodomains in synaptic and extrasynaptic areas preceding their internalization. These changes are subunit dependent, preferentially affecting NMDAR containing GluN1 and GluN2B subunits (92). NMDARs of this subunit composition have longer desensitization kinetics (99) and are believed to be important in synaptic plasticity (100). Concordantly, other studies have shown that human NMDAR IgG antibodies lead to slower diffusion of GluN1/GluN2B heterodimers (101). This has been attributed to antibody-induced disruption of the interaction of NMDARs with EphB2R, which stabilizes NMDAR in the postsynaptic membrane (101, 102). These findings were confirmed in a model based on cerebroventricular infusion of patients' antibodies to mice via osmotic pumps (103, 104). In this model, and also after stereotactic injection of patients' CSF antibodies, the levels of NMDAR were reduced in the hippocampus, accompanied by severe impairment of long-term potentiation (LTP) and deficits in learning and memory (103, 105, 106) resembling those observed in mouse models of hippocampal deficiency of NMDARs (Table 4). In the same model, stimulation of EphB2R antagonized the effect of patients' antibodies, thus providing a potential target-specific treatment strategy (31, 101, 105). In addition to reduction of surface NMDAR expression, direct effects of the antibodies on NMDAR channel function may contribute to pathological NMDAR signaling. In single-channel electrophysiological recordings of GluN1/GluN2B–transfected HEK cells, application of patients' antibodies prolonged the open probability of NMDAR channels (97). Further studies are needed to determine whether acute changes of NMDAR current flow alter neuronal excitability. Studies with cultured neurons showed that NMDAR antibodies similarly influence the receptor density in excitatory and inhibitory neurons accompanied by a reduction of the overall density of inhibitory synapses (96). It is unknown whether similar changes occur in vivo, and whether the altered excitability would be sufficient to cause epileptic seizures. In a pas-

sive-transfer mouse model with a single intraventricular injection of patients' NMDAR antibodies, mice showed an increased susceptibility to develop seizures upon application of the chemoconvulsant pentylenetetrazol (107).

Similar to the NMDAR, AMPARs are excitatory ionotropic glutamatergic receptors and consist of four subunits. AMPARs mediate the majority of fast excitatory synaptic transmission in the CNS and are mostly composed of two GluA1 and two GluA2 subunits. In contrast to NMDARs, there is no obligatory subunit and there is a larger variability in receptor composition (108). Importantly, the presence of GluA2 determines crucial properties of the receptor: RNA editing of the Q/R site of the GluA2 subunit modifies the pore region of the receptor so that AMPARs containing GluA2 are impermeable to $Ca^{2+}$ and show a linear current-voltage relationship (109). In contrast, AMPARs without GluA2 are $Ca^{2+}$ permeable, have a larger single-channel conductance, and are inwardly rectifying, as intracellular polyamines can block the channel pore at positive membrane potentials (109, 110). Patients with anti-AMPAR encephalitis harbor antibodies against either GluA1 or GluA2 subunits, resulting in a reduction of surface levels of AMPAR (45, 111, 112).

A recent study using patients' antibodies against GluA2 demonstrated a specific antibody-induced restructuring of AMPAR composition by a synaptic scaling–like mechanism (ref. 95 and Figure 3B). This mechanism has been observed in conditions of neuronal silencing and in cell-specific knockout models of AMPAR subunits (Table 4). Patients' GluA2 antibodies led to internalization of GluA1/GluA2 heterodimeric AMPARs followed by synaptic insertion of inwardly rectifying AMPARs with increased channel conductance. In cultured neurons, confocal and STORM microscopy showed a reduction of GluA2 but not GluA1 subunits. These observations were confirmed in mice after intraventricular and hippocampal transfer of patients' antibodies. Patch-clamp electrophysiological analyses of ionic current in hippocampal neurons revealed a decrease of the levels of AMPARs, whereas the remaining receptors showed increased single-channel conductance (Figure 3B). Importantly, application of patients' GluA2 antibodies in GluA1-knockout mice also led to reduced levels of AMPAR, but the replacement with GluA1-AMPARs of higher conductance was no longer present, suggesting that GluA1 homomeric receptors are responsible for the synaptic scaling–like mechanism observed in wild-type mice (95). Interestingly, recent studies showed that in rat models of chronic temporal lobe epilepsy there was a relative increase in inwardly rectifying non-GluA2 AMPARs, which was linked to neuronal excitotoxicity and seizure development (113, 114). Determining whether the rearrangement of AMPAR subunits observed in the model of anti-AMPAR encephalitis results in increased neuronal excitability and enhanced seizure susceptibility is a goal of future studies.

*Antibodies against LGI1 induce presynaptic and postsynaptic pathology.* Limbic encephalitis with antibodies against LGI1 is the second most common form of autoimmune encephalitis, resulting in memory deficits and several types of epileptic seizures, which are often preceded by faciobrachial dystonic seizures (31). Binding of autoantibodies against LGI1 cannot induce internalization of the antibody-antigen complex, because LGI1 is a neuronally secreted protein without direct membrane anchoring (115). LGI1 contains three leucine-rich repeats (LRRs) that are flanked by two

cysteine-rich regions at the N-terminal, and seven-bladed propeller structures or epitempin (EPTP) repeats at the C-terminus (116). LGI1 forms a trans-synaptic complex that includes the presynaptic disintegrin and metalloproteinase domain–containing protein 23 (ADAM23) (which interacts with Kv1.1 potassium channels) and the postsynaptic ADAM22 (which interacts with AMPARs) (117). Mutations of LGI1 are associated with an inherited form of epilepsy called autosomal dominant lateral temporal lobe epilepsy (ADTLE) that usually presents with acoustic or visual hallucinations and partial seizures (118, 119).

