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DISSERTATION

Imaging alterations in autoimmune encephalitis: systematic review and meta-analysis

Bildgebende Veränderungen bei Autoimmunenzephalitis: systematischer Review und Meta-Analyse

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List of Abbreviations

Abbreviation	Definition
AIE	Autoimmune encephalitis
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
CA	Cornu ammonis
CASPR2	Contactin-associated protein-like 2
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
DPPX	Dipeptidyl-peptidase-like protein-6
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
D2R	Dopamine-2 receptor
FBDS	Faciobrachial-dystonic seizures
FDG-PET	^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography
GABA	Gamma-aminobutyric acid
GAD	Glutamic acid decarboxylase
GFAP	Glial fibrillary acidic protein
GlyR	Glycine receptor
IgG	Immunoglobulin G
LE	Limbic encephalitis
LFK	Luis Furuya-Kanamori
LGI1	Leucine-rich glioma-inactivated 1
mGluR1	Metabotrobic glutamate receptor 1
mGluR5	Metabotrobic glutamate receptor 5
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NMDAR	N-methyl-D-aspartate receptor
OMS	Opsoclonus-myoclonus syndrome
PERM	Progressive encephalomyelitis with rigidity and myoclonus
PNS	Peripheral nervous system
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SCLC	Small cell lung cancer
SPECT	Single photon emission tomography
VGKC	Voltage-gated potassium channels

Summary/Abstract

Considering the severity and the rapid progress of autoimmune encephalitides, an early diagnosis is essential. To facilitate diagnosis, we aim to create a deeper understanding of the condition. Therefore, we systematically review imaging alterations occurring in different subtypes of autoimmune encephalitis. Our goal is to find patterns in these changes with possible relation to the patients' clinical features. Here, we focus on autoimmune conditions caused by autoantibodies targeting neuronal cell surface structures, as these show a significantly better outcome after early diagnosis and treatment.

We first defined a search query and set up inclusion/exclusion criteria for the articles. We used PubMed and Google Scholar for articles published in 2007-2021, with a dedicated query for each autoantibody. The reports were summarized in tables regarding the neuroimaging findings in relation to their timing, the patients' demographics, and symptoms. We then visualized our results graphically. In a meta-analysis with the MetaXL statistics package, we derived a heterogeneity analysis and assessed the risk of bias to obtain a pooled summary.

Of 1.748 articles identified, 177 were included in our meta-analysis. This translates into a total of 5050 patients. The pooled prevalence of MRI changes for each autoimmune encephalitis subtype varies from 0.11 (CI: 0-0.33) for igLON5 disease to 0.86 (CI: 0.7-0.97) for AMPAR encephalitis. We find that nearly all heterogeneity values obtained in our pooling analysis are still high and show a considerable variation (I^2 0-90 %). This implies that pooling all antibodies in summarized studies is still challenging. It could be due to several factors, such as the diverse underlying pathologies or the small number of patients currently included in the studies. However, our results confirm the findings of prior, smaller meta-analyses and further enhance their results. When pooling the prevalence of MRI changes over all subtypes collectively, the statistical findings of our meta-analysis are in excellent agreement with the results in studies most recently published.[11]

To explore whether the heterogeneity is lower when considering a different subset of the imaging data, we analyzed the MRIs of the post-acute disease stage. This was only feasible for the two encephalitis subtypes with the most published cases (NMDAR and LGI1). For LGI1 encephalitis, we found similar heterogeneity between the studies reporting acute and post-acute MRI changes (I^2 76 % vs. 74 %), while for NMDA, encephalitis I^2 was significantly lower (I^2 73 % vs. 61 %).

The encephalitis subtype where we found the most significant result was anti-$GABA_b$ encephalitis. Here we detected a high pooled prevalence of MRI changes (0.63) associated with a low heterogeneity (I^2 19 %) while including a larger number of studies (12).

Zusammenfassung/Abstract

Aufgrund des Schweregrads und der raschen Progredienz der Autoimmunenzephalitiden ist eine frühzeitige Diagnose entscheidend. Um die Diagnose zu erleichtern, möchten wir ein tieferes Verständnis der Erkrankung schaffen. Daher untersuchen wir systematisch die bei den Autoimmunenzephalitiden auftretenden bildgebende Veränderungen. Unser Ziel ist es, Muster in den Veränderungen zu finden, die mit den klinischen Merkmalen der Patienten assoziiert sind. Wir konzentrieren uns hier auf Autoimmunenzephalitiden, die durch neuronale Zelloberflächenantikörper verursacht werden. Diese weisen bei einer frühzeitigen Diagnose und Therapie einen deutlich besseren Verlauf auf.

Zunächst definierten wir eine Suchanfrage und legten Aus-/Einschlusskriterien für die Artikel fest. Für jeden Autoantikörper wurde eine dedizierte Abfrage in PubMed und Google Scholar angewendet auf Artikel, die zwischen 2007-2021 veröffentlicht wurden. Die Artikel wurden in Tabellen zusammengefasst, in denen die Befunde der neurologischen Bildgebung in Bezug auf den Zeitpunkt, die demografischen Merkmale und Symptome der Patienten dargestellt wurden. Unsere Ergebnisse haben wir in mit FSLeyes erstellten Grafiken visualisiert. In einer Meta-Analyse mit dem Statistikpaket MetaXL poolten wir die Ergebnisse, führten eine Heterogenitätsanalyse durch und bewerteten das Risk of Bias.

Von 1.748 identifizierten Artikeln wurden 177 ≙ 5050 Patienten in unsere Meta-Analyse aufgenommen. Die gepoolte Prävalenz von MRT-Veränderungen für die einzelnen Subtypen schwankt zwischen 0,11 (CI: 0-0,33) für die igLON5-Erkrankung und 0,86 (CI: 0,7-0,97) für die AMPAR-Enzephalitis. Die in unserer Pooling-Analyse ermittelten Heterogenitätswerte variieren ebenfalls, sind jedoch meist hoch (I^2 0-90 %). Daraus zeigt sich, dass es schwierig ist, die Antikörper in Studien zusammenzufassen. Dies könnte z.B. auf die unterschiedlichen zugrundeliegenden Pathologien und häufigen Einzelfallstudien zurückzuführen sein. Unsere Ergebnisse bestätigen jedoch die Ergebnisse früherer, kleinerer Meta-Analysen. Bei Berücksichtigung aller Autoantikörper gemeinsam, stimmen unsere statistischen Ergebnisse für die gepoolte Prävalenz von MRT Veränderungen hervorragend mit zuletzt veröffentlichten Studien[1] überein[1].

Um zu untersuchen, ob die Heterogenität sinkt bei Betrachten einer Subgruppe, haben wir MRT Veränderungen des postakuten Krankheitsstadiums analysiert. Dies war nur für die beiden Subtypen mit den meisten veröffentlichten Fällen möglich. Bei der LGI1-Enzephalitis fanden wir eine ähnliche Heterogenität zwischen den Studien des akuten und postakuten Zustands (I^2 76 % vs. 74 %), bei NMDA-Enzephalitis sankt I^2 deutlicher in der postakuten Analyse (I^2 73 % vs. 61%).

Für Anti-$GABA_b$-Enzephalitis fanden wir das signifikanteste Ergebnis. Hier stellten wir eine hohe gepoolte Prävalenz von MRT-Veränderungen (0,63) fest, bei einer geringen Heterogenität (I^2 19 %) und Einbezug einer größeren Anzahl von Studien (12).

1 Introduction

The term encephalitis refers to a heterogeneous group of neuroinflammatory chronicle illnesses. 20 % of all forms of encephalitis are immune-modulated, often through autoantibodies.[2] Usually, the immune system functions to protect the body from pathogens. In some cases, however, it mistakenly starts attacking healthy functioning body tissue. These mechanisms are referred to as autoimmune reactions, which are carried out via autoantibodies.

Autoimmune diseases are becoming increasingly recognized in our society. Around 7-9 % of the population suffer from one of more than eighty different autoimmune conditions.[3] The exact cause is usually unknown and probably based on a multifactorial genesis. Various factors, such as genetics or environmental influences, can play an important role. Autoantibodies can be directed against different structures in the body, for instance, against cells of the central nervous system (CNS). As a result, an autoimmune encephalitis (AIE) can develop.

Until the 1960s, inflammatory and degenerative brain changes were assumed to be restricted to areas caudal of the basal ganglia.[4] With the description of the first cases of a paraneoplastic syndrome displaying significant changes in the medial temporal lobe, the term 'limbic encephalitis' (LE) was coined. The patients identified presented with cognitive and behavioral changes, as well as seizures. In addition, they were suffering from an underlying small cell lung cancer (SCLC). In post-mortem histological studies, lesions were found spreading to different brain regions, although mainly concentrated in the limbic grey matter. At that time, the 'limbic encephalitis' was believed to be nearly always of paraneoplastic origin.[5–7] The term limbic encephalitis today describes an inflammation of brain tissue with clinical or radiological restriction to the limbic system. The limbic system involves the mediotemporal lobes, as well as frontobasal and cingular areas. Although the syndrome is well-defined, it is still not sufficiently understood.[8]

In the following years, similar disorders with autoantibodies directed against brain structures were identified. In patients with paraneoplastic cerebellar ataxia, the first autoantibody directed against a cell surface structure was discovered, targeting the metabotrobic glutamate receptor 1 (mGluR1).[9] In two patients with characteristic symptoms of LE and no known paraneoplastic antibodies, immunoglobulin G (IgG) targeting voltage-gated potassium channels (VGKC) was detected.[10] Only one of these patients had an associated tumor. Subsequently, an increasing number of autoimmune encephalitides without an underlying malignancy were discovered. These subtypes proved sensitive to immunotherapy and correlated with a better prognosis.[11,12]

In 2007, with the finding of anti-N-methyl-D-aspartate receptor (NMDAR) antibodies,[13] the most frequent subtype of AIE was discovered, accounting for around 4 % of all encephalitides.[2] Since then, numerous novel neuronal autoantibodies and their associated clinical syndromes have been identified.

It is common to subdivide the autoantibody-mediated forms of encephalitis into two groups.[2] On the one hand, there are the ones that are associated with autoantibodies targeting proteins on neuronal cell surfaces or synapses. On the other hand, there are antibodies directed against intracellular antigens. The antibodies directed against intracellular antigens most frequently bind to the neuronal nuclear antigen Hu. Other antibodies were found targeting cytosolic or synaptic vesicular proteins such as Amphiphysin, CV2/CRMP5, Yo, or Ri.[14] These types of autoimmune encephalitides are considered of mainly paraneoplastic origin. As opposed to the direct immune responses of cell surface autoantibodies, the onconeural antibodies' immune reaction is carried out via cytotoxic T-cells. Overall, the patients have a lower response to immunotherapy or cancer treatment and, therefore, a poorer outcome.[2] This project will only acknowledge the types of encephalitis related to antibodies against the different neuronal cell surface structures. These show similarities for each subtype, respectively, regarding presentation and outcome. In contrast, a broader phenotype is created by antibodies to intracellular onconeural proteins.

Nevertheless, the condition associated with antibodies targeting neuronal cell surface structures is characterized by various limbic and extra-limbic symptoms. Typical symptoms are, for instance, cognitive impairment, confusion, seizures, personality, and behavioral changes, as well as other neurological or psychiatric manifestations. Furthermore, the patients often show rapid clinical deterioration. Especially in the early disease stage, however, the symptoms might resemble those of infectious encephalitis (e.g., fever, diarrhea, cerebrospinal fluid pleocytosis). This diverse spectrum of symptoms demonstrates the challenge of diagnosis based on a typical syndrome. Today, the diagnosis usually relies on antibody testing and responsiveness to immunotherapy.[15] As these are not always available, especially not at disease onset, the patients' diagnosis is often delayed. In addition, not every clinic can carry out extensive testing, and antibody levels can still be negative in the early stages. Likewise, testing different therapeutic strategies on the patients should not be the way to find a diagnosis.

Taking into account the often-misleading diverse clinical presentations, Graus et al.[15] published criteria to classify the probability of autoimmune encephalitis. For a further overview of typical neuroimaging features and related clinical syndromes, we reviewed existing data on the different types of autoimmune encephalitis. We thereby aimed to find characteristic imaging patterns specific to each underlying autoantibody. Clearly, describing typical patterns will not apply to all cases, as unique disease manifestations will always exist. Nevertheless, it is feasible to identify patterns based on the patients' characteristic clinical appearances combined with their imaging findings. We hope our work can serve as a guide to create a deeper understanding of this entity and thereby facilitate an earlier diagnosis.

1.1 Previous work

The imaging data of patients with autoimmune encephalitis are comparatively sparse due to the relative rarity and novelty of the entity. Many studies in the field are case studies and, therefore, cannot provide a required overview. Moreover, earlier studies usually focus on either one autoantibody or one imaging modality. Hence, it is essential to compile and evaluate the data systematically. Some examples of recently published studies following this approach are described below:

A systematic review concerned with magnetic resonance imaging (MRI) and ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) of anti-NMDAR encephalitis patients was published in 2018.[16] The review presents the typical MRI changes associated with anti-NMDAR encephalitis. However, other neuronal cell surface antibodies and advanced imaging modalities are not considered. Another [1]recent systematic review and meta-analysis conducted by Bordonne et al.[1] analyze the use of FDG-PET imaging to diagnose autoimmune encephalitis. MRI data are briefly discussed, but again no advanced imaging modalities are reviewed. Moreover, only some neuronal cell surface autoantibodies are included, and a much smaller number of studies and patients are evaluated (267 vs. 5050 patients in this study).

A related publication from 2015 gives a narrative review of articles with neuroimaging data[17]. As in this study, we also mainly focus on data from clinical routine MRI. We include additional modalities such as FDG-PET, single photon emission tomography (SPECT), diffusion tensor imaging (DTI), and functional analysis if available. As in [17], we attempt to provide means for facilitating and accelerating diagnosis and finding information regarding long-term outcomes. New findings, including newly diagnosed patients, novel autoantibodies, and advanced imaging modalities, have continuously been published over the past years. Thus, we are now able to evaluate a higher number of affected patients.

In the next section, we will give an introduction to the antibody profile of each autoimmune encephalitis subtype in alphabetic order.

1.2 Autoimmune encephalitis antibody targets

AMPAR
The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are ionotropic glutamatergic receptors transmitting fast excitatory signals. The AMPARs consist of a combination of four subunits (GluA1-GluA4) together with auxiliary subunits. The composition of the receptors varies in different brain regions and mediates receptor properties. The highest density of AMPARs can be found in the hippocampus. There, for instance, AMPARs usually consist primarily of GluA1 and GluA2 subunits. Patients with AMPAR encephalitis mostly harbor antibodies targeting the GluA2 subunit.[18]

DPPX
The dipeptidyl-peptidase-like protein-6 (DPPX) is an auxiliary membrane subunit of Kv4.2 potassium channels. It is involved in increasing the channels' surface expression and conductance. The high expression of DPPX in areas such as the hippocampus, striatum, cerebellum, and plexus myentericus is consistent with the main symptoms associated with this subtype of autoimmune encephalitis.[19]

D2R
Dopamine receptors are g-protein-coupled receptors for catecholaminergic neurotransmission. Five of these receptors (D1-D5) have been discovered so far. These receptors were divided into two groups based on their structure, as well as biochemical and pharmacological features.[20] The receptors are particularly highly expressed in the basal ganglia, cortex, hippocampus, and substantia nigra. Especially the Dopamine-2 receptor (D2R), however, has shown a strong association with the control of movement and behavior.[21]

GABA receptors
Gamma-aminobutyric acid (GABA) is the main transmitter for neuronal inhibition throughout the CNS. To inhibit neuronal activity, GABA binds ionotropic $GABA_a$ receptors or metabotropic $GABA_b$ receptors. These receptors modulate synaptic excitability and plasticity.[22] They are widely distributed all over the CNS. However, predominant locations are in the pre-and post-synaptic regions of the hippocampus, thalamus, cerebellum, and medulla spinalis.[23,24] In contrast to the g-protein coupled $GABA_b$ receptor, the $GABA_a$ receptor is ligand-gated and therefore mediates faster inhibitory neurotransmission.[25]

- **$GABA_a$ receptor**
  Petit-Pedrol and colleagues[25] discovered a selective reduction of the absolute number of the synaptic $GABA_a$ receptors in the presence of anti-$GABA_a$ receptor antibodies. In contrast to other forms of autoimmune encephalitis, an extra-synaptic relocation of the synaptic receptors is considered.

- **$GABA_b$ receptor**
  In studies on animal models, the pharmacological or genetic disruption of $GABA_b$ receptors has led to seizures, memory deficits, and changes in learning and behavior. These manifestations resembled the phenotype of limbic encephalitis. Additionally, some polymorphisms of the $GABA_b$ receptor in humans have been associated with temporal lobe epilepsy.[26] This reflects well the patients' clinical presentation.

GAD
As an intracellular synaptic protein, glutamic acid decarboxylase (GAD) is not a classical neuronal cell surface antigen. Autoantibodies usually target the 65 kilodalton isoform of GAD (GAD-65), one of the main isoforms of the glutamic acid decarboxylase. GAD-65 is solely located in presynaptic terminals. Nevertheless, it can temporarily be presented at the cell surface during vesicle

exocytosis and thereby directly interact with autoantibodies.[27] Accordingly, it is considered to be in an intermediate position as an intracellular antigen with a partially extracellular domain activity.

GFAP
In 2016, Fang and colleagues[28] detected a novel autoimmune astrocytopathy with autoantibodies targeting the glial fibrillary acidic protein (GFAP). GFAP is an intermediate filament exclusively found in astrocytes. The pathogenesis behind this form of astrocytopathy has not yet been fully understood. The GFAP astrocytopathy seems to unite the features of neuronal cell surface structure antibody-associated encephalitides while the antigen is an intermediate filament.

Glycine-R
Glycine is one of the major neurotransmitters for inhibitory pathways in the CNS. The glycine receptor (GlyR) is predominantly expressed in the pontine brainstem and spinal cord. Accordingly, a disruption of the GlyR typically leads to a clinical presentation involving generalized symptoms of CNS hyperexcitability and brainstem dysfunction.[29]

IgLON5
The IgLON proteins are neuronal cell adhesion molecules with important functions during brain development. IgLON5 was the latest identified member of the IgLON family.[30]

mGluR
The metabotrobic glutamate receptors 1 and 5 (mGluR 1, 5) belong to group I of mGluRs. They both show similar mechanisms of action with an activation resulting in the potentiation of NMDA receptor activity and excitotoxicity. Moreover, both are localized predominantly in post-synapses.[31]

- **mGluR1**
  The mGluR1 is primarily found in the dendritic spines of cerebellar Purkinje cells.[32]

- **mGluR5**
  The mGluR5 is mainly expressed in post-synaptic terminals of the hippocampus and amygdala.[33]

Neurexin-3α
In 2016, Gresa-Arribas et al.[34] identified a novel autoantibody targeting the presynaptic cell adhesion molecule Neurexin-3α. Neurexins function as cell adhesion molecules and are pivotal for the development and maturation of synapses.[34]

NMDAR
The anti-NMDAR encephalitis is the best-studied subtype of autoimmune encephalitides with antibodies targeting cell surface structures. The anti-NMDAR antibodies usually form against the NR1/NR2 subunits of the glutamatergic cation channel.[35]

VGKC
VGKCs are widely distributed in neurons over the CNS and peripheral nervous systems (PNS). The channels are essential for returning to the resting state after the depolarization of a cell.[36] For many years, autoantibodies directed against VGKCs were assumed to cause very heterogenic clinical manifestations. In 2010, it was discovered that the autoantibodies, in reality, target proteins associated with the VGKC complex and not the potassium channels themselves. The associated proteins leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) are considered to be directly pathogenic. The related clinical syndromes with either LGI1 or CASPR2 antibodies are now well-defined. However, antibodies targeting the VGKC complex without reactivity to LGI1 or CASPR2 are frequent and can be present in healthy people. Therefore, it is questionable whether they are of clinical relevance.[37] Considering this, our review will only include VGKC autoantibodies with differentiation regarding LGI1 or CASPR2.

- **CASPR2**
  CASPR2 is a cell adhesion molecule. Its predominant locations in the CNS are in the hippocampus and cerebellum. Furthermore, it is also highly expressed in the PNS. The location of the antigen reflects well the typical clinical manifestations of anti-CASPR2-associated encephalitis.[38]

- **LGI1**
  LGI1 is a secreted constituent of the VGKC complex. It is predominantly found in the hippocampus and temporal cortex. Antibodies directed against LGI1 are the antibodies most frequently associated with the VGKC complex. In the Netherlands, an incidence of 0.83/million people per year was detected for anti-LGI1 encephalitis.[39]

2 Methods

This section describes the methods we used to conduct the literature search and the statistical analysis. Overall, this systematic review follows the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We preregistered our protocol in the database for open science framework (OSF; https://osf.io/ved8s).