Antibodies of patients with anti-LGI1 encephalitis bind to the LRR and EPTP domains of LGI1 (refs. 120, 121, and Figure 3C). In cultured neurons, these antibodies reversibly decrease postsynaptic clusters of ADAM22 by interfering with the interaction of LGI1 and ADAM22 (120). Using an animal model based on cerebroventricular transfer of patients' IgG antibodies, a more complex pathophysiology involving pre- and postsynaptic LGI1-dependent signaling has been revealed (121). In the hippocampus of infused mice, total and postsynaptic levels of AMPARs were reduced, confirming previous in vitro findings (120). In addition, the levels of presynaptic Kv1.1 were also decreased, indicating antibody-induced disruption of presynaptic LGI1/ADAM23/Kv1.1 signaling (121). This involvement of presynaptic Kv1.1 channels resulted in increased neuronal excitability with higher presynaptic release probability and reduced synaptic failure rate, leading to increased glutamatergic transmission, which likely enhances the susceptibility to develop seizures (121). An increase of neuronal excitability was also reported in a previous in vitro study using the IgG fraction of a patient with antibodies presumably against LGI1 (122). Moreover, mice infused with LGI1 antibodies developed severe memory dysfunction with concomitant impairment of synaptic LTP. Interestingly, these changes were independent of Kv1.1 signaling, suggesting they were caused by altered postsynaptic AMPAR recruitment induced by patients' LGI1 antibodies (121).

These functional and molecular findings resemble those obtained in genetic mouse models of LGI1 deficiency or mutations (Table 4), but the clinical features in anti-LGI1 encephalitis are different from those in ADTLE. A lower degree of LGI1 disruption in the autoimmune model along with coexisting inflammatory changes in patients with anti-LGI1 encephalitis could explain some of these differences. It has also been shown that most of the mutated forms of LGI1 related to ADTLE are no longer secreted by neurons (115, 123, 124), indicating fundamental differences in the pathophysiology of the autoimmune and genetic LGI1 models.

*Antibodies against the GABAbR are selective GABAb1R antagonists.* Different from NMDAR and AMPAR, the ionotropic receptors for the excitatory neurotransmitter glutamate, the GABAbR is a G protein–coupled receptor for the inhibitory neurotransmitter GABA. The encephalitis with antibodies against GABAbR is associated with early and prominent epileptic seizures (47, 48). GABAbRs are heterodimeric receptors composed of a GABAb1a or GABAb1b subunit together with a GABAb2 subunit. The GABAb1 subunit contains the GABA binding site and determines receptor localization, and the GABAb2 subunit activates the G protein (125). GABAbRs are located mainly at the perisynaptic membrane and can serve as auto- and heteroreceptors, influenc-

ing synaptic function in the range of seconds to minutes (126). Genetic models of GABAbR deficiency show several abnormalities in neuronal and synaptic function (Table 4). Antibodies from patients with anti-GABAbR encephalitis bind to several epitopes in the N-terminal region of the GABAb1a and GABAb1b subunits (47, 127). Unlike antibodies targeting ionotropic receptors, patients' GABAbR antibodies do not induce receptor internalization in cultured neurons; instead, the antibodies interfere directly with inhibitory GABAbR function, as they antagonize the effects of the GABAb1 agonist baclofen (ref. 127 and Figure 3D). Since baclofen usually reduces the frequency of miniature excitatory postsynaptic currents in cultured neurons, this antibody-induced effect is most likely mediated by presynaptic mechanisms (31, 127). These findings suggest a pathogenic mechanism of patients' antibodies leading to severe refractory seizures. Future studies should assess the pre- and postsynaptic effects of patients' antibodies in an animal model and whether they alter the regulatory function of GABAbRs in network activity.

## Current challenges and future investigations in autoimmune epilepsy

There is a pressing need to clarify the definition of autoimmune epilepsy. It is frequently implied that any disorder with seizures and autoantibodies is autoimmune epilepsy (128–130). Consequently, most autoimmune encephalitides are routinely categorized as autoimmune epilepsy irrespective of the disease provoking the seizures, type of antibody, or definition of epilepsy (128, 131). This extensively used assumption is inaccurate and has led to the development of score systems for antibody prevalence in epilepsy (APE) that are based on the same clinical insights and diagnostic criteria used for antibody-associated encephalitis, resulting in an important selection bias (132). Indeed, patients with multiple symptoms of autoimmune encephalitis have the highest APE scores, whereas those with pure or predominant seizures have the lowest (e.g., faciobrachial dystonic seizures, or drug-resistant temporal lobe epilepsy with GAD65 autoimmunity).

The acute phase of most antibody-mediated encephalitis with seizures can last several months, yet the risk of epilepsy is small (53, 54). Patients with these diseases should have a reasonable follow-up (we propose 1 year) before the diagnosis of epilepsy is considered in those who continue having seizures or need sustained antiepileptic medication. The length of this follow-up has not been previously established and is open to reassessment; however, during this observation period, patients should be considered to have an autoimmune seizure disorder, but not epilepsy. This is important for two reasons: first, a premature diagnosis of epilepsy can lead to unnecessary and prolonged use of antiepileptic medication; and second, according to the ILAE, epilepsy might "resolve" but not be "cured," thus, it becomes a preexisting condition that confers important socioeconomic implications (4).

A separate problem is the patients with new-onset seizures of unclear etiology who are antibody negative. These include most patients with Rasmussen's encephalitis, subsets of patients with new-onset refractory status epilepticus (NORSE) (133, 134), and patients with idiopathic seizures and inflammatory CSF findings (Table 1). Without biomarkers of adaptive immunity, a definite diagnosis of autoimmune seizures cannot be established. The presence of CSF pleocytosis or oligoclonal bands and the clinical response to steroids or immune modulation (e.g., plasma exchange) are not reliable indicators of autoimmunity because they can occur in nonautoimmune inflammatory diseases in which the indicated pathways of innate immunity are involved (e.g., interferonopathies) (135), or in disorders of unclear etiology (e.g., seronegative limbic encephalitis or central nervous system vasculitis) (136–138).

Antibodies against astrocytes (glial fibrillary acidic protein [GFAP]) and oligodendrocytes (myelin-oligodendrocyte glycoprotein [MOG]) are associated with meningoencephalomyelitis and neuromyelitis optica spectrum disorders, but in some cases they occur with seizures (refs. 139, 140, and Table 1). Particularly, MOG antibodies are detected in approximately 50% of children with acute disseminated encephalomyelitis, and less frequently in a form of cortical encephalitis with seizures (141, 142). Whereas these antibodies are rarely included in serological screening panels for suspected autoimmune seizures or epilepsy (62), others that are included should be discontinued. For example, antibodies against voltage-gated potassium channels (VGKCs) are not useful biomarkers of brain-specific autoimmunity unless antigen-specific assays demonstrate that the targets are LGI1 or CASPR2 (two proteins complexed to VGKC) (143, 144). This and the fact that many patients with antibody-mediated encephalitis do not develop epilepsy explain why, in epilepsy clinics, the number of cases with genuine autoimmune epilepsy is limited to those with GAD65 antibodies, and even a smaller number of cases with LGI1 or other antibodies (145–147). Although Hashimoto encephalopathy is an ill-defined disorder (148) and the autoimmune mechanisms are unclear, this disorder is often considered in the differential diagnosis of autoimmune epilepsy (refs. 149, 150, and Tables 1 and 5).

A common feature of all types of autoimmune epileptic seizures is the refractoriness to antiepileptic drugs unless immunotherapy is concurrently used (130). It is currently unclear whether some antiepileptics are better than others in patients with these disorders.

A task for the future is to determine whether genetic factors, or variable involvement of inflammatory pathways, may enhance the likelihood of seizures in patients with autoimmune encephalitis. It is also unclear why the spectrum of autoimmune encephalitis is different in children as compared with that in adults (135); in practice, these differences are important because they change the approach to differential diagnosis (Table 5).

The antibody-mediated encephalitides represent a new biomedical frontier, helping to better understand the role of ion channels, receptors, and other synaptic proteins in neurological function and seizures. The associated antibodies can be used to determine how blocking, reducing the levels, or altering the surface dynamics of specific synaptic proteins changes neuronal excitability or synaptic plasticity or can potentially induce seizures. Although several models of antibody pathogenicity have been developed, no animal model of antibody-mediated clinical seizures is yet available. Given that the autoantibodies are frequently synthesized within the CNS (66, 151), treatments designed to remove systemic antibodies are often suboptimal, resulting in protracted clinical courses (53). A better understanding of the physiopathology of these diseases should lead to novel

treatment strategies. This is supported by experiments showing that an agonist of EphB2, a tyrosine kinase that regulates excitatory synapse formation (152), was able to antagonize the effect of patients' NMDAR antibodies (101, 105), or that a positive allosteric modulator of NMDAR accelerated the recovery of NMDAR function in neurons exposed to patients' antibodies (153). For anti-GABAbR encephalitis, preliminary studies show that activation of the B2 subunit, bypassing the B1-blocking effect of the antibodies, lessens the increased neuronal excitability (127). A current challenge is to extend these types of studies to other antibody-mediated encephalitis, with the goal of developing drugs to be tested in clinical trials.