2.1 Literature search

Our literature search was conducted using the bibliographic databases Medline via PubMed and Google Scholar. The actual search was done in February-August 2021. To identify papers meeting our eligibility criteria, we used the following search terms: Encephalitis AND Imaging OR "Magnetic Resonance Imaging" OR "Positron Emission Tomography Computed Tomography" OR "Tomography, Emission-Computed, Single-Photon" OR radiolog*, including their related terms, respectively, that were searched over the use of Medical Subject Headings (MeSH) terms. This search algorithm assures the detection of all possible imaging modalities.

For each search, we required that the name of the antibody appears in the paper's title or abstract. Only peer-reviewed journal articles published between 2007-2021 in the English language were taken into consideration. Furthermore, the studies had to describe human patients with the diagnosis of antibody-positive autoimmune encephalitis (meeting the diagnostic criteria of Graus and colleagues[15]).

All titles and abstracts of the potentially relevant articles were screened for eligibility; the retrieved full texts were assessed again to decide about consistency with the inclusion criteria. The articles were screened by one reviewer (MS), if there was any ambiguity regarding the inclusion of a study, a second reviewer (JH) was consulted. In case of any further discrepancies, a third party was then consulted (CF). For the largest groups, the LGI1- and NMDA-receptor antibodies, we restricted the eligible articles to case series studies (≥ 3 patients)/ longitudinal studies only. Articles describing a patient cohort consisting of less than three patients were excluded. For the antibody targets with less published patient data, we also collected single case studies. These were used to aggregate features of the associated entities and thereby obtain an overview for our review section. However, single case studies were excluded from the meta-analysis.

All patients with more than one antibody targeting neuronal cell structures in their serum or cerebrospinal fluid (CSF) were excluded. For larger cohort studies, we tried to extract only the patients with overlapping antibodies in order to still be able to include the ones congruent with our inclusion criteria. Additionally, all patients with other underlying conditions that could affect brain imaging were excluded. This was done as these imaging changes could not clearly be assigned to the specific antibody-associated encephalitis we were analyzing. Here again, we tried to only exclude the patients with the comorbidities and not exclude the whole study. In case of redundant patient data, due to multiple descriptions of the same patient cohort, we tried to exclude only the single patients that had previously been reported. If this restriction was not feasible, we selected the data of the larger cohort. Furthermore, we examined the reference lists of selected papers to retrieve additional relevant publications.

We used the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports[40] to further assess the methodological quality and bias evaluation of the respective studies.

Finally, we extracted data regarding the cohort size, the imaging method applied, the timing of examination, the type, and region of possible imaging alterations, the patients' demographics, and the co-occurring symptoms. Furthermore, we analyzed the potential limitations of each study. These variables, together with the publication details, were assembled in MS-Excel®.

2.2 Statistical analysis

As heterogeneity was expected across the selected studies, we applied the random effects model. We used the implementation of a random effects model as given in the MetaXL software, version 5.3.[41] MetaXL offers several methodical advantages over other methods for computing prevalences. Thus, MetaXL can prevent confidence intervals from exceeding the boundaries 0 and 1 and offers graphical plots of prevalence and heterogeneity of studies, as well as plots for bias estimators. Moreover, MetaXL allows for estimating the pooled prevalence across a set of studies with the double arcsine transformation.

Our goal was to compute the pooled prevalence of imaging alterations for each autoantibody target separately. Here, we considered MRI alterations of the acute disease stage. The number of patients in the studies varied considerably over the set of antibodies we looked at. Thus, for some antibodies, only very small numbers of patient data have been reported in the literature, while more patient data are already available for other antibodies. In addition to the variable manifestation associated with the different subtypes, this is another explanation as to why we chose to consider each antibody separately in the first step.

To visually assess heterogeneity across our studies, we generated Forest Plots. In addition to the graphical representation of prevalences proportional to the weight of the respective primary studies, the Forest Plot also shows the overall pooled prevalence, the width, and the overlap of the 95 %-confidence intervals (CIs).

Statistical heterogeneity across the studies was measured using the I^2 statistic.[42] The I^2 coefficient estimates the proportion of the across-study variance that is associated with heterogeneity instead of sampling error. Instead of testing whether heterogeneity is present, I^2 assesses to what extent the existing heterogeneity impacts the results of the meta-analysis.[42,43] Hence, an I^2 of 0 % indicates that any variation between the results is due to chance alone.[44] Likewise, higher values of I^2 correspond to more substantial heterogeneity across the studies. An I^2 value higher than 50 % suggests significant heterogeneity. The variance between the studies was further assessed with Cochran's Q statistics, which is based on a chi-square ($\chi 2$) distribution. For the calculations, we applied a level of statistical significance of 0.05 with CIs of 95 %.

We attempted to rate the study quality for each study individually with the Quality effects model.[45] As the questions to be evaluated for this type of quality assessment were not answerable for many studies, we decided that such quality rating for individual studies is not possible in our analysis or at least beyond the scope of this dissertation. Therefore, we set the quality index to 1 for all studies, which is the highest score.

We generated Funnel Plots to assess bias (publication and related). We again used MetaXL here. Funnel Plots are scatter plots with one dot per study. They show the double arcsine prevalence against the precision or standard error. To calculate the standard error, the standard deviation of the studies is divided by the square root of the sample size.[46] To confirm our findings, we further used the Doi Plot, which provides another graphical method for bias assessment. In addition, the Luis Furuya-Kanamori (LFK) index was applied for the detection and quantification of asymmetry in the Doi Plots.[47] LFK index values ± 1 were considered consistent with asymmetry. As described above, we excluded studies with less than three patients from our analysis to prevent bias.

2.2.1 Heterogeneity analysis in MetaXL

As an example, for the use of the MetaXL program, we first conducted a test run with a simple synthetic dataset. This is described in the following section.

We created a template for an analysis based on prevalences, as this was most suitable for our data. To illustrate the calculations of basic functions in MetaXL, our example should easily be reproducible and, above all, should give predictable results. In this example, we consider only three studies. We used N as the total number of patients meeting our inclusion criteria for each study respectively. The category 'changes' described the proportion of these patients showing imaging changes on MRI studies. The category 'no changes' meant no imaging alterations on MRI. The first study compromises ten patients. We assume five of these present with imaging changes, and five patients have a normal MRI. The second study consists of 100 patients, 50 with imaging alterations and 50 without. The last study in our synthetic example has 1000 participants, of which 500 have alterations on MRI and 500 have no MRI changes. Note again that this is just a synthetic example.

We then ran MetaXL on this example and analyzed the results. The findings of the application of the random effects model in MetaXL can be depicted in a Forest Plot (Figure 1). The plot gives a first impression on the heterogeneity across the studies. On the right side of the plot, the weight of each study is shown as a percentage. The weighting is based on the size of the study cohort. In the graph, this is depicted as the size of the rectangle. The CIs are illustrated in the Forest Plot as horizontal lines passing through the rectangles. The length of each line describes the width of the CI for the respective study.

As depicted in the plot, the confidence intervals decrease from study 1-3, hence becoming narrower as the size of the study increases. This means the results of a study with a greater sample size would typically be considered more reliable. Therefore, we expect the confidence interval for those studies to be smaller. The pooled confidence interval finally should have the smallest CI. Here the pooled CI appears to be identical to the CI of study 3, the largest study. We suppose this is due to number rounding.

In our example, the prevalence for each study and also the pooled prevalence equals 0.5. This is the expected result in our synthetic example, as we had classified 50 % of the patients in category 1 and 50 % in category 2.

[42]We generated the heterogeneity coefficients I^2 and Cochran's Q to identify and quantify the inter-study heterogeneity.[42] The heterogeneity values I^2 and Q are 0, as the studies are perfectly homogenous in our small example.

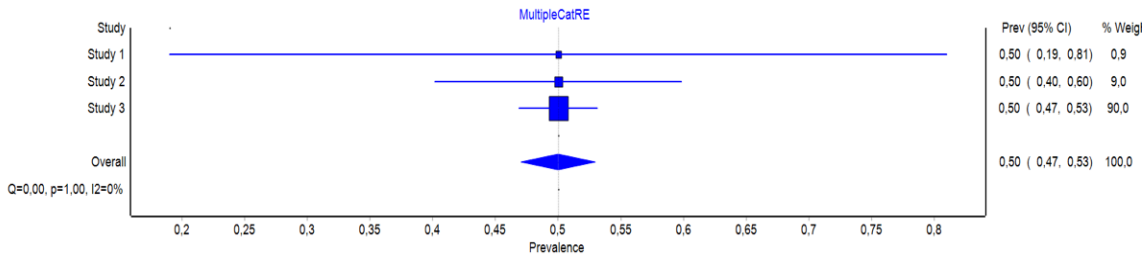


Figure 1: Forest Plot for synthetic dataset

For the next example, we create two new synthetic studies. Studies 1 and 2 each consist of 100 patients. We change the values of the patient proportion with and without imaging changes to achieve greater differences between the studies, and hence a more realistic scenario. Therefore, we determined that 40 patients in study 1 and 50 patients in study 2 had alterations in brain imaging.

As expected for this example, we see increasing heterogeneity statistics Q and I^2 and a larger pooled CI (Figure 2).

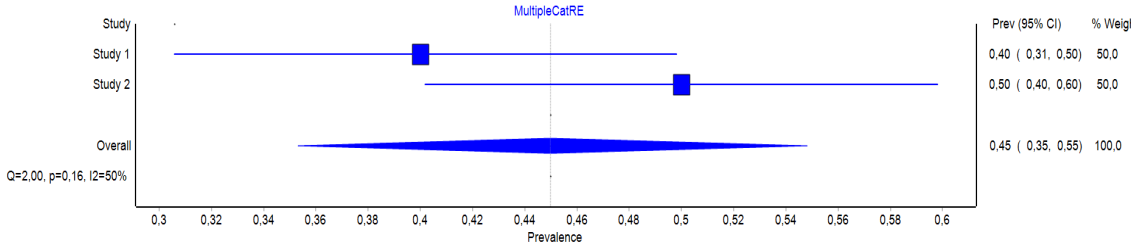


Figure 2: Forest Plot for synthetic dataset

2.2.2 Risk of bias analysis in MetaXL

To assess the risk of bias, especially publication bias, with a visual approach, we used the Funnel Plot function from MetaXL. This is illustrated in the following two figures. The first figure shows a Funnel Plot from MetaXL's internal collection of sample data distributed with the software release in version 5.3 of MetaXL.

As noted, one dot in the Funnel Plot corresponds to one study. An asymmetry in the Funnel Plot would suggest bias. Thus, the Funnel Plot shown in Figure 3a suggests bias in the data.

For the same data set, we computed the DOI Plot and obtained a consistent result visualizing major asymmetry (Figure 3b). This is supported by the associated LFK index of -9.35.

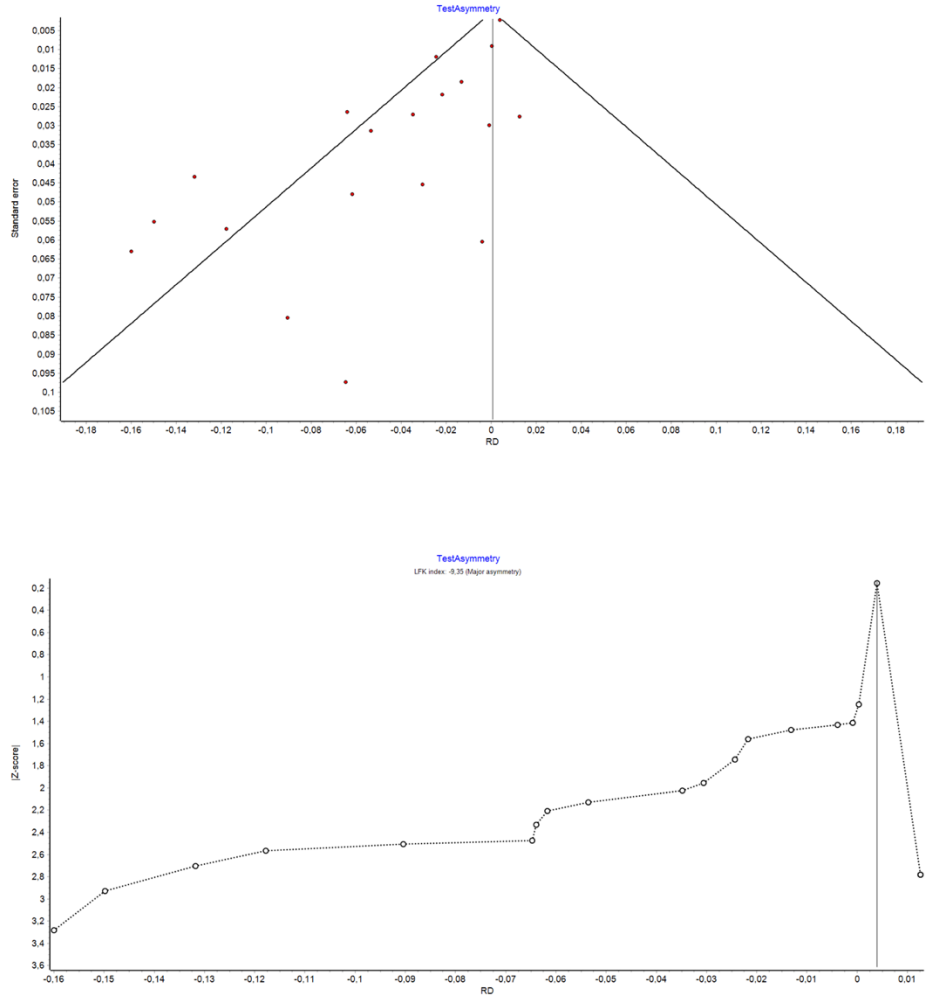


Figure 3 a, b: Funnel Plot and DOI Plot for sample data set from MetaXL

To illustrate the symmetric case, we use the data set from our own meta-analysis (Figures 4 a and b) for the $GABA_b$ antibody (see also the results section).

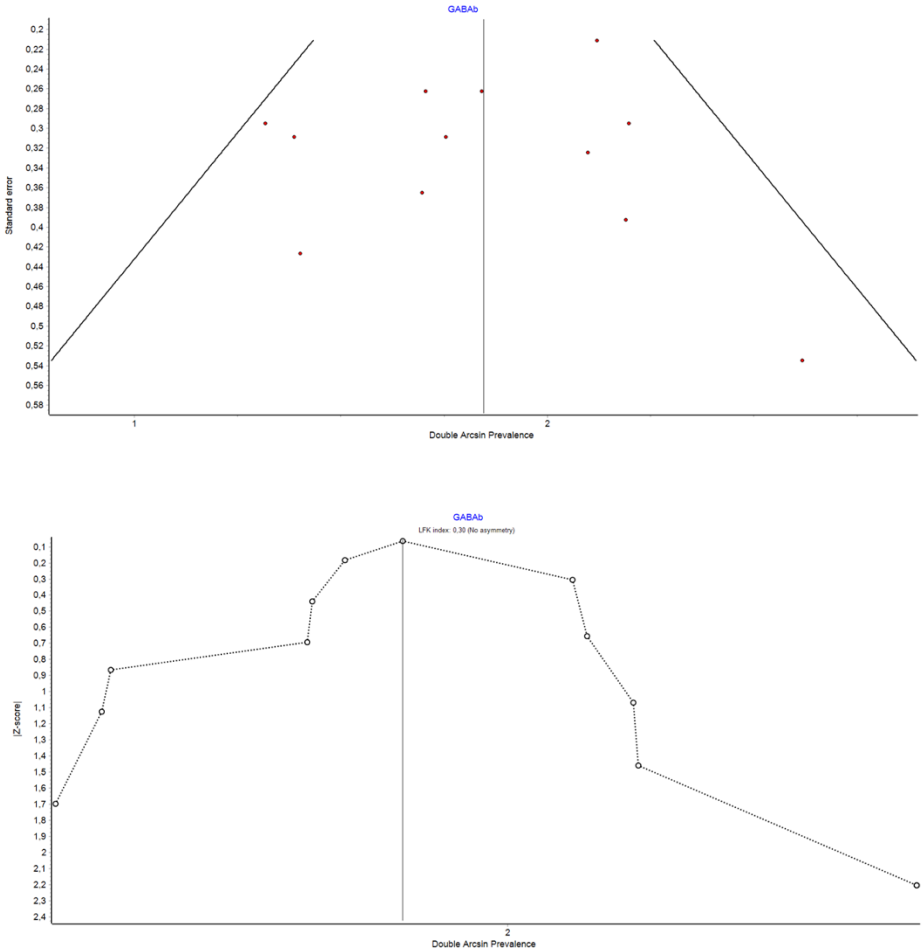


Figure 4 a, b: Funnel Plot and DOI Plot for the $GABA_b$ antibody

3 Results

3.1 Literature search

In this section, we describe the results of the literature search conducted for our systematic overview of the autoimmune encephalitis subtypes and associated imaging alterations.

Our systematic literature search generated a total of 1699 articles. Another 49 articles were found via the articles' reference sections.

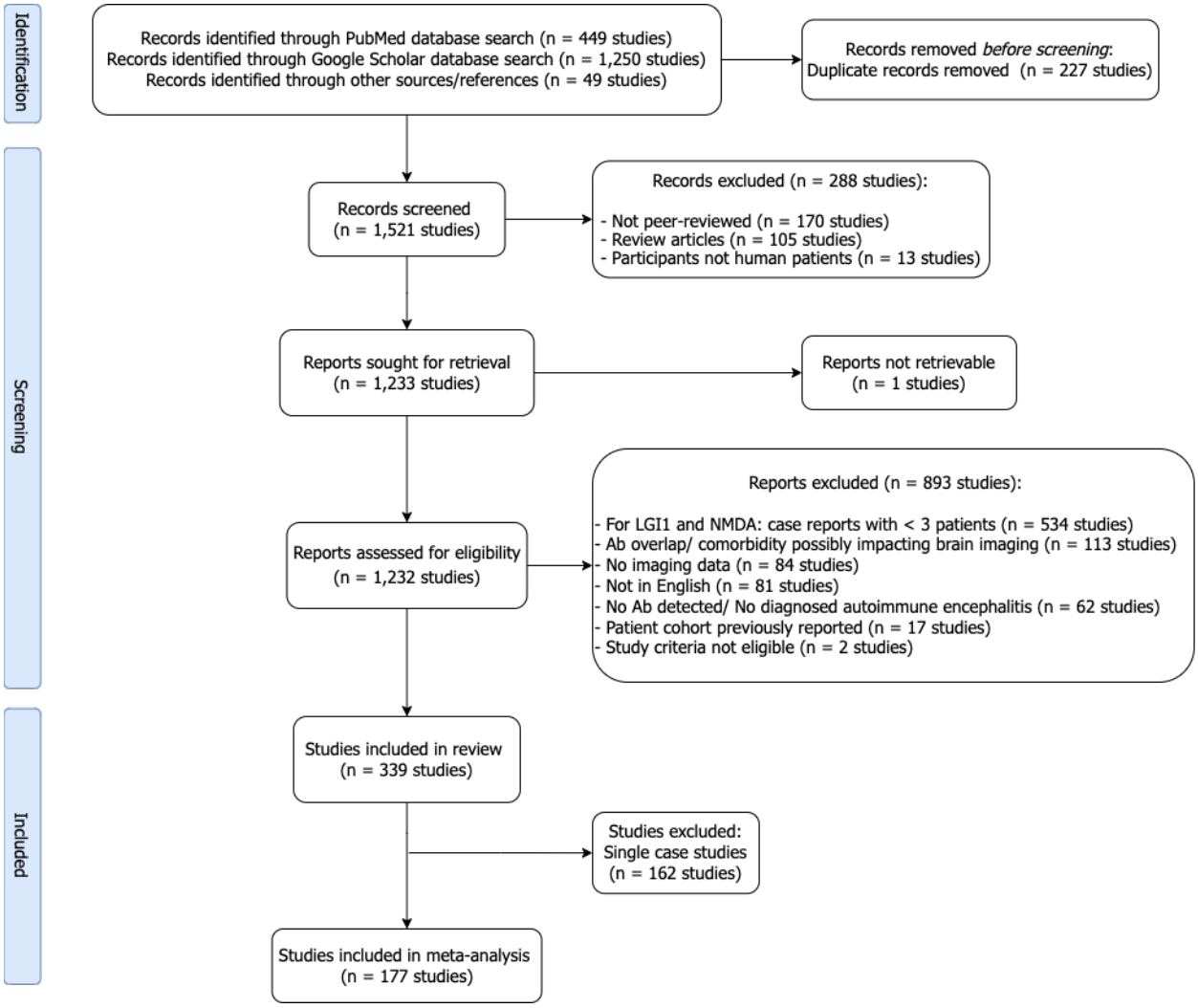


Figure 5: PRISMA Flow Diagram
From: Page et al. (2021): The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ[48]

After removing 227 duplicate entries, 1,521 studies were screened based on their title and abstract. We first assessed whether the articles underwent a peer review and removed 170 articles published as conference posters, preprints, editorials, or in similar formats. In the next step, we removed 105 review articles that did not contain any first-hand patient data. 13 articles were removed as the participants examined were not human patients but animals.