1. Marchi N, Granata T, Janigro D. Inflammatory pathways of seizure disorders. *Trends Neurosci*. 2014;37(2):55–65.
2. Scheffer IE, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512–521.
3. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. *Nat Rev Neurol*. 2011;7(1):31–40.
4. Fisher RS, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475–482.
5. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. *Lancet*. 2006;367(9516):1087–1100.
6. Perucca E, French J, Bialer M. Development of new antiepileptic drugs: challenges, incentives, and recent advances. *Lancet Neurol*. 2007;6(9):793–804.
7. Delezenne C. Sérums néurotoxiques. *Ann Inst Pasteur*. 1900;14:686–704.
8. Mihailović LT, Cupić D. Epileptiform activity evoked by intracerebral injection of anti-brain antibodies. *Brain Res*. 1971;32(1):97–124.
9. Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. *Pediatrics*. 1996;97(3):375–379.
10. Rasmussen T, Olszewski J, Lloydsmith D. Focal seizures due to chronic localized encephalitis. *Neurology*. 1958;8(6):435–445.
11. Crespel A, et al. Inflammatory reactions in human medial temporal lobe epilepsy with hippocampal sclerosis. *Brain Res*. 2002;952(2):159–169.
12. Choi J, et al. Cellular injury and neuroinflammation in children with chronic intractable epilepsy. *J Neuroinflammation*. 2009;6:38.
13. Dubé CM, Brewster AL, Richichi C, Zha Q, Baram TZ. Fever, febrile seizures and epilepsy. *Trends Neurosci*. 2007;30(10):490–496.
14. Ong MS, Kohane IS, Cai T, Gorman MP, Mandl KD. Population-level evidence for an autoimmune etiology of epilepsy. *JAMA Neurol*. 2014;71(5):569–574.
15. Shavit YB, Graus F, Probst A, Rene R, Steck AJ. Epilepsia partialis continua: a new manifestation of anti-Hu-associated paraneoplastic encephalomyelitis. *Ann Neurol*. 1999;45(2):255–258.
16. Bernal F, Graus F, Pifarré A, Saiz A, Benyahia B, Ribalta T. Immunohistochemical analysis of anti-Hu-associated paraneoplastic encephalomyelitis. *Acta Neuropathol*. 2002;103(5):509–515.
17. Rogers SW, et al. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. *Science*. 1994;265(5172):648–651.
18. Watson R, et al. Absence of antibodies to glutamate receptor type 3 (GluR3) in Rasmussen encephalitis. *Neurology*. 2004;63(1):43–50.
19. Bien CG, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain*. 2005;128(pt 3):454–471.
20. Al Nimer F, et al. Phenotypic and functional complexity of brain-infiltrating T cells in Rasmussen encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(1):e419.
21. Schwab N, et al. CD8+ T-cell clones dominate brain infiltrates in Rasmussen encephalitis and persist in the periphery. *Brain*. 2009;132(pt 5):1236–1246.
22. Bauer J, et al. Astrocytes are a specific immunological target in Rasmussen's encephalitis. *Ann Neurol*. 2007;62(1):67–80.
23. Levite M. Autoimmune epilepsy. *Nat Immunol*. 2002;3(6):500.
24. Solimena M, Folli F, Aparisi R, Pozza G, De Camilli P. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. *N Engl J Med*. 1990;322(22):1555–1560.
25. Peltola J, et al. Autoantibodies to glutamic acid decarboxylase in patients with therapy-resistant epilepsy. *Neurology*. 2000;55(1):46–50.
26. Giometto B, Nicolao P, Macucci M, Tavolato B, Foxon R, Bottazzo GF. Temporal-lobe epilepsy associated with glutamic-acid-decarboxylase autoantibodies. *Lancet*. 1998;352(9126):457.
27. Graus F, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016;15(4):391–404.
28. Nagel A, Engel AG, Lang B, Newsom-Davis J, Fukuoka T. Lambert-Eaton myasthenic syndrome IgG depletes presynaptic membrane active zone particles by antigenic modulation. *Ann Neurol*. 1988;24(4):552–558.
29. Vincent A, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain*. 2004;127(pt 3):701–712.
30. Dalmau J, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61(1):25–36.
31. Dalmau J, Geis C, Graus F. Autoantibodies to synaptic receptors and neuronal cell surface proteins in autoimmune diseases of the central nervous system. *Physiol Rev*. 2017;97(2):839–887.
32. Dalmau J, Graus F. Antibody-mediated encephalitis. *N Engl J Med*. 2018;378(9):840–851.
33. Armangue T, 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.
34. van Sonderen A, et al. Anti-LGI1 encephalitis is strongly associated with HLA-DR7 and HLA-DRB4. *Ann Neurol*. 2017;81(2):193–198.
35. Kim TJ, et al. Anti-LGI1 encephalitis is associated with unique HLA subtypes. *Ann Neurol*. 2017;81(2):183–192.
36. Mueller SH, et al. Genetic predisposition in anti-LGI1 and anti-NMDA receptor encephalitis. *Ann Neurol*. 2018;83(4):863–869.
37. Binks S, et al. Distinct HLA associations of LGI1 and CASPR2-antibody diseases. *Brain*. 2018;141(8):2263–2271.
38. Vora NM, Holman RC, Mehal JM, Steiner CA, Blanton J, Sejvar J. Burden of encephalitis-associated hospitalizations in the United States, 1998-2010. *Neurology*. 2014;82(5):443–451.
39. Jmor F, Emsley HC, Fischer M, Solomon T, Lewthwaite P. The incidence of acute encephalitis syndrome in Western industrialised and tropical countries. *Virol J*. 2008;5:134.
40. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. *Clin Infect Dis*. 2012;54(7):899–904.
41. van Sonderen A, Petit-Pedrol M, Dalmau J, Titulaer MJ. The value of LGI1, Caspr2 and voltage-gated potassium channel antibodies in encephalitis. *Nat Rev Neurol*. 2017;13(5):290–301.
42. Dalmau J, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7(12):1091–1098.
43. Viaccoz A, et al. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. *Neurology*. 2014;82(7):556–563.
44. Irani SR, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain*. 2010;133(pt 6):1655–1667.
45. Lai M, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol*. 2009;65(4):424–434.
46. Joubert B, et al. Clinical spectrum of encephalitis

associated with antibodies against the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor: case series and review of the literature. *JAMA Neurol*. 2015;72(10):1163–1169.

47. Lancaster E, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol*. 2010;9(1):67–76.

48. Höftberger R, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. *Neurology*. 2013;81(17):1500–1506.

49. Spatola M, et al. Encephalitis with mGluR5 antibodies: symptoms and antibody effects. *Neurology*. 2018;90(22):e1964–e1972.

50. van Sonderen A, et al. The clinical spectrum of Caspr2 antibody-associated disease. *Neurology*. 2016;87(5):521–528.

51. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. *J Child Neurol*. 2012;27(11):1460–1469.

52. Sai Y, Zhang X, Feng M, Tang J, Liao H, Tan L. Clinical diagnosis and treatment of pediatric anti-N-methyl-D-aspartate receptor encephalitis: a single center retrospective study. *Exp Ther Med*. 2018;16(2):1442–1448.

53. Titulaer MJ, 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.

54. Armangue T, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr*. 2013;162(4):850–856.e2.

55. Höftberger R, et al. Encephalitis and AMPA receptor antibodies: novel findings in a case series of 22 patients. *Neurology*. 2015;84(24):2403–2412.

56. López-Chiriboga AS, et al. LGI1 and CASPR2 neurological autoimmunity in children. *Ann Neurol*. 2018;84(3):473–480.

57. van Sonderen A, et al. Anti-LGI1 encephalitis: clinical syndrome and long-term follow-up. *Neurology*. 2016;87(14):1449–1456.

58. Petit-Pedrol M, 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.

59. Spatola M, et al. Investigations in GABAA receptor antibody-associated encephalitis. *Neurology*. 2017;88(11):1012–1020.

60. Malter MP, Helmstaedter C, Urbach H, Vincent A, Bien CG. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. *Ann Neurol*. 2010;67(4):470–478.

61. Gresa-Arribas N, et al. Antibodies to inhibitory synaptic proteins in neurological syndromes associated with glutamic acid decarboxylase autoimmunity. *PLoS One*. 2015;10(3):e0121364.

62. Korff CM, Dale RC. The immune system in pediatric seizures and epilepsies. *Pediatrics*. 2017;140(3):e20163534.

63. Carreño M, et al. Epilepsy surgery in drug resistant temporal lobe epilepsy associated with neuronal antibodies. *Epilepsy Res*. 2017;129:101–105.

64. Graus F, Ribalta T, Campo E, Monforte R, Urbano A, Rozman C. Immunohistochemical analysis of the immune reaction in the nervous system in paraneoplastic encephalomyelitis. *Neurology*. 1990;40(2):219–222.

65. Bien CG, et al. Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. *Brain*. 2012;135(pt 5):1622–1638.

66. Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. *Neurology*. 2011;77(6):589–593.

67. Camdessanché JP, et al. Brain immunohisto-pathological study in a patient with anti-NMDAR encephalitis. *Eur J Neurol*. 2011;18(6):929–931.

68. Bauer J, et al. Innate and adaptive immunity in human epilepsies. *Epilepsia*. 2017;58(suppl 3):57–68.

69. van Vliet EA, Aronica E, Vezzani A, Ravizza T. Review: Neuroinflammatory pathways as treatment targets and biomarker candidates in epilepsy: emerging evidence from preclinical and clinical studies. *Neuropathol Appl Neurobiol*. 2018;44(1):91–111.

70. Vezzani A, Dingledine R, Rossetti AO. Immunity and inflammation in status epilepticus and its sequelae: possibilities for therapeutic application. *Expert Rev Neurother*. 2015;15(9):1081–1092.

71. Iori V, Frigerio F, Vezzani A. Modulation of neuronal excitability by immune mediators in epilepsy. *Curr Opin Pharmacol*. 2016;26:118–123.

72. Vezzani A, Viviani B. Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. *Neuropharmacology*. 2015;96(pt A):70–82.

73. Rojas A, et al. Cyclooxygenase-2 in epilepsy. *Epilepsia*. 2014;55(1):17–25.

74. Cerri C, Caleo M, Bozzi Y. Chemokines as new inflammatory players in the pathogenesis of epilepsy. *Epilepsy Res*. 2017;136:77–83.

75. Fabene PF, et al. A role for leukocyte-endothelial adhesion mechanisms in epilepsy. *Nat Med*. 2008;14(12):1377–1383.

76. Librizzi L, Regondi MC, Pastori C, Frigerio S, Frassoni C, de Curtis M. Expression of adhesion factors induced by epileptiform activity in the endothelium of the isolated guinea pig brain in vitro. *Epilepsia*. 2007;48(4):743–751.

77. van Vliet EA, da Costa Araújo S, Redeker S, van Schaik R, Aronica E, Gorter JA. Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy. *Brain*. 2007;130(pt 2):521–534.

78. Cacheaux LP, et al. Transcriptome profiling reveals TGF-beta signaling involvement in epileptogenesis. *J Neurosci*. 2009;29(28):8927–8935.

79. Heinemann U, Kaufer D, Friedman A. Blood-brain barrier dysfunction, TGFβ signaling, and astrocyte dysfunction in epilepsy. *Glia*. 2012;60(8):1251–1257.

80. Kim SY, et al. TGFβ signaling is associated with changes in inflammatory gene expression and perineuronal net degradation around inhibitory neurons following various neurological insults. *Sci Rep*. 2017;7(1):7711.

81. Berg AT, Darefsky AS, Holford TR, Shinnar S. Seizures with fever after unprovoked seizures: an analysis in children followed from the time of a first febrile seizure. *Epilepsia*. 1998;39(1):77–80.

82. Dubé CM, et al. Epileptogenesis provoked by prolonged experimental febrile seizures: mechanisms and biomarkers. *J Neurosci*. 2010;30(22):7484–7494.

83. Maroso M, et al. Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. *Nat Med*. 2010;16(4):413–419.

84. Walker A, et al. Proteomic profiling of epileptogenesis in a rat model: focus on inflammation. *Brain Behav Immun*. 2016;53:138–158.

85. Ravizza T, et al. High Mobility Group Box 1 is a novel pathogenic factor and a mechanistic biomarker for epilepsy. *Brain Behav Immun*. 2018;72:14–21.

86. Shi Y, Zhang L, Teng J, Miao W. HMGB1 mediates microglia activation via the TLR4/NF-κB pathway in coriaria lactone induced epilepsy. *Mol Med Rep*. 2018;17(4):5125–5131.

87. O'Neill LA, Kaltschmidt C. NF-κB: a crucial transcription factor for glial and neuronal cell function. *Trends Neurosci*. 1997;20(6):252–258.

88. Balosso S, et al. A novel non-transcriptional pathway mediates the proconvulsive effects of interleukin-1β. *Brain*. 2008;131(pt 12):3256–3265.

89. Viviani B, et al. Interleukin-1beta enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. *J Neurosci*. 2003;23(25):8692–8700.

90. Roseti C, et al. GABAA currents are decreased by IL-1β in epileptogenic tissue of patients with temporal lobe epilepsy: implications for ictogenesis. *Neurobiol Dis*. 2015;82:311–320.

91. Hu S, Sheng WS, Ehrlich LC, Peterson PK, Chao CC. Cytokine effects on glutamate uptake by human astrocytes. *Neuroimmunomodulation*. 2000;7(3):153–159.

92. Ladépêche L, et al. NMDA receptor autoantibodies in autoimmune encephalitis cause a subunit-specific nanoscale redistribution of NMDA receptors. *Cell Rep*. 2018;23(13):3759–3768.

93. Leypoldt F, et al. Investigations on CXCL13 in anti-N-methyl-D-aspartate receptor encephalitis: a potential biomarker of treatment response. *JAMA Neurol*. 2015;72(2):180–186.

94. Hughes EG, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci*. 2010;30(17):5866–5875.

95. Haselmann H, et al. Human autoantibodies against the AMPA receptor subunit GluA2 induce receptor reorganization and memory dysfunction. *Neuron*. 2018;100(1):91–105.e9.

96. 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.

97. Gleichman AJ, Spruce LA, Dalmau J, Seeholzer SH, Lynch DR. Anti-NMDA receptor encephalitis antibody binding is dependent on amino acid identity of a small region within the GluN1 amino terminal domain. *J Neurosci*. 2012;32(32):11082–11094.