We then obtained the full texts of the articles. One full text was not retrievable. The remaining full texts were assessed for eligibility through control of congruency with our further inclusion criteria.

We excluded 81 articles as their corresponding full texts were not published in English. In 62 articles, the patients referred to did not have a diagnosis of AIE, or no antibodies could be detected. 84 articles did not consist of imaging data and were therefore excluded. We removed 113 articles with patients having concomitant neuronal autoantibodies or suffering from a comorbidity (see also Table 1) with possible influence on brain imaging. If we found articles where single patients did not fulfill our inclusion criteria, we attempted only to exclude those patients while keeping the data of the remaining patients. Seventeen articles had to be excluded as the patient cohort described had previously already been published. Assessing several other studies, we were able to extract only the patient data that had been reported earlier. Thus, we could keep those articles with the remaining patients for our analysis. Two articles implemented study criteria that were not eligible for us. They either excluded all patients with alterations in brain imaging or exclusively included patients with this characteristic in their study.

The evaluation with the JBI critical appraisal tool was in agreement with our previous study selection, as our prior decision of study inclusion/ exclusion had already been based on very similar questions.

A summary of our literature search is visualized with the PRISMA Flow diagram (Figure 5). Altogether, every article we detected with our search query is shown only once in this enumeration. Although, one article could have been excluded for more than one of the described criteria.

The references included in the statistical analysis are listed in the appendix.

Non-autoimmune Encephalitis	Oncological	Neuroinfectious/ Neuroinflammatory	Miscellaneous
CMV-Encephalitis	Astrocytoma	Toxoplasmosis	Brain trauma
EBV-Encephalitis	Glioblastoma	Cryptococcosis	
HSV-Encephalitis	Meningioma	Neurosyphilis	
VZV-Encephalitis	CNS lymphoma	Creutzfeldt-Jakob	
Hashimoto-Encephalitis	Brain metastasis	COVID-19	
Tick-borne Encephalitis	Pineablastoma	HIV	
West-Nile-Encephalitis		Multiple sclerosis	
Japanese-Encephalitis		Huntington's disease	
		Systemic Lupus Erythematosus	
		Secondary cerebral vasculitis in connective tissue disease	
		Alzheimer’s disease	

Table 1: List of comorbidities that led to exclusion due to possible influence on brain imaging
CMV Cytomegalovirus; EBV Epstein-Barr virus; HIV human immunodeficiency virus; HSV Herpes simplex virus; VZV Varicella-zoster virus

3.2 Imaging characteristics for each autoantibody target

In the following tables, we summarize the findings of our literature search. Furthermore, we connect the antibody characteristics to imaging alterations as reported in the literature.

Antibody target: AMPAR

Patients with reported neuroimaging	44
MRI	Most patients show alterations; T2/FLAIR increased signal of medial temporal lobe associated with clinical manifestation of LE; patients with more diffuse symptoms show widespread changes involving cortical regions, basal ganglia, insula, cerebellum, deep white matter, and septal nuclei Follow-up: some cases develop atrophy, preferably affecting hippocampus and amygdala
Contrast-enhanced MRI	Case with contrast enhancement in cerebellum bilaterally, corresponding to MRI hyperintensities and hypermetabolism on FDG-PET
Positron emission tomography (FDG-PET)	Single cases with cerebellar or hippocampal hypermetabolism and diffuse hypometabolism in nucleus caudatus and multiple cerebral cortex regions (mainly frontal, temporal, occipital)
Single photon emission tomography (SPECT)	-

Table 2: Imaging characteristics for patients with antibodies targeting AMPAR

Table 2 shows our search results for anti-AMPAR encephalitis. Here, our literature search generated 46 articles. 19 of these met our inclusion criteria. These 19 articles reported data from 44 patients. Several patients with concomitant neuronal autoantibodies were detected. These were mainly directed against NMDAR, collapsin response-mediator protein-5 (CRMP5), and SRY-Box Transcription Factor 1 (SOX). Furthermore, single patients with concomitant antibodies targeting Amphiphysin or the $GABA_b$ receptor were described.[8,128,129]

Clinical presentation
In a study of ten patients with typical symptoms of LE, antibodies targeting the GluA1 and GluA2 subunits of the AMPAR were first discovered.[128] Consistent with this finding, anti-AMPAR encephalitis patients overall characteristically present with LE.[130] However, a study on a consecutive series of patients found that the patients not only exhibit typical LE symptoms.[131] Two of the four examined patients were described with rapidly progressive abnormal behavior resembling acute psychosis. The patients exclusively showed psychiatric symptoms such as confusion and agitation, personality changes including apathy, and aggressive behavior. No additional neurologic symptoms appeared. On MRI and FDG-PET imaging, no abnormal changes could be observed. The authors suggested the typical LE syndrome to be associated with the pronounced expression of GluR1/2 subunits of AMPARs in the hippocampus and other limbic regions. An extension of the clinical presentation beyond the clinical profile of LE was explained due to the wide expression in further areas such as the cerebral cortex, basal ganglia, and cerebellum.[131]

Another presentation with pronounced psychotic features was reported for a 73-year-old female.[132] Her predominant symptoms included agitation, paranoid persecutory delusions, visual and auditory hallucinations. MRI investigations detected occipital cortical changes, as well as alterations of the deep white matter. The limbic region was not involved.

A case series study on 22 patients, of which 16 were adherent to our criteria for AMPAR encephalitis patients, identified four syndromes: 10 patients presented with characteristic LE, 3 with limbic impairment and diffuse encephalopathy, one showed symptoms of LE that were preceded by motor dysfunction, another presented with psychosis and bipolar depression.[8] Of the 10 patients with distinctive symptoms of LE, all but one appeared to have MRI signal increases in the temporal lobe. The patients presenting more diffuse encephalopathic symptoms also displayed more widespread changes. These involved various cortical and subcortical regions such as the parietal, frontal, or temporal cortex, basal ganglia, and deep white matter. This reinforces the hypothesis of an association of a clinical presentation of LE with changes within the (medial) temporal lobe. On the other hand, a more diverse clinical image seems to be associated with diffuse imaging changes involving various brain regions.

In follow-up investigations, patients often show signs of sclerosis or atrophy: in a study of three patients with prominent memory deficits, all presented with bilateral T2/FLAIR increased signal on MRI, exclusively affecting the medial temporal lobes.[130] On follow-up images, available for two patients, both displayed hippocampal and amygdalar sclerosis. One of the patients had developed a laminar pattern resembling necrosis in the hippocampal CA 1 and CA 2, along with atrophy in more posterior sectors.

Another example is reported of a 33-year-old female who presented with typical symptoms of LE on hospital admission.[133] Brain MRI demonstrated a T2/FLAIR hyperintensity confined to the left hippocampus. Over a period of three months, the hyperintensity evolved to affect both hippocampi. The hyperintensities then subsequently developed from unilateral to bilateral hippocampal atrophy.

Additional imaging modalities

On FDG-PET imaging, the 33-year-old female patient described above showed unilateral left hippocampal hypermetabolism.[133] The increased metabolism persisted with the application of aggressive immunotherapy, while no signs of CNS inflammation were found. After potentiating the antiepileptic treatment, the hypermetabolism showed significant regression, which was in line with the patient's notable clinical improvement.

An interesting case of a 30-year-old pregnant woman was characterized by Wei et al.: the patient presented with LE and status epilepticus.[134] She showed hyperintensities in the insula, mesial temporal lobe, and caudate nucleus on initial MRI FLAIR sequences. Within five days, she developed severe bilateral cortical atrophy. The atrophy developed without any hypoxic event and during controlled status epilepticus. On subsequent images, the hyperintense lesions resolved, while the atrophy remained. FDG-PET showed consistent marked hypometabolism of the caudate nuclei and over several cerebral cortex regions was identified. Hypoperfusion was further seen in the brain stem.

A further unusual clinical presentation was described in an 18-year-old male.[129] He presented with memory deficits and behavioral changes. After admission, he developed an ocular flutter and severe ataxia. On MRI, he showed increased T2/FLAIR signal and contrast enhancement of the bilateral cerebellum. Furthermore, the patient presented corresponding hypermetabolism on FDG-PET imaging. Following immunomodulatory therapy, the patient fully recovered.

Miscellaneous remarks

Seven of the ten first discovered anti-AMPAR encephalitis patients were congruent to our inclusion criteria.[128] All seven patients were women in later adulthood with an age median of 60 years. This adequately reflects the demographic characteristics of the disease with a preference for older females.[132] The entity is usually treatment-responsive, and clinical symptoms are fully reversible.[128,135]

Furthermore, an associated malignancy of the lung, breast, or thymus is typical for AMPAR encephalitis. Of the two larger case series studies that met our inclusion criteria, 11 of 22 patients had tumors in one of these organs.[8,128] One single patient of those was detected with an ovarian teratoma.

Patients' antibodies targeting AMPAR have proven to alter the synaptic localization and the number of AMPAR clusters selectively. While cell surface AMPARs are internalized, the number of intracellular AMPARs remains the same. Thus, the total number of AMPARs decreases. The decrease in AMPAR number is more pronounced at the synapses; the dendrites are less affected. The reduction of AMPAR-mediated synaptic transmission can further lead to a compensatory decrease in inhibitory synaptic transmission. However, with the removal of the antibodies, the receptor density can fully recover.[128,136]

AMPARs were discovered to play an essential role in the expression of long-term potentiation, which refers to a synaptic process crucial for memory formation. Continuous application of human GluA2 autoantibodies to mice severely impaired memory and cognition. These findings are consistent with the patients' characteristic presentation of memory deterioration and confusion.[18,136] Interestingly, a decreasing AMPAR antibody titer improves memory impairment with a recovery of the ability to form new memories.[135]

Antibody target: CASPR2

Patients with reported neuroimaging	194
MRI	Frequently unremarkable, in particular for Morvan syndrome or neuromyotonia LE patients: majority with characteristic T2/FLAIR signal increases in mesial temporal lobe, preferably affecting amygdala with extension to hippocampus; supratentorial white matter blurring or other non-specific white matter lesions in few cases Follow-up: normalization of signal changes in most cases, some show progress to hippocampal atrophy; patients with cerebellar ataxia often develop cerebellar atrophy
Contrast-enhanced MRI	Diffuse heterogenous enhancement of lesions involving basal ganglia and mediotemporal lobe reported in single case; circumscribed enhancement in mediotemporal lobe in another case
Positron emission tomography (FDG-PET)	Several cases with unremarkable MRI despite prominent metabolic changes on PET imaging: diffuse hypometabolism predominantly involving orbitofrontal cortex, temporal lobe (particularly mediotemporal areas) and single cases with changes in nucleus accumbens, parietal and occipital regions, cerebellum, insula; fewer cases with hypermetabolic uptake, mainly affecting mediotemporal lobe Follow-up: resolution of focal metabolic changes
Single photon emission tomography (SPECT)	Single case with frontotemporal hypoperfusion while normal MRI; other case with slightly reduced cerebral blood flow in subcortical and periventricular regions

Table 3: Imaging characteristics for patients with antibodies targeting CASPR2

As described in Table 3, for CASPR2, our literature search yielded 62 references. Several studies were excluded due to co-occurring anti-LGI1 antibodies.[107–112] Furthermore, we found some patients with anti-GAD or anti-MOG antibodies.[114] In total, 26 articles met our inclusion criteria which refers to 194 patients.

Clinical presentation

The clinical spectrum of patients with CASPR2 autoantibodies is diverse but distinctive. The three most frequently associated clinical syndromes are LE, acquired neuromyotonia, and Morvan syndrome. LE is confined to the brain, whereas neuromyotonia affects the peripheral nerves. Morvan

syndrome combines peripheral nerve hyperexcitability, dysautonomia, and encephalopathy with characteristic insomnia. Therefore, it involves the PNS and the CNS.[115,116]

In a phenotypical evaluation of 51 CASPR2-IgG positive patients, 47 % exclusively displayed central manifestations, 39 % had peripheral manifestations, and 14 % showed symptoms of both peripheral and central involvement.[38] Older age was detected as the main predictor for CNS involvement. The central manifestations mainly included seizures (49 % of all patients affected, mostly complex-partial), cognitive decline (39 %), personality changes (33 %), and sleep disturbances (33 %). LE was present in 18 % of the patients. Peripheral involvement was particularly represented by sensory-motor symptoms (53 %) and neuropathic pain (46 %). Autonomic symptoms appeared in 27 % of the patients. Another cohort study involving 38 patients revealed LE as the most frequent clinical manifestation. 42 % of the patients were affected. 29 % suffered from Morvan syndrome. Other frequent symptoms were PNS hyperexcitability, autonomic dysfunction, cerebellar disorder, insomnia, and weight loss.[107]

MRI findings
An unremarkable MRI is frequent for patients with anti-CASPR2 antibodies. Especially MRIs of patients with only acquired neuromyotonia or Morvan syndrome typically remain unremarkable.[117] Nonetheless, most patients with characteristic LE symptoms show abnormalities on MRI. These are usually T2/FLAIR signal increases involving the mesial temporal lobe. In some cases, the signal changes evolve into hippocampal atrophy.[118,119] Of the large cohort study with 51 patients mentioned above, 22 had available MRI data. Less than 40 % of these patients showed alterations on brain MRI.[38] 22 % displayed T2 mesiotemporal signal increases, and 15 % had developed mesial temporal sclerosis. All patients with mesial temporal sclerosis had central manifestations.

An example of a 60-year-old male with neurocognitive deterioration, seizures, neuromyotonia, and cerebellar ataxia showed mild edema of the amygdala with hippocampal atrophy on FLAIR sequences. His DWI revealed a cytotoxic edema of the right cerebellum that persisted despite aggressive treatment.[120] Other patients presenting with cerebellar ataxia were described with cerebellar atrophy on follow-up imaging investigations.[38,121]

Supratentorial white matter blurring has been considered characteristic of LE with antibodies previously known as VGKC complex antibodies. Accordingly, an investigation on supratentorial white matter blurring in patients with anti-CASPR2 antibodies revealed that two among six were affected. The blurring is considered an effect of structural myelin changes as hypomyelination.[122]

Additional imaging modalities
Despite an unremarkable MRI, several patients display metabolic changes on FDG-PET images. This is particularly characteristic of patients with acquired neuromyotonia or Morvan syndrome. The FDG-PET changes often appear as diffuse cortical hypometabolism involving the frontal or temporal areas.[123–125]

Miscellaneous remarks
The clinical manifestations of patients with anti-CASPR2 antibodies can be related to the presence of the antibody in the CSF or serum. Patients with antibodies in the serum seem to suffer more frequently from LE and seizures. Moreover, those patients only seldomly have an underlying malignancy. However, patients who harbor anti-CASPR2 autoantibodies exclusively in the serum usually present with Morvan syndrome or acquired neuromyotonia. Furthermore, they often have an associated thymic malignancy. In total, around 20-50 % of the patients with anti-CASPR2 autoantibodies have an underlying malignancy. These are most frequently thymomas.[14,117]

Overall, we found that larger cohort studies show a highly predominant proportion of older males for this type of autoimmune disorder.[38,107,126,127]

Antibody target: D2 receptor

Patients with reported neuroimaging	18
MRI	T2/FLAIR hyperintensities in basal ganglia (Nucleus caudatus, putamen, globus pallidus, striatum) in most patients; DWI/ADC: one patient each with restricted diffusion in striatum and internal capsule Follow-up: some cases develop atrophy in basal ganglia, predominantly putamen
Contrast-enhanced MRI	Many patients show enhancement of basal ganglia
Positron emission tomography (FDG-PET)	-
Single photon emission tomography (SPECT)	-

Table 2: Imaging characteristics for patients with antibodies targeting D2 receptors

Table 4 summarizes the imaging characteristics in anti-D2R encephalitis. For this subtype, the number of published cases is scarce. In total, we retrieved 18 references, of which only four publications were eligible for us. Accordingly, we obtained data from 18 patients.

Clinical presentation
In 2012, Dale et al.[21] identified autoantibodies directed against D2Rs in children with clinical or radiological features compatible with basal ganglia encephalitis. Subsequent studies show that only children have been detected to harbor autoantibodies targeting the D2R. The children typically display prominent movement disorders, in particular dystonia and parkinsonism.[137] Further symptoms seen in the majority of the cases include lethargy and psychiatric disturbance, such as agitation, emotional lability, and anxiety.[21]

MRI findings
On acute MRIs, most patients present T2/FLAIR signal increases restricted to the basal ganglia and mainly affecting the caudate, putamen, globus pallidus, striatum, and substantia nigra.[21,137,138]

In follow-up studies, four of eleven examined patients developed atrophy and gliosis of previous lesions. In these patients, noticeable clinical symptoms persisted. Patients showing reversibility of initial imaging abnormalities usually also clinically recovered.[21,137,138]

Antibody target: DPPX

Patients with reported neuroimaging	24
MRI	Less than half of the patients with alterations; Some show diffuse non-specific white matter sions, few cases display additional T2/FLAIR increased signal in mesiotemporal lobes, basal ganglia, frontal lobe, brainstem, or cerebellum; Follow-up: two patients with temporal lobe atrophy on FLAIR/T2; single case with cerebellar atrophy
Contrast-enhanced MRI	-
Positron emission tomography (FDG-PET)	Three cases with diffuse hypometabolism in cortical regions, basal ganglia, caudate nucleus, temporal lobe or thalamus; One case with hypermetabolism in extraocular muscles
Single photon emission tomography (SPECT)	-

Table 3: Imaging characteristics for patients with antibodies targeting DPPX

Table 5 describes the imaging findings of patients positive for anti-DDPX antibodies. 26 articles were retrieved for anti-DDPX encephalitis, and 12 of those met our inclusion criteria. Several patients with overlapping anti-GAD antibodies were excluded during the article screening.[139] Only a small number of patients with imaging changes on MRI were detected.

Clinical presentation
Patients typically suffer from prodromal refractory diarrhea causing severe progressive weight loss. Piepgras et al.[19] suggest this might be associated with anti-DPPX-antibody-induced hyperexcitability of enteric neurons which leads to gastrointestinal hyperactivity. Most patients subsequently develop symptoms of encephalitis with prominent cognitive decline, especially regarding short-term memory. Moreover, CNS hyperexcitability is common, typically appearing with hyperekplexia, myoclonus, seizures, or tremors. This often goes along with cerebellar or brainstem impairment.[140,141]

MRI findings
Less than half of the cases show alterations on MRI. The changes are mainly limited to nonspecific white matter lesions.[140,142] The MRI of two patients demonstrated temporal lobe atrophy on T2/FLAIR sequences.[140,143] One of these patients had a 2-year progression of cognitive and behavioral dysfunction with CNS hyperexcitability, brainstem, and cerebellar dysfunction.[140] The other had been suffering from gastrointestinal symptoms, cognitive decline, psychiatric disturbances, CNS hyperexcitability, and dysautonomia for 3 years. Over time he additionally developed severe pruritus.[143] Another young patient reported with prominent neurogenic pruritus and an unremarkable MRI at presentation developed cerebellar atrophy on follow-up images 17 years after onset.[141]

Additional imaging modalities
On FDG-PET investigations, three cases showed diffuse hypometabolism:

- A 54-year-old male with cognitive decline and gastrointestinal symptoms presented hypometabolism of cortical regions and basal ganglia.[144]

- Hypometabolism was further described in the frontal cortex with strikingly reduced uptake of the caudate in a 68-year-old patient with diarrhea, cognitive impairment, disorientation, and tremor.[19]
- The last case presented lower FGD uptake in the temporal lobe and thalamus.[145] His clinical manifestation included progressive dementia and insomnia.