98. Kreye J, et al. Human cerebrospinal fluid monoclonal N-methyl-D-aspartate receptor autoantibodies are sufficient for encephalitis pathogenesis. *Brain*. 2016;139(pt 10):2641–2652.

99. Vicini S, et al. Functional and pharmacological differences between recombinant N-methyl-D-aspartate receptors. *J Neurophysiol*. 1998;79(2):555–566.

100. Shipton OA, Paulsen O. GluN2A and GluN2B

subunit-containing NMDA receptors in hippocampal plasticity. *Philos Trans R Soc Lond B Biol Sci*. 2014;369(1633):20130163.

101. Mikasova L, et al. Disrupted surface cross-talk between NMDA and Ephrin-B2 receptors in anti-NMDA encephalitis. *Brain*. 2012;135(pt 5):1606–1621.

102. Nolt MJ, et al. EphB controls NMDA receptor function and synaptic targeting in a subunit-specific manner. *J Neurosci*. 2011;31(14):5353–5364.

103. Planagumà J, et al. Human N-methyl D-aspartate receptor antibodies alter memory and behaviour in mice. *Brain*. 2015;138(pt 1):94–109.

104. Malviya M, et al. NMDAR encephalitis: passive transfer from man to mouse by a recombinant antibody. *Ann Clin Transl Neurol*. 2017;4(11):768–783.

105. Planagumà J, et al. Ephrin-B2 prevents N-methyl-D-aspartate receptor antibody effects on memory and neuroplasticity. *Ann Neurol*. 2016;80(3):388–400.

106. Würdemann T, et al. Stereotactic injection of cerebrospinal fluid from anti-NMDA receptor encephalitis into rat dentate gyrus impairs NMDA receptor function. *Brain Res*. 2016;1633:10–18.

107. Wright S, et al. Epileptogenic effects of NMDAR antibodies in a passive transfer mouse model. *Brain*. 2015;138(pt 11):3159–3167.

108. Schwenk J, et al. High-resolution proteomics unravel architecture and molecular diversity of native AMPA receptor complexes. *Neuron*. 2012;74(4):621–633.

109. Greger IH, Watson JF, Cull-Candy SG. Structural and functional architecture of AMPA-type glutamate receptors and their auxiliary proteins. *Neuron*. 2017;94(4):713–730.

110. Isaac JT, Ashby MC, McBain CJ. The role of the GluR2 subunit in AMPA receptor function and synaptic plasticity. *Neuron*. 2007;54(6):859–871.

111. Gleichman AJ, Panzer JA, Baumann BH, Dalmau J, Lynch DR. Antigenic and mechanistic characterization of anti-AMPA receptor encephalitis. *Ann Clin Transl Neurol*. 2014;1(3):180–189.

112. Peng X, Hughes EG, Moscato EH, Parsons TD, Dalmau J, Balice-Gordon RJ. Cellular plasticity induced by anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor encephalitis antibodies. *Ann Neurol*. 2015;77(3):381–398.

113. Egbenya DL, Hussain S, Lai YC, Xia J, Anderson AE, Davanger S. Changes in synaptic AMPA receptor concentration and composition in chronic temporal lobe epilepsy. *Mol Cell Neurosci*. 2018;92:93–103.

114. Malkin SL, et al. Changes of AMPA receptor properties in the neocortex and hippocampus following pilocarpine-induced status epilepticus in rats. *Neuroscience*. 2016;327:146–155.

115. Sirerol-Piquer MS, et al. The epilepsy gene LGI1 encodes a secreted glycoprotein that binds to the cell surface. *Hum Mol Genet*. 2006;15(23):3436–3445.

116. Staub E, et al. The novel EPTP repeat defines a superfamily of proteins implicated in epileptic disorders. *Trends Biochem Sci*. 2002;27(9):441–444.

117. Fukata Y, et al. Disruption of LGI1-linked synaptic complex causes abnormal synaptic transmission and epilepsy. *Proc Natl Acad Sci U S A*. 2010;107(8):3799–3804.

118. Morante-Redolat JM, et al. Mutations in the LGI1/Epitempin gene on 10q24 cause autosomal dominant lateral temporal epilepsy. *Hum Mol Genet*. 2002;11(9):1119–1128.

119. Kalachikov S, et al. Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. *Nat Genet*. 2002;30(3):335–341.

120. Ohkawa T, 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.

121. Petit-Pedrol M, et al. LGI1 antibodies alter Kv1.1 and AMPA receptors changing synaptic excitability, plasticity and memory. *Brain*. 2018;141(11):3144–3159.

122. Lalic T, Pettingill P, Vincent A, Capogna M. Human limbic encephalitis serum enhances hippocampal mossy fiber-CA3 pyramidal cell synaptic transmission. *Epilepsia*. 2011;52(1):121–131.

123. Di Bonaventura C, et al. Low penetrance and effect on protein secretion of LGI1 mutations causing autosomal dominant lateral temporal epilepsy. *Epilepsia*. 2011;52(7):1258–1264.

124. Striano P, et al. A novel loss-of-function LGI1 mutation linked to autosomal dominant lateral temporal epilepsy. *Arch Neurol*. 2008;65(7):939–942.

125. Schwenk J, et al. Native GABA(B) receptors are heteromultimers with a family of auxiliary subunits. *Nature*. 2010;465(7295):231–235.

126. Kulik A, et al. Subcellular localization of metabotropic GABA(B) receptor subunits GABA(B1a/b) and GABA(B2) in the rat hippocampus. *J Neurosci*. 2003;23(35):11026–11035.

127. Jain A, Lancaster E, Dalmau J, Balice-Gordon RJ. Autoantibodies in the CSF of anti-GABA receptor encephalitis patients block activation of GABA receptors in vitro. *Ann Neurol*. 2015;78(suppl_19):S77.

128. Bien CG, Holtkamp M. "Autoimmune epilepsy": encephalitis with autoantibodies for epileptologists. *Epilepsy Curr*. 2017;17(3):134–141.

129. Nabbout R. Autoimmune and inflammatory epilepsies. *Epilepsia*. 2012;53(suppl 4):58–62.

130. Toledano M, Pittock SJ. Autoimmune epilepsy. *Semin Neurol*. 2015;35(3):245–258.

131. Dubey D, et al. Retrospective case series of the clinical features, management and outcomes of patients with autoimmune epilepsy. *Seizure*. 2015;29:143–147.

132. Dubey D, et al. Predictive models in the diagnosis and treatment of autoimmune epilepsy. *Epilepsia*. 2017;58(7):1181–1189.

133. Gaspard N, et al. New-onset refractory status epilepticus: etiology, clinical features, and outcome. *Neurology*. 2015;85(18):1604–1613.

134. Iizuka T, et al. Cryptogenic NORSE: its distinctive clinical features and response to immunotherapy. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(6):e396.

135. Wells E, et al. Neuroimmune disorders of the central nervous system in children in the molecular era. *Nat Rev Neurol*. 2018;14(7):433–445.

136. Toledano M, et al. Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy. *Neurology*. 2014;82(18):1578–1586.

137. Graus F, et al. Syndrome and outcome of antibody-negative limbic encephalitis. *Eur J Neurol*. 2018;25(8):1011–1016.

138. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. *Lancet Neurol*. 2011;10(6):561–572.

139. Dubey D, et al. Autoimmune GFAP astrocytopathy: prospective evaluation of 90 patients in 1 year. *J Neuroimmunol*. 2018;321:157–163.

140. Jarius S, et al. MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. *J Neuroinflammation*. 2018;15(1):134.

141. Ogawa R, et al. MOG antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(2):e322.

142. Hamid SHM, et al. Seizures and encephalitis in myelin oligodendrocyte glycoprotein IgG disease vs aquaporin 4 IgG disease. *JAMA Neurol*. 2018;75(1):65–71.

143. van Sonderen A, et al. The relevance of VGKC positivity in the absence of LGI1 and Caspr2 antibodies. *Neurology*. 2016;86(18):1692–1699.

144. Graus F, Gorman MP. Voltage-gated potassium channel antibodies: game over. *Neurology*. 2016;86(18):1657–1658.

145. Nóbrega-Jr AW, et al. Mesial temporal lobe epilepsy with hippocampal sclerosis is infrequently associated with neuronal autoantibodies. *Epilepsia*. 2018;59(9):e152–e156.

146. Borusiak P, et al. Autoantibodies to neuronal antigens in children with focal epilepsy and no prima facie signs of encephalitis. *Eur J Paediatr Neurol*. 2016;20(4):573–579.

147. Garcia-Tarodo S, Datta AN, Ramelli GP, Maréchal-Rouiller F, Bien CG, Korff CM. Circulating neural antibodies in unselected children with new-onset seizures. *Eur J Paediatr Neurol*. 2018;22(3):396–403.

148. Graus F, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry*. 2004;75(8):1135–1140.

149. Alink J, de Vries TW. Unexplained seizures, confusion or hallucinations: think Hashimoto encephalopathy. *Acta Paediatr*. 2008;97(4):451–453.

150. Zhou JY, Xu B, Lopes J, Blamoun J, Li L. Hashimoto encephalopathy: literature review. *Acta Neurol Scand*. 2017;135(3):285–290.

151. Gresa-Arribas N, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol*. 2014;13(2):167–177.

152. Dalva MB, et al. EphB receptors interact with NMDA receptors and regulate excitatory synapse formation. *Cell*. 2000;103(6):945–956.

153. Warikoo N, et al. Positive allosteric modulation as a potential therapeutic strategy in anti-NMDA receptor encephalitis. *J Neurosci*. 2018;38(13):3218–3229.

154. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. *N Engl J Med*. 2003;349(16):1543–1554.

155. Ariño H, et al. Anti-LGI1-associated cognitive impairment: presentation and long-term outcome. *Neurology*. 2016;87(8):759–765.

156. Irani SR, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. *Brain*. 2013;136(pt 10):3151–3162.

157. Joubert B, et al. Characterization of a subtype of

autoimmune encephalitis with anti-contactin-associated protein-like 2 antibodies in the cerebrospinal fluid, prominent limbic symptoms, and seizures. *JAMA Neurol*. 2016;73(9):1115–1124.

158. Irani SR, et al. Morvan syndrome: clinical and serological observations in 29 cases. *Ann Neurol*. 2012;72(2):241–255.

159. Dale RC, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. *Brain*. 2012;135(pt 11):3453–3468.

160. Hara M, et al. DPPX antibody-associated encephalitis: main syndrome and antibody effects. *Neurology*. 2017;88(14):1340–1348.

161. Carvajal-González A, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. *Brain*. 2014;137(pt 8):2178–2192.

162. Gresa-Arribas N, et al. Human neurexin-3α antibodies associate with encephalitis and alter synapse development. *Neurology*. 2016;86(24):2235–2242.

163. Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology*. 2012;79(11):1094–1100.

164. Sonderen AV, et al. Predictive value of electroencephalography in anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry*. 2018;89(10):1101–1106.

165. Thompson J, et al. The importance of early immunotherapy in patients with faciobrachial dystonic seizures. *Brain*. 2018;141(2):348–356.

166. Flanagan EP, et al. Basal ganglia T1 hyperintensity in LGI1-autoantibody faciobrachial dystonic seizures. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(6):e161.

167. Navarro V, et al. Motor cortex and hippocampus are the two main cortical targets in LGI1-antibody encephalitis. *Brain*. 2016;139(pt 4):1079–1093.

168. Feyissa AM, et al. Antiepileptic drug therapy in autoimmune epilepsy associated with antibodies targeting the leucine-rich glioma-inactivated protein 1. *Epilepsia Open*. 2018;3(3):348–356.

169. Tobin WO, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. *Neurology*. 2014;83(20):1797–1803.

170. Forrest D, et al. Targeted disruption of NMDA receptor 1 gene abolishes NMDA response and results in neonatal death. *Neuron*. 1994;13(2):325–338.