Hypermetabolism in the extraocular muscles on FDG-PET images was described in a single case with prominent nystagmus.[146] All these cases with altered glucose metabolism on FDG-PET imaging had an unremarkable clinical MRI.

Miscellaneous remarks
Typically, this disease entity affects men of higher age predominantly.

Antibody target: $GABA_a$

Patients with reported neuroimaging	36
MRI	Alterations are frequent: mainly confluent lesions with increased T2/FLAIR signal in (mesio-) temporal lobe, (orbital-) frontal cortex, parietal and occipital lobes, insula, basal ganglia, cerebellum, in some cases combined with diffusion restriction Follow-up: resolution of lesions in many cases, some patients with subsequent generalized atrophy
Contrast-enhanced MRI	Contrast enhancement in left parietal lobe in single case and focal leptomeningeal enhancement in other case
Positron emission tomography (FDG-PET)	Few active epileptic foci, mostly occipital in one patient
Single photon emission tomography (SPECT)	-

Table 4: Imaging characteristics for patients with antibodies targeting $GABA_a$ receptors

In Table 6, we describe the imaging findings yielded by our search for anti-$GABA_a$ receptor encephalitis patients. We found 12 references, of which 7 adhere to our inclusion criteria. $GABA_a$ antibodies frequently appeared with concomitant neuronal antibodies, especially those targeting NMDAR, $GABA_b$ receptors, or GAD.[25,147]

Clinical presentation

Petit-Pedrol and colleagues[25] first identified antibodies targeting the $GABA_a$ receptor in 2014. The patients they examined suffered from a syndrome with prominent refractory seizures, status epilepticus, cognitive and behavioral changes. The cases with high titers of $GABA_a$ receptor antibodies in serum and CSF were more likely to develop fulminant, rapidly progressive encephalopathy. Those patients all demonstrated additional abnormalities on CSF, including pleocytosis, increased protein concentration, and oligoclonal bands. A broader range of clinical manifestations was observed in a patient cohort with lower serum antibody titers and without CSF positivity. These patients presented with distinct clinical syndromes such as the stiff-person syndrome or the opsoclonus-myoclonus syndrome.[148]

MRI findings

Alterations on acute MRIs are seen in the majority of cases. These were most frequently multifocal, confluent lesions with increased T2/FLAIR signal in cortical or subcortical areas.[147] Some cases subsequently develop generalized atrophy on follow-up examinations. However, it has not clearly been stated whether MRI changes develop due to autoimmune reactivity or prolonged epileptic seizures.[149]

Miscellaneous remarks

The disease was found to affect men in earlier adulthood predominantly. Considering the higher percentage of thymic epithelial neoplasm throughout the patient population, an association with these appears likely.

Antibody target: $GABA_b$

Patients with reported neuroimaging	137
MRI	Imaging alterations corresponding to typical manifestation of LE: majority with T2/FLAIR signal increase in mediotemporal lobe; cerebellar, brainstem, basal ganglia, or frontal lobe involvement, multiple small lacunar infarctions, and white matter demyelination observable in some cases; single case with longitudinally extensive myelopathy in thoracic cord Follow-up: remission of hyperintense lesions and swelling, occasionally remaining atrophy, particularly temporal
Contrast-enhanced MRI	Few patients with weak temporal contrast enhancement, one case with enhancement of adjacent meninges
Positron emission tomography (FDG-PET)	Pronounced increased metabolism especially over mediotemporal and temporal lobe, in some cases over basal ganglia; hypometabolism distributed over various cortex regions, postcentral, angular and marginal gyrus
Single photon emission tomography (SPECT)	Single case with increased uptake in temporal cortex, pre- and post-central gyri; decreased uptake in frontal and parietal lobe, thalamus, cerebellum, supramarginal, parahippocampal, and rectal gyrus Follow-up: increased uptake in bilateral cuneus and persisting decreased uptake in bilateral frontal lobes and thalamus

Table 5: Imaging characteristics for patients with antibodies targeting $GABA_b$ receptors

Table 7 shows typical imaging findings detected for patients with $GABA_b$ encephalitis.

Clinical presentation
Lancaster and colleagues[26] retrospectively evaluated patients with typical clinical manifestations of paraneoplastic or immune-mediated LE. The authors thereby discovered novel autoantibodies directed against the extracellular epitopes of the $GABA_b$ receptor. These autoantibodies were present in several patients displaying prominent seizures and characteristic LE manifestations.

Subsequent studies on patients with anti-$GABA_b$ receptor encephalitis confirmed that seizures are the most frequent symptom.[150,151] In a study on eleven Chinese patients, all presented with generalized complex tonic-clonic seizures as one of their earliest symptoms. The authors suggested early prominent seizures as characteristic of this type of encephalitis. In addition, the seizures were accompanied by limbic symptoms in all but one patient.[152] The limbic dysfunction typically manifested in cognitive decline with memory deficits and confusion. Additionally, patients

often showed behavioral disorders, involuntary movements, and disturbance of consciousness.[26,150,153] Further neuropsychologic changes were found to affect the visuospatial ability and temporal orientation.[22,154]

MRI findings

Imaging findings were usually consistent with typical manifestations of LE. On MRI, most patients showed a signal increase in the mediotemporal region on T2/FLAIR sequences.[26,151,154] Furthermore, single patients exhibited a laminar necrosis-like pattern in the outer aspects of the hippocampal CA 1 and 2. This specific pattern histologically correlates to a 'pan-necrosis' involving neuronal and glial cells, as well as blood vessels. It had previously been described as imaging finding in vulnerable brain areas related to metabolic disturbances such as hypoxia. As prolonged seizures often provoke hypoxia, they were considered a primary trigger. However, the changes could not be attributed to seizures, as in a study, only half of the affected patients experienced seizures (2/4).[155] Nevertheless, this finding was not specific for $GABA_b$-receptor encephalitis but has also been described in the context of other types of LE, such as AMPAR encephalitis.[155]

Other features reported in multiple patients (10/38) were leukoaraiosis and diffuse ischemic lesions in the cerebral white matter.[152,154,156,157]

After treatment, patients usually showed a resolution of previous imaging changes, consistent with the amelioration of clinical symptoms.[158–160] Few patients demonstrated remaining atrophy in cortical regions.[22,152,157,161]

Additional imaging modalities

On FDG-PET imaging, 7 of 22 examined cases meeting our inclusion criteria presented increased FDG uptake in the medial temporal area.[152,157,158] However, some of these patients were only investigated on metabolic changes in the medial temporal region. Other brain areas with potential changes were not considered.[152] Overall, only a few patients demonstrated consistent medial temporal changes on MRI. Most had an unremarkable MRI or non-specific white matter lesions.

Metabolic changes on FDG-PET images in other areas were described in single cases with increased metabolism in the basal ganglia or decreased metabolism over cortical regions such as the postcentral, angular or marginal gyrus.[157]

In a 62-year-old woman with prominent generalized convulsive seizures, LE, and an unremarkable MRI, the brain perfusion was assessed using 123I-IMP-SPECT.[162] The SPECT detected hypoperfusion of the frontal, parietal and medial temporal lobes, the thalamus, and the cerebellum. This was accounted to the high prevalence of $GABA_b$ receptors in these regions. Furthermore, increased perfusion of the motor strip and left temporal lobe was additionally revealed on SPECT. The imaging changes were considered to be associated with some of the patient's characteristic symptoms, such as the seizures, orolingual dyskinesia, and Wernicke aphasia. Following corticosteroid therapy, the neuropsychiatric symptoms resolved, and brain perfusion showed substantial improvement. Only small regions of increased uptake in the cuneus and decreased uptake in the frontal lobe and thalamus persisted.[162]

Miscellaneous remarks

The clinical spectrum might be broader than the typical symptoms and imaging changes associated with LE. As the $GABA_b$ receptor is highly expressed in the cerebellum, symptoms associated with cerebellar dysfunction can become apparent and have been described in single cases:

- A 69-year-old patient presented with a prominent cerebellar syndrome consisting of gaze nystagmus, rotational vertigo, and dysarthria. On imaging examinations, he displayed large T2-hyperintense lesions in the brainstem and cerebellum.[159]
- Another patient exhibited an isolated paraneoplastic cerebellar ataxia. On MRI, solely non-specific microangiopathic lesions in frontal brain regions were found.[163]

- A pediatric case of a three-year-old boy presented with opsoclonus-myoclonus syndrome (OMS).[164] Imaging examinations showed hyperintensities in the brainstem and cerebellum on diffusion-weighted sequences. This led to the diagnosis of rhombencephalitis. The diagnosis was revised to $GABA_b$ encephalitis shortly after when the lesions became hyperintense on T2/FLAIR sequences and evolved to the basal ganglia.
- Finally, a woman of 33 years presented symptoms of LE, which were associated with OMS. She never developed seizures, and no underlying tumor was detected. The authors could not state a clear correlation between OMS and $GABA_b$ receptor antibodies as the antibody testing was not performed at the time of the OMS. Nevertheless, they suggest an association as highly likely considering previously reported cases also presenting with cerebellar symptoms. The patient received methylprednisolone pulse therapy. Four years after treatment, signs of temporal and frontal involvement persisted. She showed impairment of short- and long-term memory, as well as temporal disorientation. Consistent with the clinical presentation of the patient, marked frontal and temporal lobe atrophy remained on MRI.[22]

Other unusual manifestations have been reported in single cases, also contributing to the wider clinical picture:

- A case of a 71-year-old patient with multiple myeloma exhibited progressive encephalomyelopathy. He displayed longitudinally extensive hyperintensities in the thoracic cord on T2-weighted images.[165]
- Another patient developed refractory hypotension during the course of the disease. While other symptoms significantly improved with therapy, the patient's blood pressure remained low. The authors, therefore, suggest an associated impairment of autonomic nerve function.[24]

The primary demographic of $GABA_b$ receptor encephalitis was found to be men in later adulthood.[153,155,166] Furthermore, the entity has a high association with tumors. SCLCs are especially frequent. Accordingly, Maureille and colleagues[153] detected cancer in all 22 examined patients, 20 of them presenting an SCLC. In other patient cohorts, around half of the patients show a concomitant lung cancer, often pathologically confirmed as SCLC.[26,150,161] Additionally, a few cases with underlying neuroendocrine tumors in various locations have been described.[167,168] Since neuroendocrine tumors have common immunohistochemistry markers with SCLCs, an association with $GABA_b$ receptor encephalitis is considered.[168]

Antibody target: GAD

Patients with reported neuroimaging	231
MRI	Marked T2/FLAIR hyperintense signal in mediotemporal lobes, especially affecting hippocampus and amygdala Follow-up: progression of lesions to significant sclerosis or atrophy; single cases with cerebellar atrophy
Contrast-enhanced MRI	Some cases with faint contrast enhancement of lesions
Positron emission tomography (FDG-PET)	Metabolic changes in almost all patients, predominantly affecting medial temporal lobes
Single photon emission tomography (SPECT)	3/3 cases with temporal increased perfusion

Table 6: Imaging characteristics for patients with antibodies targeting GAD

Table 8 gives an overview of the imaging changes of patients with GAD antibodies.

Clinical presentation
With autoantibodies deactivating the enzyme function of GAD-65, the synthesis of GABA is blocked. GABA is one of the main inhibitory neurotransmitters throughout the brain. Therefore, its blockage can have serious consequences. Low GABA levels lead to an increased firing frequency of nerve cells.[27] As a result, patients with high titers of anti-GAD-65 typically exhibit heterogenous clinical manifestations such as stiff person syndrome (SPS), cerebellar ataxia, epilepsy, or LE.[169]

56 patients with GAD-65 autoantibodies were divided into two groups depending on their GAD-65 antibody concentration in the CSF.[170] 36 patients were detected with a high antibody concentration (cut-off value 10,000 IU/ mL) and 20 patients with a low concentration. Of the 36 patients with a high concentration, 32 displayed the characteristic associated syndromes: LE was seen in nine patients, chronic epilepsy in another nine, SPS in seven, cerebellar ataxia in three, and six patients presented with an overlap of two or more of these syndromes. The clinical spectrum of patients with lower antibody concentrations was broader, and many displayed concomitant neuronal autoantibodies, polyradiculoneuropathies, and other non–immune-mediated diseases.

MRI findings
From the study mentioned above[170], 46 % (15/32) of the patients with high antibody concentration showed alterations on brain imaging. Only 7.6 % (1/13) with low antibody concentration and assessable imaging data had neuroimaging changes. The imaging changes were not further specified.

Other studies report higher percentages of patients with changes on standard brain MRIs. Two exemplary studies, together describing 26 patients, find imaging changes on brain MRIs in 100 % of the patients.[171,172] The changes were detected in mesiotemporal structures in all patients.

Besides the mediotemporal lobe, other regions may also be affected on standard brain imaging. An example was reported by[173]: a young female was admitted to the hospital due to Epilepsia partialis continua. She quickly developed severe encephalopathy with coma and refractory status epilepticus. The MRI demonstrated prominent bilateral lesions of the frontal lobes. The patient

had a poor response to initial immunotherapy. However, alleviation of her symptoms was observed after the escalation of treatment. The frontal lobes' signal changes fully resolved, leaving residual frontal atrophy.

Although some patients were described with complete resolution of former imaging changes,[174–177] significant sclerosis and volume loss remained in many patients, especially in the mesial temporal region.[178–182] An exemplary study reported four young girls that presented mainly with LE symptoms.[183] However, one of these solely exhibited temporal lobe epilepsy. She was the only one clinically fully recovering following intravenous immunoglobulin therapy. The other three adolescents showed persisting memory impairment and epilepsy. In follow-up examinations, the three girls developed temporal atrophy on MRI.

Additional imaging modalities

We found a very high proportion of metabolic changes on FDG-PET images in GAD encephalitis patients. All but one[73] of the patients meeting our inclusion criteria presented FDG-PET changes. Five studies with a total of 22 patients found changes in FDG uptake in all examined patients.[184–186] These changes were mainly affecting the mesial temporal region. Further locations of metabolic changes detected in the patients are described below:

- A study reporting three patients with gait ataxia, cognitive and behavioral dysfunction found metabolic changes on FDG-PET images in all three patients.[73] Brain MRI detected changes in only two of them. One of the patients exclusively presented with gait ataxia. He showed cerebellar atrophy on MRI and hypometabolism in the cerebellum on FDG-PET imaging. Another patient with more pronounced behavioral disturbances presented MRI changes restricted to the mesial temporal lobe. Correspondingly, he showed increased metabolism in the mesial temporal region. Furthermore, he displayed increased metabolism in the basal ganglia and parieto-temporal hypometabolism. The third patient with cognitive disturbances and gait ataxia was reported with a normal MRI, although showing hypermetabolic changes in the basal ganglia and brainstem.

- Another study described seven patients whom all presented with typical clinical syndromes: chronic epilepsy (5), LE (3), SPS (3), and cerebellar ataxia (2).[187] Six (86 %) of these patients displayed abnormal signals in the hippocampus and temporal lobe on MRI. A decreased temporal lobe metabolism was reported for all six patients examined with FDG-PET. Four of them showed additional hypometabolism in the frontal lobe, parietal lobe, or temporoparietal junction.[184–186]

A comparison of eleven GAD antibody-positive and eleven age-matched paraneoplastic antibody-positive LE patients analyzed the patients' outcomes.[171] A significantly lower proportion of GAD antibody-positive patients became seizure-free and improved cognitively with immunomodulatory treatment. Moreover, on MRI, larger volumes for the amygdala, presubiculum, and subiculum were observed compared to the patients with paraneoplastic antibodies. Interestingly, the hippocampus was initially described as affected in all patients with GAD antibodies. Over time only 73 % of the patients still showed hippocampal changes. The amygdala, on the contrary, was involved in 73 % of the GAD antibody-positive patients at disease onset. In follow-up studies, 91 % of these patients had developed changes in the amygdala.

As changes in amygdalar and hippocampal volume are frequently reported in LE patients, a study was conducted to quantify those.[188] Twelve patients with GAD autoantibody-associated LE were assessed regarding the volume of these two regions. A fully automated volumetry revealed significantly larger amygdalar volumes in the acute disease stage compared to healthy control participants. The hippocampal volume showed no difference between patients and controls. During follow-up, a subsequent normalization of the previous changes was noted. No significant correlation between the GAD antibody concentration and volumetric features could be observed.

These findings are supported by a case study portraying a patient with LE characterized in particular by marked memory deficits.[189] Especially the loss of autonoetic awareness related to autobiographical memories was striking. On MRI, the patient displayed bilateral swelling of the mesial temporal region. In subsequent volumetric analysis, a volume increase of the left amygdala in relation to normative data was confirmed. The pronounced affection of the left amygdala might have played a role in the patient's strong antero- and retrograde memory disturbances. On follow-up images, the hippocampal volumes decreased, while the left amygdala remained enlarged.

To further investigate long-term gray matter volume changes, voxel-based morphometry was conducted on eight patients.[190] In the early disease stages, no changes were identified for the patients with GAD antibody-related LE. Nonetheless, a delineated area of reduced gray matter volume was detected in the right frontoparietal operculum in the chronic disease stage.

An assessment of structural connectivity and network topology in GAD-associated LE patients found significant alterations.[191] The GAD antibody-associated LE patients were compared to a control group and epilepsy patients with hippocampal sclerosis. Compared to the other groups, they displayed widespread changes in global network topology concerning integration and segregation. Eighteen brain regions with a decrease in node strength were detected, involving both hemispheres. There was a significant reduction in 10 of these nodes compared to the patients with hippocampal sclerosis. Additionally, connection weights were reported to be significantly lower in 11 connections compared to the healthy control patients.

Miscellaneous remarks

A combination of a case series study and literature review evaluated the patients' outcomes after receiving intravenous methylprednisolone, immunoglobulin, or both.[185] They further compared the therapeutic effect depending on the primary clinical manifestation of the patients. Unfortunately, the study detected only poor response (< 50 % effectiveness) to both therapeutical regimens. No significant difference was found regarding the effectiveness of the treatments, nor associated with the clinical manifestations. Solely patients with SPS seemed to show a slightly better response to therapy. In conclusion, anti-GAD encephalitis overall does not show great responsiveness to immunotherapy.

Another therapeutical approach was reported for four young female patients with refractory temporal lobe epilepsy associated with mesial temporal sclerosis.[192] One of them showed bitemporal hypoperfusion on FDG-PET. Ictal SPECT investigations detected temporal hypoperfusion in all the examined patients. As immunotherapy could not achieve clinical improvement, the patients received brain-responsive neurostimulation of both hippocampi. The treatment proved to be effective and markedly reduced the seizures.

Encephalitis with autoantibodies targeting GAD-65 often appears with other autoimmune conditions, most frequently type 1 diabetes and thyroid dysfunctions. Around 70 % of the patients with anti-GAD-65 encephalitis exhibit one or more autoimmune comorbidity.[193] Apart from GABAergic neurons, GAD-65 enzyme is exclusively expressed in endocrine tissue, such as pancreatic β-cells. This might explain the high prevalence of concomitant autoimmune conditions.[194]

GAD antibody-associated encephalitis only rarely appears as a paraneoplastic syndrome. However, the risk for associated cancer is higher for elderly patients, males, patients with concomitant $GABA_b$ receptor autoantibodies, or patients with LE as the primary clinical presentation. Lung or thymic neoplasms are the most frequently detected cancers in those patients.[195] Additionally, in many patients 24h intrathecal synthesis of oligoclonal IgG bands and IgG are reported.[170,187]

Antibody target: GFAP

Patients with reported neuroimaging	71
MRI	Diffuse white matter lesions, most prominent around ventricles; longitudinally extensive intramedullary spinal cord lesions
Contrast-enhanced MRI	Characteristic periventricular/-vascular radial enhancement pattern; enhancement extending to brainstem and spinal cord, also affecting leptomeninges in some cases
Positron emission tomography (FDG-PET)	Dispersed metabolic changes primarily involving brainstem area
Single photon emission tomography (SPECT)	-

Table 7: Imaging characteristics for patients with antibodies targeting GFAP

In Table 9, the imaging findings of our literature search for GFAP encephalitis are summarized. Of 35 articles detected with our search algorithm, 19 were included in our work, reporting imaging data of 71 patients.

Clinical presentation
Flanagan et al.[196] studied 102 patients to explore if the presence of autoantibodies targeting GFAP induces the development of meningoencephalomyelitis. 83 patients showed an inflammation that affected the meninges, the brain, the spinal cord, or all three of these regions. The phenotype was predominately observed in patients with antibodies in the CSF. They further described patients experiencing a subacute onset of memory deterioration, confusion, and psychiatric and meningeal features (headache, photophobia, neck stiffness).

Other frequent manifestations among the patients we found were myelopathic symptoms, cerebellar ataxia, autonomic dysfunction, postural tremor, and abnormal vision due to optic disk edema.[28]

MRI findings

A high percentage of patients shows abnormalities on brain MRI. The radiological findings resemble those of CNS vasculitis, magnetic resonance angiography, however, reveals no abnormalities.[196–198] Of two larger cohort studies reporting 32 patients eligible for our inclusion criteria, 18 showed diffuse T2 hyperintensities. These were preferably located in the periventricular white matter. In some cases, T2 hyperintensities could also be observed in the leptomeninges. Independently, marked gadolinium enhancement was found in 22 patients. The enhancement usually showed a characteristic linear perivascular enhancement pattern, in radial orientation to the ventricles. In addition, enhancement extending to the leptomeninges, brainstem, cerebellum, or ependyma could be present. Only seven patients had an unremarkable MRI. These patients still exhibited prominent clinical symptoms, such as dementia, meningitis, cranial or peripheral neuropathy, encephalitis with optic neuritis, dysautonomia, and epilepsy.[28,196]

An unusual manifestation is shown in Figure 6 in a patient who experienced prominent tetraparesis, among other symptoms.

An interesting observation was made by Kimura et al.[199]. They detected six of twelve patients with bilateral signal changes of the posterior thalamus on brain MRI. The authors suggested these lesions as characteristic features of GFAP astrocytopathy. However, they most frequently found hyperintensities on T2/FLAIR sequences in the basal ganglia. Furthermore, four out of eight patients showed linear perivascular radial gadolinium enhancement patterns. All patients they reported, initially described fever and headache followed by encephalopathy. This was accompanied either by symptoms of meningitis, myelitis, or both.

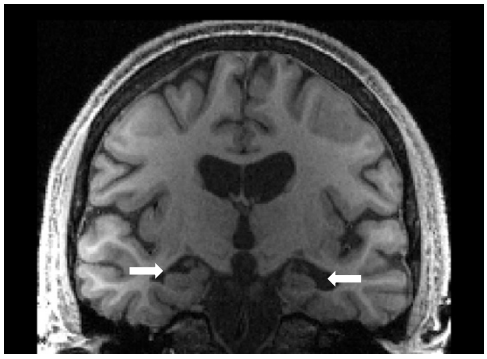


Figure 6: hippocampal and global atrophy in GFAP astrocytopathy

A 33-year-old male initially hospitalized for fever and headache developed rapidly progressive high-grade tetraparesis, along with respiratory muscle insufficiency. In the course of his illness, he showed depressive mood disorder and in neuropsychological testing isolated moderate anterograde memory deficit. His brain MRI was unremarkable in the acute disease stage, while T2 hyperintensities were found multi-segmentally in the myelon (not shown).
The coronal T1-weighted sequences at six months follow-up revealed severe bilateral hippocampal volume loss (see arrows) and moderate global atrophy. On T2-weighted/FLAIR sequences, the MRI showed hyperintensities of the periventricular white matter, the periaqueductal gray matter, the pedunculi cerebelli bilaterally, and multi-segmentally in the myelon (not shown). The patient stabilized with IV methylprednisolone therapy, although the pronounced leg-accentuated tetraparesis and mild cognitive impairment persisted.

Regarding the patients with available spinal cord MRI, 13 of 21 cases showed radiological signs of myelitis.[28,196,200–202] Twelve of these cases had hyperintense longitudinally extensive intramedullary lesions on T2 defined as ≥3 affected vertebral segments. Many exhibited concomitant central canal or spinal leptomeningeal enhancement. All but three of the patients showed corresponding symptoms of myelitis. Two further patients presented with clinical myelitic symptoms. However, these two had an unremarkable MRI of the spinal cord.[28,196,200–202]

Additional imaging modalities

In addition to the characteristic findings on MRI, all patients undergoing FDG-PET examinations presented altered glucose metabolism. Stereotactic surface projections demonstrated mixed patterns of metabolic changes affecting particularly the medial temporal lobes, brainstem, and spinal cord. Other regions, such as the motor cortex or basal ganglia, were also involved in some cases.[197,201,203]

In a female patient, hypermetabolism on axial fused FDG-PET/CT scanning was noted, corresponding to extensive spinal lesions on MRI. This patient exhibited progressive cognitive impairment while myelitis symptoms were absent. Her dementia was confirmed to improve by corticosteroid therapy.[201]

Miscellaneous remarks

GFAP is an astrocyte-specific intermediate filament and, therefore, should not be directly accessible to autoantibodies within the intact glial cell. Nevertheless, it is associated with astrocyte loss and decreasing GFAP expression. Furthermore, the disorder does not appear as a classical cytotoxic T-cell-mediated autoimmune condition, as it is exclusively steroid-responsive and presents with inflammatory seeming MRI scans and CSFs.[196] Accordingly, most of the patients we found exhibited signs of inflammatory CSF with an elevated level of leucocytes, proteins, or oligoclonal bands.[28] Flanagan and colleagues[196] speculate that, in addition to T-lymphocytes, other inflammatory immune components contribute to the disease mechanism. They further suggest that the inflammatory response itself, involving chemokines' release, may be associated with neuronal apoptosis that spreads to healthy nervous system tissue.

The usually favorable response to immunomodulatory treatment can be demonstrated in studies by decreasing mRS scores from admission to discharge.[199] Flanagan and colleagues[196] confirm that corresponding to the clinical symptoms, also MRI abnormalities frequently remitted with corticosteroid treatment. On the other hand, of three reported cases with extensive brain lesions and prominent linear perivascular radial gadolinium enhancement, only the enhancement resolved with treatment. None of their hyperintense lesions on T2-weighted sequences improved. Accordingly, two of these cases only had a poor clinical response to treatment.[201,205] Another study by Dubey and colleagues[206] associated the lack of response to first-line therapy with co-existing antibodies or underlying malignancy.[205]

Antibody target: Glycine receptor

Patients with reported neuroimaging	18
MRI	Majority with unremarkable MRI, non-specific white matter lesions in few patients; single cases with T2/FLAIR hyperintensities temporal, occipital, spinal, cerebellar, or general and cerebellar atrophy
Contrast-enhanced MRI	-
Positron emission tomography (FDG-PET)	-
Single photon emission tomography (SPECT)	-

Table 8: Imaging characteristics for patients with antibodies targeting Glycine receptors

Table 10 describes the imaging characteristics of patients with Gly-R antibodies. As depicted in the table, imaging data were found for 17 patients, only including MRIs without contrast enhancement.

Clinical presentation
In 2008, a patient was described with characteristic subacute onset of progressive encephalomyelitis with rigidity and myoclonus (PERM). The patient had no abnormal changes on MRI and responded well to immunomodulatory treatment. However, unlike previously described cases presenting with PERM, he was not positive for GAD autoantibodies. In subsequent examinations, the patient was then discovered positive for autoantibodies targeting the a1-subunit of the glycine-gated chlorine channel.[29] In the following years, more patients were reported with autoantibodies targeting the GlyR and presenting with PERM.

PERM is a hyperexcitability syndrome similar to SPS. In contrast to the SPS, which is usually limited to the lumbar spine and proximal lower limb, PERM appears with generalized rigidity, myoclonus, hyperekplexia, and brainstem signs.[206] Moreover, in around 30 % of the cases, PERM is associated with dysautonomia. In addition, several cases presenting with ocular motor dysfunction and cranial nerve paresis have been reported.[207] The clinical spectrum of patients with anti-GlyR antibodies was further extended by descriptions of patients with bilateral progressive inflammatory optic neuropathy,[208] seizures, and pruritus with dermatomal distribution.[209]

MRI findings
None of the patients we found exclusively positive for anti-GlyR autoantibodies had specific changes on their brain MRIs.[29,206,208–211] Non-specific changes were reported in single cases. Furthermore, one 62-year-old male with PERM was reported with general atrophy of both cerebral hemispheres and the cerebellum. Another patient was described with non-enhancing T2 signal changes of the bilateral cerebellum and occipital white matter.[206]

Three of a cohort of 36 patients with MRI data showed non-specific white matter changes; two had small vessel disease, one had generalized atrophy, and four had FLAIR lesions. Two of the patients with FLAIR lesions showed inflammations of the temporal lobe. 23 of these patients underwent spinal MRI, where five displayed mainly short or patchy spinal lesions. However, there was no testing for concomitant anti-GAD antibodies, which sometimes overlap with anti-GlyR antibodies. Therefore, these results are not clearly attributable to anti-GlyR antibodies.[212]

Miscellaneous remarks
The CSF of patients with antibodies targeting the GlyR typically shows inflammatory changes with pleocytosis and oligoclonal bands.[206]

Antibody target: IgLON5

Patients with reported neuroimaging	41
MRI	Unremarkable MRI in most patients; Few patients with diffuse changes, such as FLAIR/T2 hyperintensities in temporal and frontal lobe, callosy body, hypothalamus, periventricular and juxtacortical white matter; some show atrophy in brainstem, cerebellum, or hippocampus DWI: one case with diffusion restriction in tegmentum and lateral ventricle Follow-up: significant volume decrease of lesions in one case, whilst residual hypothalamic T2 hyperintensities in other case, mild global atrophy in third patient
Contrast-enhanced MRI	Single case with contrast enhancement in right temporal lobe, disappearance in follow-up
Positron emission tomography (FDG-PET)	Hypermetabolism in left frontal and temporal lobe, bilateral caudate and putamen in one case; primary sensorimotor cortices, basal ganglia and cerebellum in another case, with hypometabolism in other cortex regions
Single photon emission tomography (SPECT)	One case initially without abnormal findings, on follow-up slightly reduced IBZM binding in left caudate

Table 9: Imaging characteristics for patients with antibodies targeting IgLON5

Table 11 summarizes our findings for patients with igLON5 antibodies.

Clinical presentation
In patients with abnormal sleep behavior and obstructive sleep apnea, Sabater and colleagues[30] discovered a novel autoantibody directed against the neuronal cell adhesion molecule IgLON5.

Of a large cohort study, all 22 patients presented sleep disturbances such as parasomnia, sleep apnea, insomnia, or excessive daytime sleepiness over time.[213] In addition to the sleep disorder, 20 patients suffered from bulbar dysfunction and 16 from gait instability. Features of dysautonomia and movement disorders were present in 14 patients. Cognitive impairment was less frequent and affected nine patients.

MRI findings
MRI alterations were present in four patients (18 %) of the study described above. The patients displayed atrophy mainly affecting the cerebellum and brainstem (3) or hippocampus (1).[213]

Further studies could also only identify a small number of patients with changes on MRI. Hansen et al.[214] characterized a case with prominent memory impairment, sleeping disorder, dysphagia,

and ataxia. The patient displayed hyperintense lesions of the periventricular and juxtacortical white matter on MRI. These changes were persistent on follow-up MRI after seven months, then accompanied by mild general atrophy.

Other diffuse changes were observed in single cases:

- A 75-year-old female presented with acute confusion, somnolence, and personality changes. On MRI, she showed signal increases on T2/FLAIR images in the callosal body, the frontal lobe, and the temporal lobe. The temporal hyperintensities were associated with faint contrast enhancement.[215]

- Signal increases were further described in the hypothalamus in a patient with cognitive, behavioral, motor, and sleep disturbances.[216]

- Another case presented with scattered diffusion restriction in the left tegmentum and lateral ventricle. He had characteristic symptoms of IgLON5 disease along with left abducent paralysis.[217]

Additional imaging modalities

FDG-PET scans were obtained of a 64-year-old patient with a characteristic clinical manifestation involving severe sleep disorder, ataxia, and bulbar dysfunction.[218] She displayed increased glucose metabolism in primary sensorimotor cortices, basal ganglia, and cerebellum. Other cortex regions showed a decreased metabolism. The hippocampal FDG uptake was unremarkable, and no alterations were observed on clinical MRI. After immunotherapy, a regression of the lesions was observed. This corresponded to an improvement of the clinical symptoms.

Another 64-year-old patient examined by IBZM-SPECT presented with severe lower limb stiffness, dystonia, and pronounced impairment of executive functions.[219] He showed slightly reduced IBZM binding in the left caudate on the SPECT images while presenting an unremarkable MRI.[219]

Miscellaneous remarks

Although most patients show normal routine MRIs, the midbrain tegmentum and hypothalamus were affected in later autopsy studies of some patients. This is consistent with the expected dysfunction of mesencephalic nuclei associated with frequent gait and balance disorders.[213]

Furthermore, several studies reported only minor effects of immunomodulatory treatment on the patients' clinical symptoms. Only three of 28 patients treated with immunotherapy showed marked clinical improvement.[30,213] The lack of response to immunosuppression despite a decreasing antibody concentration could be attributed to a primary neurodegenerative origin of the disorder.[30] The IgLON5 disease seems to combine inflammatory aspects with a tauopathy's neuropathological characteristics.[213,220]

Moreover, Gaig and colleagues[213] described a median of two years between symptom onset and diagnosis. They found the late initiation of immunotherapy due to the delayed diagnosis as a possible cause for the frequently persisting symptoms.

The IgLON5 disease shows a strong association with the human leukocyte antigen HLADRB1*10:01 and HLA-DQB1*05:01. This was demonstrated by all four examined patients being positive for these haplotypes in the first reported case series.[30] In one of the larger cohort studies, another 13 of 15 patients showed these HLA haplotypes.[213] The authors additionally discovered the prevalence of the DRB1*10:01 allele to be 36 times higher than in the general population.

Antibody target: LGI1

Patients with reported neuroimaging	776
MRI	During stage of FBDS: no changes/ basal ganglia lesions often contralateral to side affected by the FBDS LE stage: majority with T2/FLAIR hyperintense lesions of medial temporal lobes Follow-up: mainly atrophy of the mediotemporal area
Contrast-enhanced MRI	Some cases with mediotemporal contrast enhancement
Positron emission tomography (FDG-PET)	Hypermetabolism of basal ganglia (FBDS stage) and medial temporal lobe (LE stage) frequent, lateralization described
Single photon emission tomography (SPECT)	Abnormal perfusion of temporal regions in single cases

Table 10: Imaging characteristics for patients with antibodies targeting LGI1

Table 12 gives an overview of our imaging findings for anti-LGI1 encephalitis patients.

Clinical presentation
Most patients with antibodies targeting LGI1 develop non-paraneoplastic LE. Accordingly, around 30 % of LE cases are related to anti-LGI1 antibodies.[88] The patients typically present with prominent cognitive impairment and confusion. Neuropsychological assessment performed during a period of two years after disease onset reveals spatial navigation as most impaired, followed by normative data.[39] However, the most characteristic symptoms associated with anti-LGI1 antibodies are faciobrachial-dystonic seizures (FBDS). These seizures are almost pathognomonic for anti-LGI1 antibodies. They are present in around 50 % of the patients. FBDS are brief seizures occurring with a very high frequency. They typically only affect one side of the face and the ipsilateral upper limb (in some cases involving the lower limb). They usually precede the onset of the cognitive disturbances as the earliest symptom of LE. Typically, FBDS show no improvement with antiepileptic drugs but respond well to immunotherapy.[37] Another characteristic symptom is hyponatremia. In a patient cohort of 76, hyponatremia was present in 74 %.[90]

Apart from the typical symptoms, an unusual syndrome preceding the development of encephalitis was detected in three among 14 evaluated patients.[89] Around two months before the anti-LGI1-associated encephalitis, those three middle-aged patients presented bradycardic episodes with the necessity of pacemaker implantation.

MRI findings
Alterations on MRIs in the acute disease stage of LE are very common. The investigation mentioned above described 76 patients with anti-LGI1 antibodies. LE was found in 63 (83 %) of the patients.[90] Most of them developed additional seizures and behavioral changes. The LE patients, by definition, all had MRI changes of the mesial temporal lobe. Of the remaining patients, two (3 %) showed involvement of extra limbic regions, and the other 11 (14 %) had no evidence of inflammation in their brain images.

Neuroimaging is usually unremarkable during the stage of only FBDS and before the evolution of LE.[91] Nonetheless, some patients show basal ganglia involvement at that disease stage. The basal ganglia lesions often manifest contralateral to the side affected by the FBDS.[92]

When patients developed anti-LGI1 antibody-associated LE, the majority presented T2/FLAIR hyperintensities of the mesial temporal area on MRI. An MRI study of 76 patients analyzed the relationship between clinical manifestation and localization of imaging changes.[93] 30 % of the patients with FBDS had lesions in the basal ganglia. In contrast, only 7 % of the patients without FBDS showed lesions in that region. Moreover, the study revealed that of the patients with memory disturbances, only 18 % had changes in the basal ganglia, while 75 % of the patients without memory impairment had basal ganglia lesions. Therefore, patients with FBDS and without memory impairment were most likely to exhibit imaging changes in the basal ganglia. On the other hand, 70 % of the memory-impaired patients had changes in the mesial temporal region. None of the patients without memory impairment demonstrated lesions in the mesial temporal lobe.

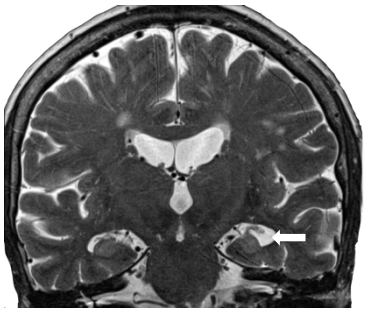


Figure 7: hippocampal lesions and atrophy (left >> right) in anti-LGI1 encephalitis

Anti-LGI1 antibodies were detected in a 73-year-old female patient after a generalized seizure and progressive cognitive deterioration. MRI showed left hippocampal T2/FLAIR-hyperintense lesions. Following immunotherapy with IV steroids and anticonvulsive treatment, symptoms fully resolved. Although a stable clinical condition, the patient presented increased antibody levels and new hyperintense lesions of the left hippocampus on MRI six months later. On follow-up after 14 months, the patient had developed bilateral (left >> right) hippocampal atrophy on coronal T2-weighted sequences (see arrow).

Over time, previous mediotemporal changes regularly evolved into hippocampal atrophy, often suggestive of sclerosis.[39,91,94] Figure 7 shows a patient with typical hippocampal atrophy in the post-acute disease stage.

A study on patients with non-defined VGKC complex autoantibodies reported imaging features that are likely to lead to mesial temporal sclerosis.[95] Patients presenting with restricted diffusion on Diffusion-weighted imaging (DWI) or with contrast enhancement of the hippocampus had a higher chance to progress to sclerosis in that region. Nonetheless, the significance of these findings is limited due to the small number of patients studied and the lack of distinction between the VGKC complex antibodies.

Additional imaging modalities

FDG-PET imaging frequently detected hypermetabolism of the basal ganglia and the medial temporal lobe. Furthermore, the imaging modality proved to be more sensitive than the MRI to detect intracranial pathologies. Numerous patients presented with unremarkable MRIs, while altered glucose metabolism was reported on FDG-PET images.[73,96,97]

To assess whether the LGI1 protein is distributed symmetrically over both brain hemispheres, FDG-PET images of 13 anti-LGI1 encephalitis patients were evaluated.[98] Eleven (84.6 %) of the patients had an asymmetrical metabolic pattern of the hippocampus. In nine (81.8 %) of these patients, there was lateralization of FDG high uptake to the left hippocampus. The asymmetry also affected the basal ganglia in seven patients (53.8 %), four (57.1 %) lateralizing to the left basal ganglia. Similar observations were made in post-mortem studies. However, these asymmetries were not apparent on brain MRIs.

Cognitive deficits unrelated to limbic involvement have been reported for patients with anti-LGI1 antibody encephalitis. Moreover, some patients show severe symptoms, while no structural damages appear on their MRIs. Therefore, a study[99] assessed brain damage with structural and functional MRI. The functional analysis revealed functional connectivity disruptions of major networks with a damaged hippocampus. Changes within the default mode network demonstrated a strong correlation with memory performance. Further networks, such as the sensory and visual networks, showed alterations in the patients even with an intact hippocampus.