171. Nakazawa K, et al. Requirement for hippocampal CA3 NMDA receptors in associative memory recall. *Science*. 2002;297(5579):211–218.

172. Shimizu E, Tang YP, Rampon C, Tsien JZ. NMDA receptor-dependent synaptic reinforcement as a

crucial process for memory consolidation. *Science*. 2000;290(5494):1170–1174.

173. Korotkova T, Fuchs EC, Ponomarenko A, von Engelhardt J, Monyer H. NMDA receptor ablation on parvalbumin-positive interneurons impairs hippocampal synchrony, spatial representations, and working memory. *Neuron*. 2010;68(3):557–569.

174. Shimshek DR, et al. Forebrain-specific glutamate receptor B deletion impairs spatial memory but not hippocampal field long-term potentiation. *J Neurosci*. 2006;26(33):8428–8440.

175. Shimshek DR, et al. Enhanced odor discrimination and impaired olfactory memory by spatially controlled switch of AMPA receptors. *PLoS Biol*. 2005;3(11):e354.

176. Lu W, et al. Subunit composition of synaptic AMPA receptors revealed by a single-cell genetic approach. *Neuron*. 2009;62(2):254–268.

177. Zhou YD, Lee S, Jin Z, Wright M, Smith SE, Anderson MP. Arrested maturation of excitatory synapses in autosomal dominant lateral temporal lobe epilepsy. *Nat Med*. 2009;15(10):1208–1214.

178. 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.

179. Seagar M, et al. LGI1 tunes intrinsic excitability by regulating the density of axonal Kv1 channels. *Proc Natl Acad Sci U S A*. 2017;114(29):7719–7724.

180. Boillot M, Lee CY, Allene C, Leguern E, Baulac S, Rouach N. LGI1 acts presynaptically to regulate excitatory synaptic transmission during early postnatal development. *Sci Rep*. 2016;6:21769.

181. Schuler V, et al. Epilepsy, hyperalgesia, impaired memory, and loss of pre- and postsynaptic GABA(B) responses in mice lacking GABA(B(1)). *Neuron*. 2001;31(1):47–58.

182. Prosser HM, et al. Epileptogenesis and enhanced prepulse inhibition in GABA(B1)-deficient mice. *Mol Cell Neurosci*. 2001;17(6):1059–1070.

183. Waldmeier PC, Kaupmann K, Urwyler S. Roles of GABAB receptor subtypes in presynaptic auto- and heteroreceptor function regulating GABA and glutamate release. *J Neural Transm (Vienna)*. 2008;115(10):1401–1411.

184. Pinatel D, et al. Inhibitory axons are targeted in hippocampal cell culture by anti-Caspr2 autoantibodies associated with limbic encephalitis. *Front Cell Neurosci*. 2015;9:265.

185. Poliak S, et al. Juxtaparanodal clustering of Shaker-like K+ channels in myelinated axons depends on Caspr2 and TAG-1. *J Cell Biol*. 2003;162(6):1149–1160.

186. Horresh I, Poliak S, Grant S, Bredt D, Rasband MN, Peles E. Multiple molecular interactions

determine the clustering of Caspr2 and Kv1 channels in myelinated axons. *J Neurosci*. 2008;28(52):14213–14222.

187. Jia Z, et al. Selective abolition of the NMDA component of long-term potentiation in mice lacking mGluR5. *Learn Mem*. 1998;5(4–5):331–343.

188. Lu YM, et al. Mice lacking metabotropic glutamate receptor 5 show impaired learning and reduced CA1 long-term potentiation (LTP) but normal CA3 LTP. *J Neurosci*. 1997;17(13):5196–5205.

189. Witkin JM, Baez M, Yu J, Eiler WJ. mGlu5 receptor deletion does not confer seizure protection to mice. *Life Sci*. 2008;83(9-10):377–380.

190. Guo W, et al. Selective disruption of metabotropic glutamate receptor 5-Homer interactions mimics phenotypes of fragile X syndrome in mice. *J Neurosci*. 2016;36(7):2131–2147.

191. Sun W, Maffie JK, Lin L, Petralia RS, Rudy B, Hoffman DA. DPP6 establishes the A-type K(+) current gradient critical for the regulation of dendritic excitability in CA1 hippocampal neurons. *Neuron*. 2011;71(6):1102–1115.

192. Lin L, et al. DPP6 loss impacts hippocampal synaptic development and induces behavioral impairments in recognition, learning and memory. *Front Cell Neurosci*. 2018;12:84.

193. Ohkawa T, et al. Identification and characterization of GABA(A) receptor autoantibodies in autoimmune encephalitis. *J Neurosci*. 2014;34(24):8151–8163.

194. Hirose S. Mutant GABA(A) receptor subunits in genetic (idiopathic) epilepsy. *Prog Brain Res*. 2014;213:55–85.

195. Missler M, et al. Alpha-neurexins couple Ca²⁺ channels to synaptic vesicle exocytosis. *Nature*. 2003;423(6943):939–948.

196. Aoto J, Földy C, Ilcus SM, Tabuchi K, Südhof TC. Distinct circuit-dependent functions of presynaptic neurexin-3 at GABAergic and glutamatergic synapses. *Nat Neurosci*. 2015;18(7):997–1007.

197. López-Chiriboga AS, et al. Association of MOG-IgG serostatus with relapse after acute disseminated encephalomyelitis and proposed diagnostic criteria for MOG-IgG-associated disorders. *JAMA Neurol*. 2018;75(11):1355–1363.

198. Lin JJ, et al. Antiglutamic acid decarboxylase antibodies in children with encephalitis and status epilepticus. *Pediatr Neurol*. 2012;47(4):252–258.

199. Venkatesan A, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis*. 2013;57(8):1114–1128.

200. Nabbout R, Vezzani A, Dulac O, Chiron C. Acute encephalopathy with inflammation-mediated status epilepticus. *Lancet Neurol*. 2011;10(1):99–108.