Another functional analysis of 14 patients showed significant alterations in functional connectivity microstructure compared to the healthy controls.[100] The connectivity appeared reduced in the

hippocampus, amygdala, anterior and posterior cingulate cortex, inferior frontal gyrus, and superior temporal gyrus. Lower connectivity values of the left hippocampus correlated with higher disease severity. Furthermore, lower effective connectivity was observed from the frontal cortex to the supplementary motor area. Increased connectivity, in contrast, was found in the basal ganglia and supplementary motor area. White matter microstructure analysis via DTI detected a decrease in fractional anisotropy while an increase in mean diffusivity in the deep white matter. Moreover, the regional homogeneity values for some brain regions as the caudate, middle, and superior temporal gyrus, appeared to be reduced for anti-LGI1 encephalitis patients compared to control participants.[101]

For an evaluation of hippocampal functional dynamics, patients with anti-LGI1 encephalitis and FBDS were evaluated.[102] 50 % of the patients exhibited lower hippocampal activity compared to the control participants when performing scene-encoding tasks. A higher functional connectivity within the medial temporal lobe correlated with a lower memory score in cognitive tests. Furthermore, a higher frequency of FBDS was significantly correlated to a decrease in hippocampal activity during the tasks. This observation suggested a link between the seizures and lower hippocampal activity unrelated to the structural damage of the hippocampus.

Assessing long-term outcomes showed a correlation between impaired hippocampal structure and memory deficits:

- An analysis of 30 patients related persisting cognitive impairment to changes in brain images.[103] The anti-LGI1 encephalitis patients developed sustained memory deficits regarding verbal and visuospatial memory compared to healthy control patients. There was a significant correlation between the patients' memory deficits, hippocampal atrophy, and impaired hippocampal microstructural integrity. On structural MRIs, the patients displayed severely decreased volumes of hippocampal subregions cornu ammonis (CA) 2/3 and 4, as well as the dentate gyrus. No lesions of cortical gray matter or white matter were detected. Furthermore, the necessity of early initiation of immunotherapy was underlined by a significant correlation between the time until the institution of immunosuppression and the development of memory deficits.
- A subsequent hippocampal subfield analysis included anti-LGI1 encephalitis patients in the chronic disease phase to evaluate the respective subfields' associated functions.[104] In volumetric analysis, the patients showed a global hippocampal volume decrease. Neuropsychological tests revealed a memory deficit with a noticeable reduction of pattern separation ability. These deficits were associated with lesions of the hippocampal dentate gyrus. Lesions in CA 1 were correlated with deficits in recognition memory. To analyze the role of the hippocampal subfield CA 3 in retrieving recent and remote autobiographical episodic memories, anti-LGI1 encephalitis patients with lesions restricted to the hippocampal CA 3 were compared to healthy control participants.[105] The analysis results demonstrated that damage of CA3 could provoke a loss of episodic but not semantic memory. However, internal (episodic) memory disturbances were only observed for events up to around 50 years previous to the hippocampal lesion.

Miscellaneous remarks

Patients with anti-LGI1 antibodies were predominantly males (2:1 male: female ratio) over 60 years.[37] On average, the patients' antibody titers were higher in the serum than in the CSF. Furthermore, patients usually showed no oligoclonal bands or CSF pleocytosis. Yet, an antigen-driven maturation and mutation of the B-cells of patients' CSF was observed with an extension of the intrathecal immunoglobulin repertoire.[106]

Patients with anti-LGI1-associated encephalitis showed a good response to immunotherapy. An early start of therapy could further be crucial to prevent the progression from exclusive FBDS to LE associated with subsequent persistent atrophy and memory disturbances.[91]

Antibody target: mGluR1

Patients with reported neuroimaging	25
MRI	T2/FLAIR increased signal in the cerebellum in majority of patients, very few with additional lesions, e.g., in frontal lobes and thalamus; Spectroscopy: decreased NAA/Cr Ratio and increased lactate peak of cerebellar lesions Follow-up: most patients develop persistent cerebellar atrophy over time
Contrast-enhanced MRI	Multiple cases with cerebellar leptomeningeal enhancement
Positron emission tomography (FDG-PET)	One patient described with cerebellar, cingulate and prefrontal hypometabolism in follow-up
Single photon emission tomography (SPECT)	Single case initially without abnormal findings in SPECT, on follow-up marked cerebellar hypoperfusion

Table 13: Imaging characteristics for patients with antibodies targeting mGluR1

As described in Table 13, for mGluR1 encephalitis, we found 25 patients meeting our inclusion criteria.

Clinical presentation
Due to the predominant location of mGluR1, it is not surprising that Patients with antibodies against the mGluR1 usually presented with a characteristic cerebellar syndrome. The syndrome mainly consisted of ataxia, dysmetria, oculomotor divergence, and dysarthria. This was often accompanied by behavioral, psychiatric, and cognitive changes.[31]

MRI findings
On imaging examinations, most patients showed an increased signal in the cerebellum on T2/FLAIR MRI.[221,222] Some presented with additional gadolinium enhancement in the cerebellar leptomeninges.[31] A 22-year-old female with severe cerebellar dysfunction and cognitive disturbances only displayed gadolinium enhancement restricted to the cerebellar leptomeninges on MRI. Despite a subsequent resolution of the changes, the patient developed glucose hypometabolism in cerebellar, cingulate, and prefrontal areas on FDG-PET imaging.[223]

On follow-up investigations, persistent cerebellar atrophy could be observed in many cases.[31,221] Yoshikura et al.[224] characterized a patient with typical cerebellar syndrome. The patient presented with an unremarkable MRI on first admission and cerebellar atrophy with hypoperfusion on SPECT imaging around four years after disease onset.

Antibody target: mGluR5

Patients with reported neuroimaging	11
MRI	Majority of patients with normal MRI; 36 % with alterations, mainly subtle T2/FLAIR or DWI signal increase in variable regions as mesiotemporal, frontal, parie-tooccipital regions, pons, insula, cerebellum
Contrast-enhanced MRI	One case with contrast enhancement in up-per pons in addition to signal increase
Positron emission tomography (FDG-PET)	-
Single photon emission tomography (SPECT)	-

Table 14: Imaging characteristics for patients with antibodies targeting mGluR5

As depicted in Table 14, we only found a small number of patients with antibodies targeting the mGluR5.

Clinical presentation
The predominant location of mGluR5 in the limbic region may explain the origin of the characteristic behavioral changes and memory deterioration.[33] Patients further present with various neuropsychiatric symptoms such as personality changes and hallucinations, sometimes combined with movement disorders.[225]

There is a strong association between mGluR5 encephalitis and Hodgkin's Lymphoma. The syndrome of neuropsychiatric abnormalities combined with Hodgkin's Lymphoma is defined as Ophelia syndrome.[226]

MRI findings
The majority of the cases had an unremarkable MRI.[227] If alterations were found, they could be located either in limbic or extra limbic regions. Some examples are given below:

- A 35-year-old male had typical Ophelia syndrome with cognitive and personality changes, as well as cranial nerve palsies.[226] On MRI scans, he displayed an increased signal of the upper pons on T2-weighted images, accompanied by pontine gadolinium enhancement on T1-weighted sequences.

- A second study included six young patients who met our inclusion criteria. Only one showed increased T2/FLAIR signal of the bilateral frontal, the right occipital lobes, and the cerebellum on MRI.[227] The rest had unremarkable MRIs. Nevertheless, the patients all exhibited severe symptoms such as status epilepticus, decreased level of consciousness, dysautonomia, and cognitive disturbances.

Miscellaneous remarks
Some patients showed inflammatory changes in the CSF, such as pleocytosis and oligoclonal bands.[227]

Antibody target: Neurexin-3α

Patients with reported neuroimaging	7
MRI	One case of hyperintense T2/FLAIR and DWI signal in medial temporal lobes; another case with left hippocampal hyperintensity and swelling; one patient with basal ganglia involvement
Contrast-enhanced MRI	No enhancement in two examined patients
Positron emission tomography (FDG-PET)	-
Single photon emission tomography (SPECT)	-

Table 15: Imaging characteristics for patients with antibodies targeting Neurexin-3α

The data for patients with Neurexin-3α antibody-associated encephalitis is fairly sparse. Our literature search retrieved six articles. Of these six articles, three met our inclusion criteria. As seen in Table 15, this corresponds to seven patients.

Clinical presentation
The small number of patients that have yet been described showed a resembling clinical course to patients suffering from anti-NMDA receptor encephalitis. Patients reported with autoantibodies directed against Neurexin-3α typically presented with a prodromal phase of unspecific clinical symptoms such as fever, headache, nausea, and diarrhea. These were followed by a fast progression to severe symptoms of LE, including confusion, a decline of the level of consciousness, seizures, and orofacial dyskinesias. In a study of five patients, one showed a rapid course to death.[34]

MRI findings
Alterations in neuroimaging could only be found in a few patients. MRI changes were observed in three of the seven patients we found. Two of these patients presented hyperintensities in the medial temporal lobes on T2/FLAIR imaging. They suffered from seizures, severe psychiatric disturbances, decreased level of consciousness, and orofacial dyskinesia.[34,228] However, one of them had a history of systemic lupus erythematosus. Thus, her imaging changes cannot clearly be associated with the underlying autoimmune encephalitis. The third patient with detectable MRI changes showed mild signal increase in caudate-capsule-lenticulate regions on T2/FLAIR images.[229] He had developed symptoms of encephalitis just two weeks after the recovery from malaria with plasmodium falciparum. At that point, no plasmodium parasites were found in the patient. Nevertheless, malaria can also spread to the brain and thereby affect brain imaging. Therefore, the reported MRI changes again were not clearly attributable to the antibodies.

Miscellaneous remarks
CSF pleocytosis is common in anti-Neurexin-3α encephalitis patients.

Surface Neurexin-3α was reported to be significantly reduced in the presence of the specific antibodies. With the reduction of surface Neurexin-3α, the antibodies provoked a decrease in the number and function of synapses undergoing development. However, the total number of synapses was not affected.[230] Since Neurexins are located in pre- and postsynaptic regions, various cell functions can be altered with the ablation of Neurexin-3α. This might affect mechanisms such as presynaptic neurotransmitter release and postsynaptic regulation of receptors.[34]

Antibody target: NMDAR

Patients with reported neuroimaging	3590
MRI	Clinical imaging: < 50 % with imaging alterations, mainly non-specific multifocal cortical/subcortical T2/ FLAIR hyperintensities DTI: extensive white matter lesions Functional analyses: significantly reduced hippocampal functional connectivity often with unremarkable standard MRI Follow-up: cases with atrophy, predominantly fronto-temporal
Contrast-enhanced MRI	Small number of patients, mainly affecting the meninges
Positron emission tomography (FDG-PET)	Characteristic anteroposterior gradient: occipital hypometabolism with frontotemporal hypermetabolism, degree of changes associated with disease severity; some cases with increased uptake in basal ganglia
Single photon emission tomography (SPECT)	Single cases with changes in perfusion of frontal, temporal or occipital areas with unremarkable structural MRI Follow-up: improvement of metabolic changes

Table 16: Imaging characteristics for patients with antibodies targeting NMDA receptors

Table 16 lists the results for the NMDA receptor. Our search algorithm detected 1076 articles, of which 79 were eligible for us.

Clinical presentation
The antibodies are associated with a distinct syndrome characterized by a prodromal phase of non-specific cold-like or gastrointestinal symptoms, followed by prominent cognitive disturbances such as memory changes, psychiatric and behavioral symptoms. Many patients develop additional seizures, movement disorders (mainly orofacial), dysautonomia, and a decrease in the level of consciousness.

A characteristic distribution of symptoms is represented in a large cohort study of 498 anti-NMDAR encephalitis patients: 230 (51 %) presented a viral-like prodrome; subsequently, the patients developed behavioral and cognitive symptoms (466; 95 %), movement disorders (407; 83 %), speech disorders (374; 79 %), memory impairment (337; 74 %), seizures (338; 71 %), decreased level of consciousness (330; 69 %), and autonomic dysfunction (248; 51 %).[49]

MRI findings
The majority of the anti-NMDAR encephalitis patients display unremarkable clinical routine brain MRIs. Some cases, however, present changes on MRI scans. The three largest studies meeting our inclusion criteria each include several hundreds of patients (356 patients[50]; 498 patients[49];

540 patients[51]). Around 31-33 % of the patients reported in these three studies show MRI changes (180/540= 33.34 %[51]; 112/356= 31 %[50]; 147/498= 32 %[49]). As a characteristic of anti-NMDAR encephalitis, these changes were diffuse in cortical and subcortical regions and not associated with specific brain areas. Furthermore, there appears to be a discrepancy between MRI features and the anti-NMDAR encephalitis patients' clinical severity: patients often present with severe clinical symptoms despite normal MRI scans.[52–54]

However, hippocampal lesions of the anti-NMDR encephalitis patients have been correlated to a higher score on the modified Rankin Scale (mRS) and an overall poor prognosis.[55] Those hippocampal lesions were found to be the most common brain abnormality in a study on 53 Chinese patients. Seven (28 %) of 25 patients with MRI abnormalities were described with lesions in the hippocampus only, and 11 (44 %) with alterations in the hippocampus and additional other brain regions. The other affected brain areas were mainly the temporal, frontal, parietal lobes, and the thalamus. Single cases showed involvement of the deep white matter, basal ganglia, brainstem, or cerebellum.[55] Interestingly, the study also revealed a predominance of normal brain MRIs in female anti-NMDAR encephalitis patients (19 of 28 with normal results) compared to the males. Comparing pediatric and adult patients, no difference in MRI manifestations was found.

Contrast enhancement could be observed in many patients, preferably affecting the leptomeninges.[35,56–65] Furthermore, some cases with enhancement mainly of cortical and subcortical gray matter[35,58,59,66,67] have been reported.

Despite an unremarkable standard MRI in the acute stage, anti-NMDAR encephalitis patients sometimes developed MRI changes in later disease stages.[65,68] Most studies meeting our inclusion criteria displayed improvement of MRI alterations on follow-up scans. Two exemplary studies, together including 145 patients, described imaging changes of patients in the different disease stages. They reported MRI changes in the acute stage for 79 (54.5 %) patients. Only 21 (25.6 %) of 82 patients showed MRI changes on follow-up investigations.[35,55] However, the percentage of patients with lesions on MRI in the acute stage was already much higher for these studies than the average reported number.

Another study on 244 anti-NMDAR encephalitis patients explored the patients' long-term outcomes.[61] 104 patients (42.6 %) showed signal changes in the acute disease stage on MRI scans. At the 12 months follow-up examination, brain MRIs were abnormal in 93 of 225 (41.3 %) patients. Dividing the patients into groups with favorable or poor clinical functional outcomes showed that 78 (40.8 %) of the 191 patients with favorable outcomes had changes on MRI. In comparison, 15 (44.1 %) of the 34 patients with poor outcomes had an abnormal MRI. Similar results were found in a study on 356 patients.[50] From the findings, a grading score was created to predict the neurologic function (measured by the mRS) one year after diagnosis of anti-NMDAR encephalitis. Among other variables, the score detected an abnormal MRI as highly associated with poorer neurologic function after one year.

Additional imaging modalities

Despite severe clinical symptoms, conventional MRI scans of anti-NMDAR encephalitis patients, as described, are often unspecific or negative. Therefore, evaluation of other imaging modalities is necessary.

We found ten studies with reported FDG-PET imaging that met our inclusion criteria. All but two[68,69] detected changes in FDG uptake in all the examined patients.[54,70–76] This translates into 149 patients, of which 144 showed abnormal FDG-PET scans.

On FDG-PET images, patients usually present a characteristic decreasing FDG uptake gradient from anterior to posterior.[70,71,74] The metabolic changes on FDG-PET scans often appear before MRI abnormalities develop. On the other hand, in many cases, the changes become present exclusively on FDG-PET images, while MRIs demonstrate normal results during the whole course

of the disease.[71,72] A study on five patients found the characteristic decreasing uptake gradient in all examined patients.[71] The study also detected a cerebral interhemispheric metabolic asymmetry and a crossed cerebellar diaschisis for all the participants. The MRI scans were unremarkable in all cases. Of another study with 33 patients, 18 (54 %) presented with crossed cerebellar diaschisis and two (6 %) with bilateral cerebellar hypermetabolism on FDG-PET examinations.[72] All patients showed metabolic abnormalities with scattered patterns of hyper- and hypometabolism. Severe hypermetabolism appeared particularly in the frontotemporal region, while significant hypometabolism was noted mainly in parietooccipital areas. On MRI investigations, only seven (21 %) patients showed changes.

Another study detected glucose hypometabolism as the most frequent finding in seven of eight examined patients.[75] It involved different regions, such as the occipital lobe, the parietal lobe, or the visual cortex, and was either isolated or accompanied by hypermetabolism. In addition, the authors discovered decreased metabolism in the medial occipital lobe in six of the patients. This finding was not present in any of the patients with other forms of definite AIE.

Only one publication reporting cerebral blood flow SPECT scans of anti-NMDAR encephalitis patients met our inclusion criteria.[68] Of the four examined patients, two showed changes on SPECT scans. The perfusion changes affected mainly frontotemporal brain regions and appeared for one patient solely in the stage of convalescence.

Advanced imaging modalities have been able to identify changes in brain scans in patients with unremarkable conventional MRI. Multimodal structural MRI with hippocampus subfield volumetry revealed hippocampal atrophy with impaired microstructural integrity correlating with the disease severity and duration.[77] Moreover, also the disruption of white matter integrity on DTI was suggested to correlate with the disease severity.[78,79] DTI revealed superficial white matter changes predominantly in the frontal and temporal lobes.

Furthermore, permanent white matter changes have been reported on DTI that cannot be attributed to a fully reversible antibody-dependent mechanism of NMDAR internalization. Accordingly, patients frequently remain with persisting cognitive deficits, while conventional MRI cannot detect structural brain damage.[80] In a study of 15 patients with anti-NMDAR encephalitis, all showed significant reduction in fractional anisotropy values of the white matter in widespread brain regions compared to the controls. The affected areas involved the right middle temporal gyrus, the left middle cerebellar peduncle, and the right praecuneus. Furthermore, the values for mean diffusivity of the left medial temporal gyrus and left frontal lobe were significantly elevated for patients with anti-NMDAR encephalitis compared to the controls. The observed changes in fractional anisotropy of the right praecuneus were positively correlated with the patients' fluency score as a sub-item of the Montreal Cognitive Assessment (MoCA) to assess cognitive impairment. A negative correlation was detected between the mean diffusivity value of the left frontal lobe and the total MoCA score. Moreover, the mean diffusivity value of the left medial temporal gyrus was positively correlated with the MoCA score for delayed recall.

To investigate the effects of early application of second-line intravenous immunotherapy, 15 anti-NMDAR encephalitis patients underwent resting-state functional MRI.[81] The patients had all experienced moderate to severe symptoms, measured by the mRS, during the acute disease stage. All 15 patients received first-line immunotherapy; nine were given second-line immunotherapy in addition. They were then reexamined at least six months after the initial hospital discharge and compared with healthy control participants. All patients' structural MRIs were unremarkable. However, significant changes were found regarding bilateral hippocampal functional connectivity of the patients who only received first-line therapy compared to those with second-line therapy and healthy controls. These findings correlated with significant verbal episodic memory impairment of the patients who only received first-line intravenous immunotherapy. Overall, the study found a positive correlation between hippocampal medial prefrontal cortex connectivity and memory impairment.

Miscellaneous remarks
A malignancy can be discovered in approximately 40 % of the patients.[15] The majority of these show an ovarian teratoma. This is most common in women between 12-45 years.

Leypold and colleagues[2] found a decrease in NMDARs corresponding to the antibody titer. The reduction of the total number of receptors was achieved through mechanisms of capping, cross-linking, and internalization.[2] These effects were observed in vitro for neuron cultures where complete reversibility was demonstrated with the removal of the autoantibodies. The receptor decrease was also detected in autopsy studies of anti-NMDAR encephalitis patients. These findings were consistent with the previously established hypothesis, stating that the pathogenesis is not relying on cytotoxic T-cells and complement-mediated mechanisms. It is rather considered to be a result of an antibody-directed immune response. In subsequent studies, the effect of receptor internalization by binding of the antibodies has proven to be completely reversible with treatment or sometimes even with a spontaneous decrease of antibody levels.[2]

Anti-NMDAR encephalitis and Multiple sclerosis
Anti-NMDAR encephalitis has been reported together with overlapping neuroinflammatory demyelinating disorders,[82] such as the neuromyelitis optica spectrum disorders or the myelin oligodendrocyte glycoprotein antibody disease. The patients exhibiting both anti-NMDAR encephalitis and myelin oligodendrocyte glycoprotein antibody disease or neuromyelitis optica spectrum disorder typically show a higher frequency and severity of changes on MRI.[82]

An overlap of anti-NMDAR encephalitis and demyelinating disorders as multiple sclerosis (MS) has yet only been described in a few case reports.[83–87] Most patients reported had pre-existing MS and developed anti-NMDAR encephalitis during the course of the disease. The autoimmune encephalitis often manifested itself with severe progressive memory impairment and psychosis, which is unusual for MS.[83,86] The patients reported all showed disseminated hyperintense lesions on brain and spinal MRIs consistent with the diagnosis of MS.

A female patient with a 10-year diagnosis of MS developed typical clinical symptoms of anti-NMDAR encephalitis. Her MRI presented enhancing lesions consistent with MS. The cranial PET-CT, however, revealed slight frontal hypermetabolism and significant temporo-parietooccipital hypometabolism, which is often associated with anti-NMDAR encephalitis.[83]

Lesions on MRI, which were atypical for MS and led towards the diagnosis of anti-NMDAR encephalitis, were found in the first published case of MS with concurrent NMDAR encephalitis.[84]

Synopsys of imaging data from the literature search

Table 17 gives a synopsis of the findings in this chapter.

Antibody target	Articles included	Sample size	Total with MRI alterations	Percentage with imaging alterations
AMPAR	19	44	34	77.3 %
CASPR2	26	194	75	39.5 %
D2 receptor	4	18	12	66.7 %
DPPX	12	24	8	30 %
$GABA_a$ receptor	7	36	26	72.2%
$GABA_b$ receptor	27	137	88	65.1 %
GAD	64	231	139	59.7 %
GFAP	19	71	51	71.8 %
Glycine	8	18	4	23.5 %
IgLON5	13	41	9	22 %
LGI1	38	776	518	66.8 %
mGluR1	9	25	18	72 %
mGluR5	5	11	4	36.4 %
Neurexin-3α	3	7	3	42.9 %
NMDA	79	3590	1415	39.4 %
Total	332	5222	2404	46 %

Table 17: Un-pooled prevalences of imaging changes for AIE subtypes

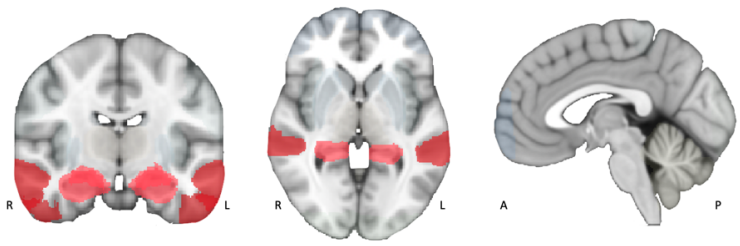
Table 17 shows the articles we found in the literature search that were adherent to the inclusion criteria for our systematic review. The results are shown for each antibody target individually. Here, we also included single case studies for the antibody targets with fewer published articles, as described above. The following columns list the corresponding numbers of included patients and the proportion with MRI changes. Overall, we found 332 articles describing a total of 5222 patients that met our inclusion criteria. 46 % of these patients had alterations on brain MRIs. The highest percentage of patients with imaging alterations was found for anti-AMPAR encephalitis, the lowest for IgLON5 disease.

3.3 Affected brain regions

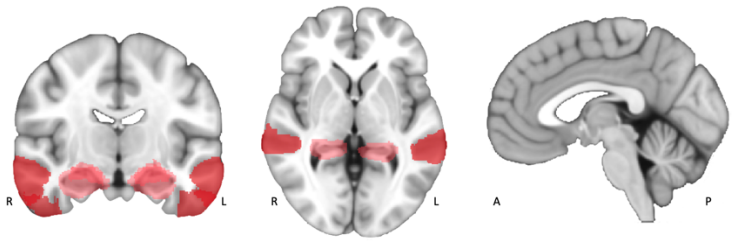
In this section, we graphically visualize the results of our literature search in terms of affected brain regions. For each autoimmune encephalitis subtype, we individually illustrate the different patterns of affected brain regions. The visualizations show the results of the patients' MRIs in the acute disease stage. These were the data predominantly found in our literature search. We used the MNI152 standard brain template and the aligned atlases in FSLeyes to create the visualizations. To get a better overview of the different brain layers, we took three central MRI slices in axial, coronal, and sagittal view for each encephalitis subtype. The areas showing abnormalities on the MRIs were highlighted with an opacity according to the proportion of patients with changes in that specific region. The ratio of patients with brain MRI changes was calculated in relation to the total number of patients examined for each encephalitis subtype respectively. A darker highlighted region indicates a higher number of patients with MRI changes in this specific region. The different brain regions were color-coded; the coding is described below. The list below shows the subdivisions of regions we represented in these visualizations.

If changes were reported in several dedicated areas for one single patient, these changes were all recorded. However, for some patients, the imaging changes could not be clearly assigned to specific regions; these changes were recorded as diffuse but were not included in the illustration. Brain regions in which less than 1 % of patients showed alterations were not represented. For illustrative purposes, the changes on the right and the left side of the brain were shown as equal here.

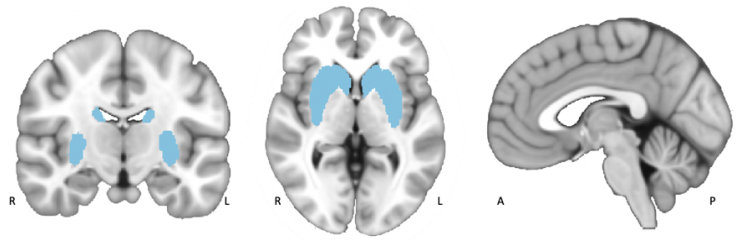
AMPAR



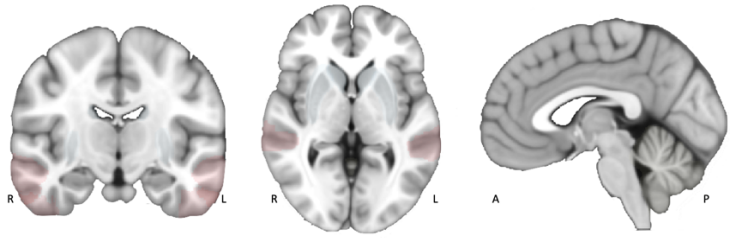
CASPR2



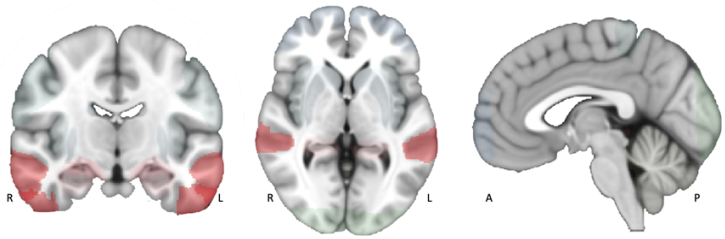
D2 receptor



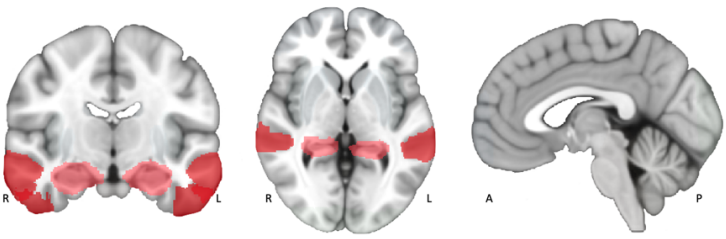
DPPX



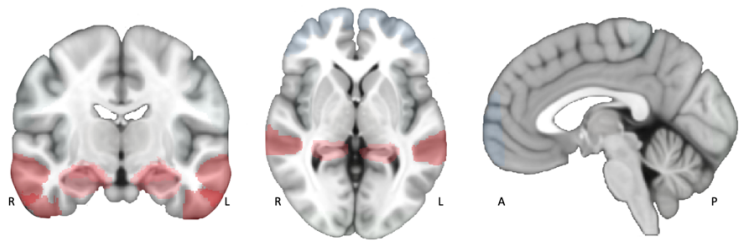
$GABA_a$ receptor



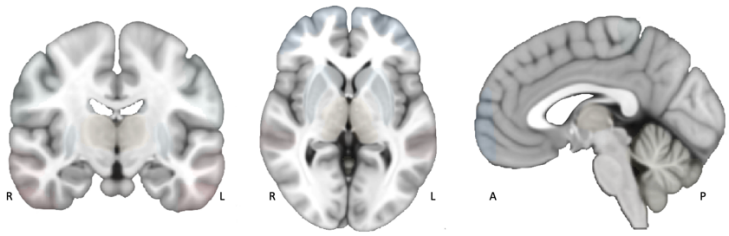
$GABA_b$ receptor



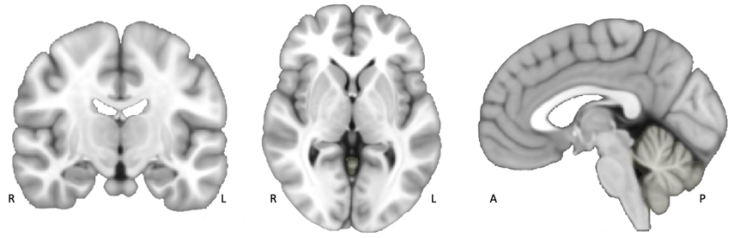
GAD



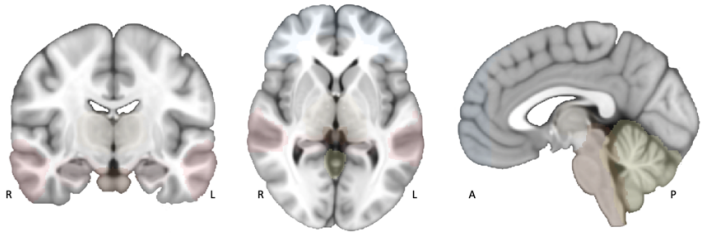
GFAP



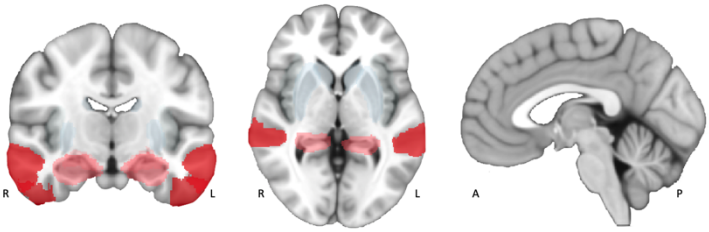
GlyR



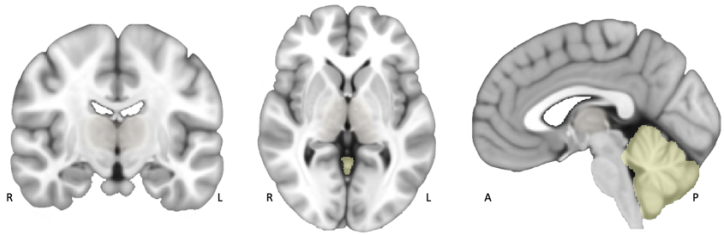
IgLON5



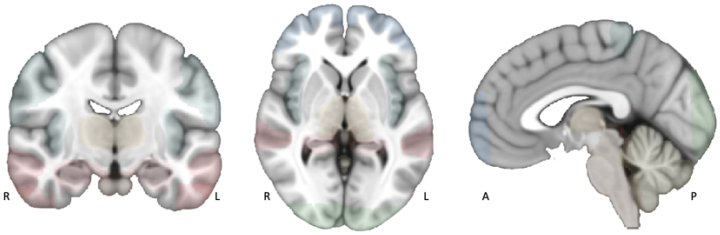
LGI1



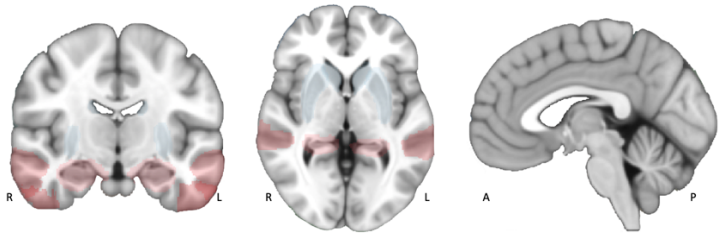
mGluR1



mGluR5



Neurexin-3α



NMDA

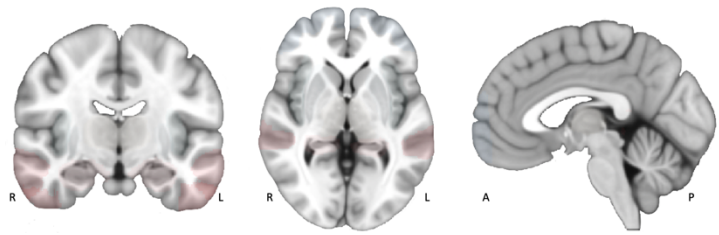


Figure 8: Visualization of frequency of MRI changes by region
Color and opacity coding for the represented brain regions. A higher opacity reflects a higher proportion of patients with MRI changes in the specific region:

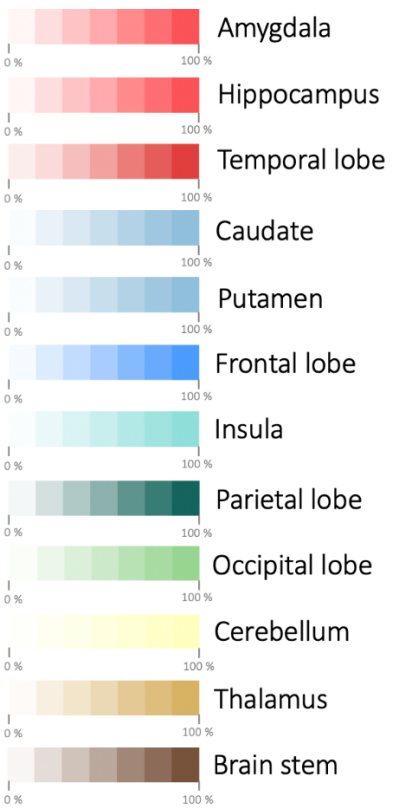


Figure 8 highlights the regions where changes on MRI were most frequently located. We can see that for most encephalitis subtypes the mesial temporal lobe was the most frequently affected region. Other regions only displayed changes on MRI in single cases. A very characteristic image is depicted for the D2 receptor encephalitis. Here, only the basal ganglia were affected on MRI scans.

The illustration for GFAP astrocytopathy suggests the prevalence of imaging changes to be comparatively low. However, this was since the predominant characteristic of GFAP astrocytopathy were white matter changes and periventricular or leptomeningeal enhancement. These were not illustrated in these visualizations.

For antibody targets such as Neurexin-3a, mGluR5, or the GlyR, we only found very few eligible patients (see Table 17). Hence, the highlighted regions for these subtypes usually only represent one single patient and are less informative.

3.4 Pooled prevalences and analysis of heterogeneity

In this section, we will present the findings of our meta-analysis. We generated Forest Plots for all cell-surface antibody encephalitis subtypes to find the pooled prevalences of MRI changes and assess heterogeneity across the included studies. We only show the Forest Plots for the two AIEs with the most published data. The plots for the remaining encephalitis subtypes can be found in the appendix. Furthermore, we also show our graphical assessment of risk of bias generated as Funnel- and DOI Plots.

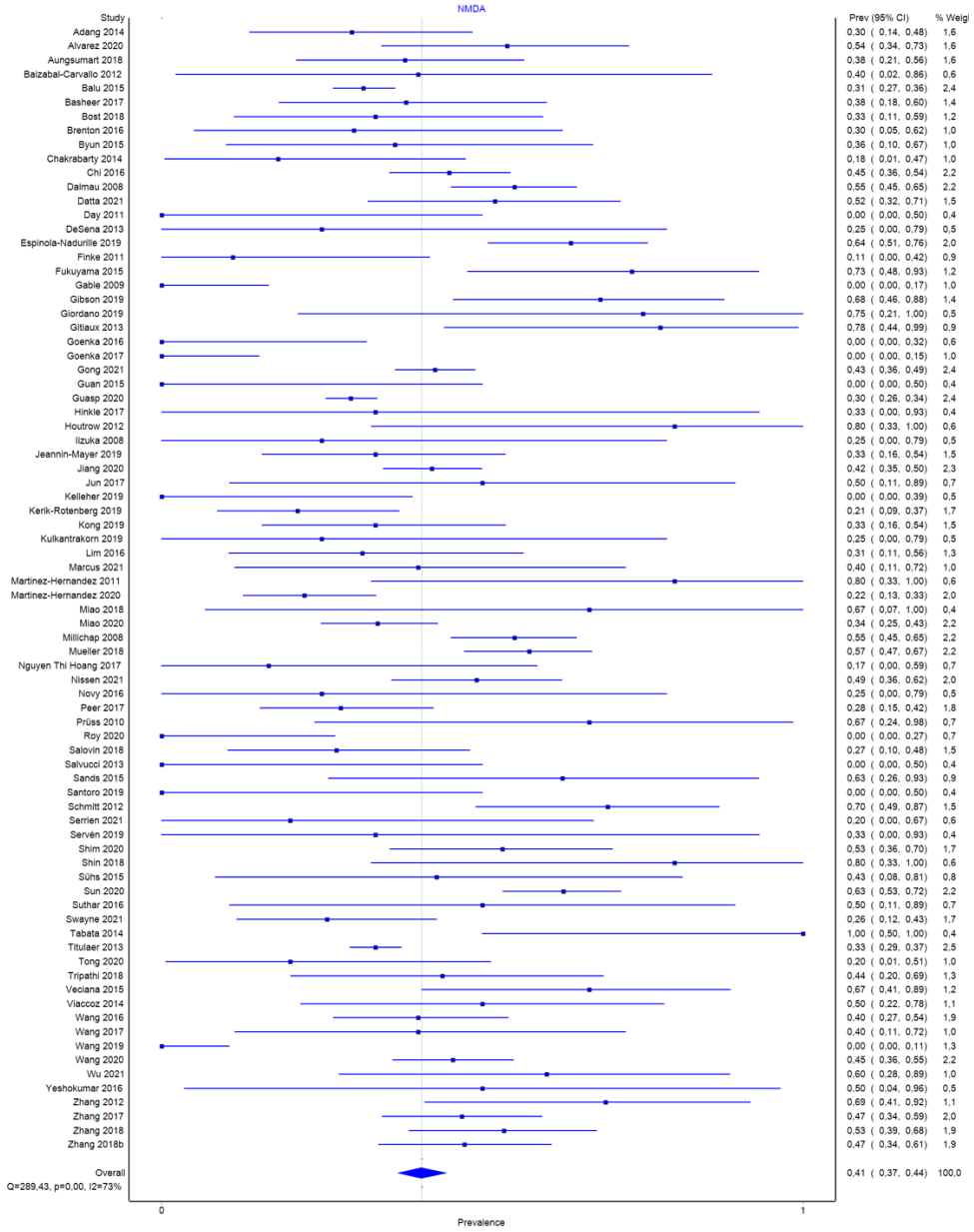


Figure 9: Forest Plot for anti-NMDA receptor encephalitis in the acute disease stage

Figure 9 represents the Forest Plot we obtained for the 79 studies we considered eligible for anti-NMDAR encephalitis. We found a pooled prevalence of 41 % (CI 0.37-0.44) for MRI changes for the patients. The heterogeneity index I^2 was 73 % ($p < 0.001$).

To assess the risk of bias, we generated a Funnel and DOI Plot (Figures 10 and 11). Both Funnel Plots and DOI Plots suggest that the risk of bias is low.

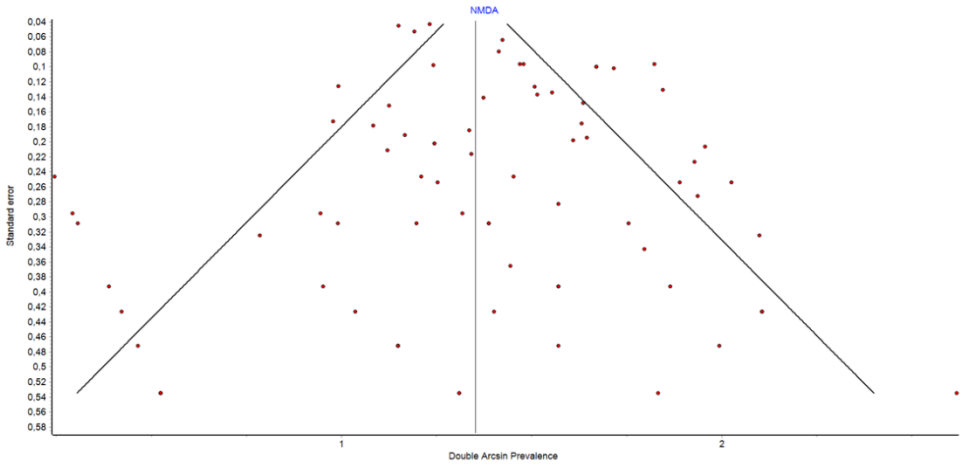


Figure 10: Funnel Plot for Anti-NMDA receptor encephalitis in the acute disease stage

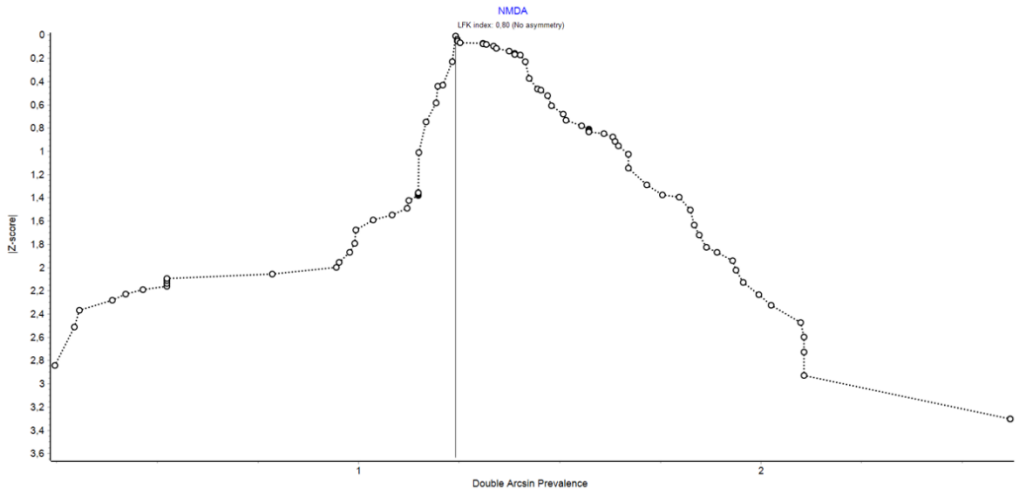


Figure 11: Doi Plot for Anti-NMDA receptor encephalitis in the acute disease stage

The Forest Plot of anti-LGI1 encephalitis is shown in Figure 12.

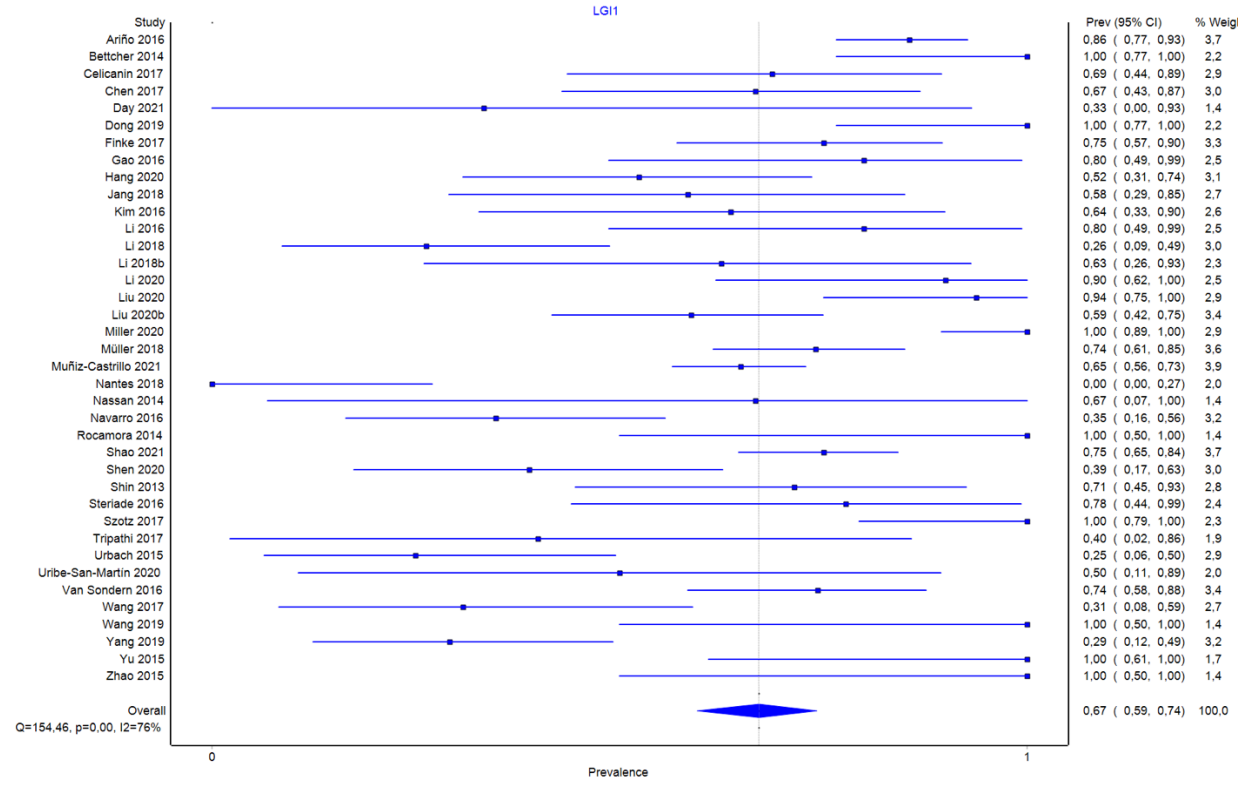


Figure 12: Forest Plot for anti-LGI1 encephalitis in the acute disease stage

The Forest Plot shows the 38 publications reporting anti-LGI1 encephalitis that were eligible for our meta-analysis. The pooled prevalence obtained was 0.67 (CI 0.59-0.74) with a heterogeneity index of 76 % (*p < 0.001).*

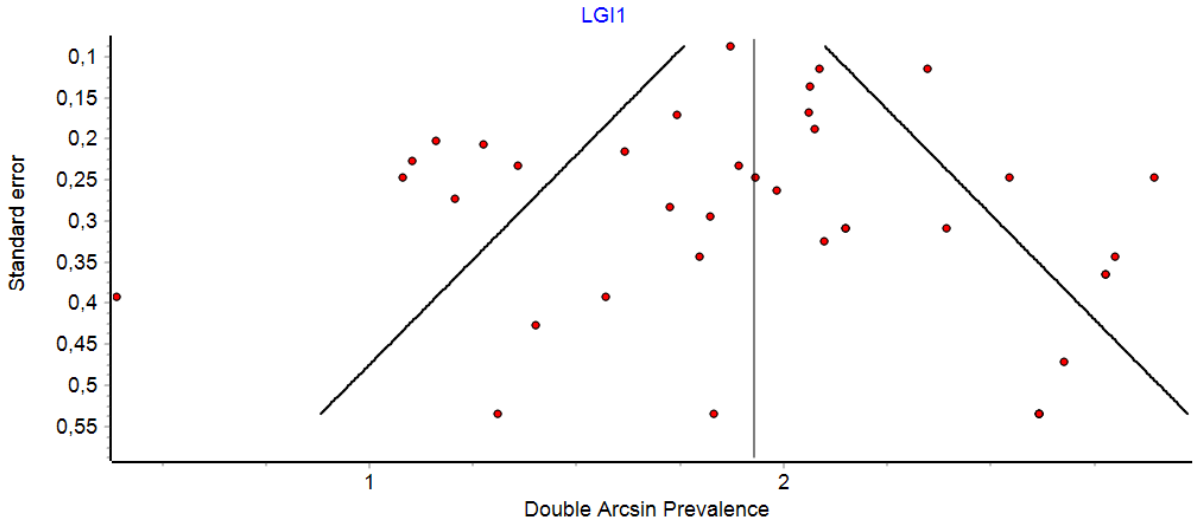


Figure 13: Funnel Plot for Anti-LGI1 encephalitis in the acute disease stage

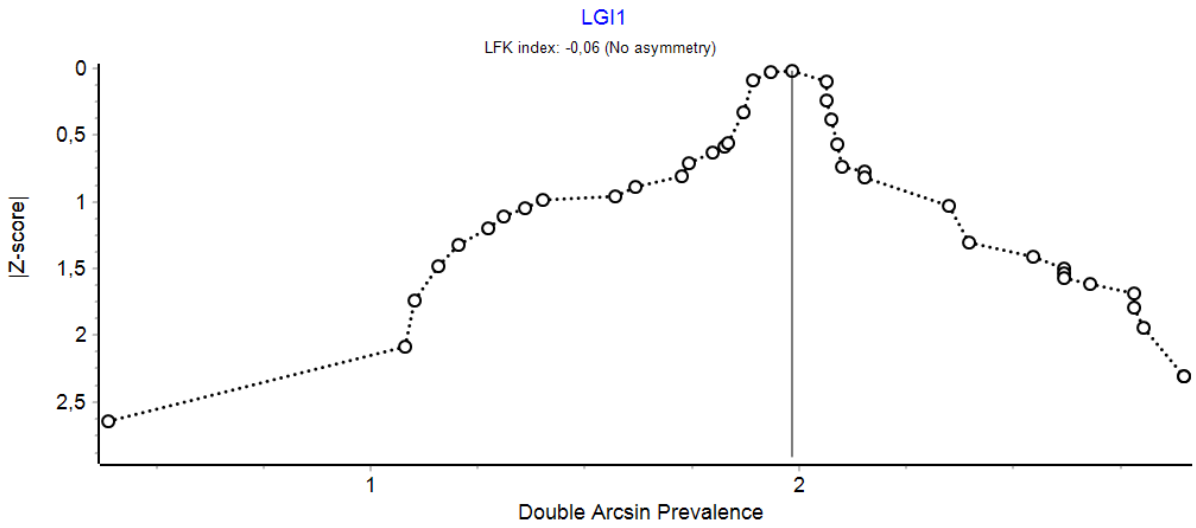


Figure 14: Doi Plot for Anti-LGI1 encephalitis in the acute disease stage

The Funnel and DOI Plot for anti-LGI1 encephalitis (Figure 13 and 14) again show high symmetry. This observation is underlined by the LFK index and suggests low risk of bias.

Moreover, the graphical risk of bias assessment yielded favorable results for nearly all explored antibody-associated encephalitides. These were supported by an LFK index underlining the absence of asymmetry. Minor asymmetry was observed for the analysis of very few AIE subtypes. However, considerable asymmetry within the bias assessment was detected for the overall pooled prevalence and anti-GAD encephalitis.

Synopsis of meta-analysis

Here we present a synopsis of our meta-analysis generated with the MetaXL software package.

Antibody target	Number of studies included	Number of patients included	Pooled prevalence	I^2	LFK-Index	Study sizes: range and median
AMPAR	3	25	0.86	0 %	1.76	3-15; 7
CASPR2	9	176	0.34	51 %	1.72	3-59; 6
D2 receptor	2	16	0.74	75 %	n/a	4-12; 8
DPPX	3	15	0.47	0 %	0.79	3-9; 3
$GABA_a$ receptor	3	31	0.70	7 %	0.15	9-13; 9
$GABA_b$ receptor	12	122	0.63	19 %	0.30	3-22; 10
GAD	13	170	0.79	90%	3.38	3-50; 6
GFAP	5	56	0.69	77 %	- 0.41	6-24; 10
GlyR	4	14	0.29	0 %	-1.10	3-4; 3.5
IgLON5	2	30	0.11	51 %	n/a	8-22; 15
LGI1	38	776	0.67	76 %	0.06	3-131; 13
mGluR1	2	18	0.69	77 %	n/a	7-11; 9
mGluR5	1	6	n/a	n/a	n/a	n/a
Neurexin-3α	1	5	n/a	n/a	n/a	n/a
NMDAR	79	3590	0.41	73 %	0.80	3-540; 12
Overall	177	5050	0.57	96 %	3.98	3-540; 10

Table 18: Pooled prevalences of imaging changes and across-study heterogeneity for AIE subtypes
The antibody targets without results for pooled prevalences yielded less than two studies adherent to our inclusion criteria. Case studies with less than three patients were excluded here. A risk of bias assessment was only feasible with more than two studies included in the analysis (n/a: not available).

In the table showing the synopsis of our collected data (Table 17), the entire patient population of our study was considered, excluding studies that did not meet our inclusion criteria. Hence, for all antibody targets apart from NMDA and LGI1, the single case studies were also included. Furthermore, we calculated the prevalences of imaging changes for each AIE subtype in that table without pooling.

For the calculation of pooled prevalences and the analysis of heterogeneity, we then excluded all single case studies. Only case series studies reporting at least three patients were included here. This was done to reduce the risk of publication bias. In the table summarizing our meta-analysis (Table 18), the prevalences are pooled for each AIE subtype, respectively. The individual values calculated for the respective antibody targets can be found in the table.

Our analysis detected considerable variation of pooled prevalences for imaging changes associated with each AIE subtype. As seen in Table 18, we found the highest prevalence of imaging changes for patients with anti-AMPAR-associated encephalitis (0.86; CI 0.70-0.97). The lowest pooled prevalence was detected for anti-IgLON5 disease (0.11; CI 0.00-0.33). However, we obtained similar results for the pooled prevalences compared to the un-pooled values. For some of the antibodies, such as LGI1, prevalences of imaging changes were the same, pooled or un-pooled (each 66 %). However, for AMPAR, D2 receptor, and DDPX encephalitis, the prevalences of changes on MRI were much higher when pooled (86 % vs. 77 %; 66.7 % vs. 74 %; 30 % vs. 47 %). We found the most considerable difference between the pooled and un-pooled prevalence for anti-GAD encephalitis. Here, we calculated a percentage of 59.7 % for imaging changes before pooling. After pooling, the generated prevalence was 79 % (0.53-0.97). The differences between the studies that might have led to this are also reflected in the highest I^2 we obtained for

the calculation of an encephalitis subtype. Furthermore, we computed the highest risk of bias within the publications for anti-GAD encephalitis. In contrast, the pooled prevalence obtained for the case of IgLON5 was much lower than without pooling (11 % vs. 22 %)

We obtained an overall pooled prevalence of 0.57 (0.46-0.68) for imaging alterations across all cell surface antibody-associated encephalitis subtypes. The overall pooled prevalence was again calculated with the MetaXL software by multiplying the pooled prevalence for each AIE subtype with the number of patients included, respectively. However, calculating an overall heterogeneity of the different antibody-associated entities could be considered misleading, see the discussion section below.

The overall heterogeneity index I^2 obtained for the analysis across all encephalitis subtypes was very high, with 96 % ($p < 0.001$). For the individual AIEs, we found varying results. The lowest heterogeneity index I^2 was detected for anti-AMPAR and anti-GlyR-associated encephalitis (0 %; $p= 0.85$; $p= 0.52$, respectively). The highest heterogeneity was found across the publications for anti-GAD encephalitis (90 %; $p < 0.001$). For this subtype, the pooled prevalence of MRI alterations was also relatively high (0.79; 0.53-0.97).

Considering the detection of such high heterogeneity between the studies, we conducted an additional subgroup analysis. In this subgroup analysis, we calculated the pooled prevalence of post-acute changes on MRI and evaluated whether the across-study heterogeneity would decrease. Post-acute imaging changes were defined as changes present at least six months after symptom onset. We could only perform such an evaluation for the two encephalitis forms with the most published cases, NMDAR and LGI1 encephalitis. For the other subtypes, not enough post-acute imaging data were available. The Forest Plots of the prevalence of MRI changes in the post-acute disease stage are shown in Figures 16 and 17.

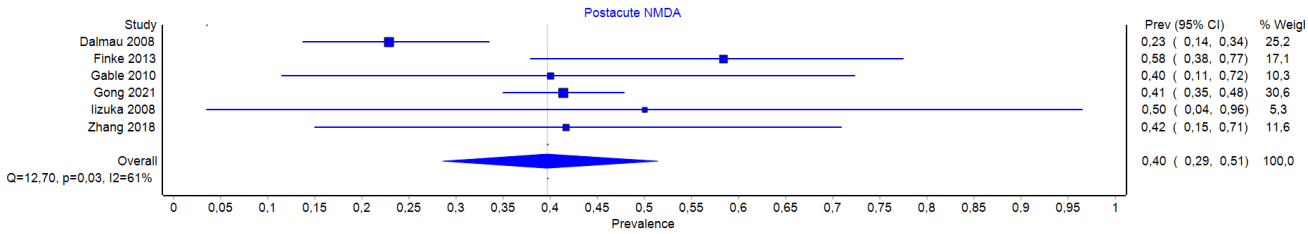


Figure 15: Forest Plot for anti-NMDAR encephalitis in the post-acute disease stage

For NMDAR encephalitis, we found six studies[35,61,65,68,79,231] with evaluable MRI data of the post-acute disease stage. This corresponds to 321 patients. The pooled prevalence of post-acute MRI alterations for NMDAR encephalitis patients was slightly lower than in the acute disease stage (0.40 vs. 0.41). The heterogeneity index I^2 was much lower in this analysis, with 61 % compared to 73 % for the evaluation of MRI changes during the acute disease stage.

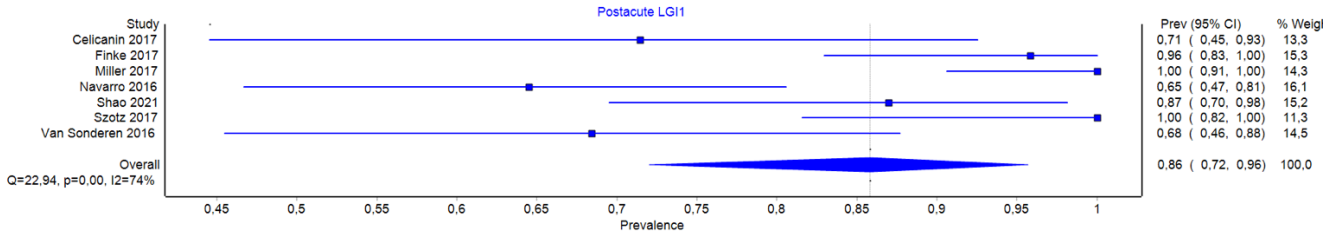


Figure 16: Forest Plot for anti-LGI1 encephalitis in the post-acute disease stage

For anti-LGI1 encephalitis, we found seven eligible studies reporting post-acute cases.[39,93,94,103,232–234] This equals 138 evaluated patients. We saw an increase in the pooled prevalence of MRI changes compared to the acute disease stage (0.86 vs. 0.67). The heterogeneity index remained approximately the same (74 % vs. 76 %).

4 Discussion

Image-based methods are the standard for first-line diagnosis of many entities. For instance, oncology is a field where imaging techniques are now the mainstay of early diagnosis and screening. In this context, the question arises as to whether image-based procedures can also be used to diagnose specific AIEs. As mentioned, some cell surface antibody-associated encephalitides correlate with oncologic diagnoses. Therefore, it would be highly desirable if, at least in these cases, brain MRI could also be used for an early diagnosis of the AIE.

Our results show that a diagnosis of AIE relying predominantly on neuroimaging is currently only possible with limitations. For some encephalitis subtypes, we found patterns of regions more likely to be affected. On standard MRIs, changes were often detected as hyperintense signals on T2/FLAIR sequences. Nevertheless, the pooled prevalences of imaging changes for some antibodies are still relatively low. The across-study heterogeneity of the published cases, in addition, is comparatively high. An exception is the case of anti-$GABA_b$, where we detected imaging changes with a pooled prevalence of 0.63 (0.54-0.73) and a low heterogeneity index I^2 of 19 % ($p= 0.25$). A high prevalence of imaging changes with a low heterogeneity across the included studies is also obtained for the anti-AMPAR and the $GABA_a$ receptor antibodies. However, for those two cases, we were only able to use three studies each, as the number of publications eligible for us was scarce. Hence, the analysis for these subtypes could not yield highly meaningful results.

The high value for heterogeneity might also partly be obtained as we did not exclude studies that only focused on a defined clinical subset of patients. These studies, for instance, exclusively reported patients with specific clinical presentations, tumors, or demographics. Nevertheless, we chose to still consider those studies for our analysis as the patient data available are already reasonably sparse.

Advanced imaging methods, such as DTI, volumetric or functional analysis, can detect structural or functional brain changes in many cases, where the standard MRI cannot. However, these modalities have yet to be widely available. Furthermore, they are more complex to implement. As it is probably not feasible to examine all patients by those imaging methods, it should be considered to examine at least the patients with a highly likely diagnosis of autoimmune encephalitis. Descriptions of the clinical presentation of the patients show that characteristic syndromes associated with the respective AIE exist. These can provide a useful hint to the underlying entity.

Some autoantibodies to neuronal targets are associated with different, each very distinct syndromes. These syndromes respectively display individual imaging features. This is the case, for instance, for anti-CASPR2 or -LGI1-associated syndromes. Therefore, assessing the prevalences and regions of imaging alterations related to the individual syndromes might be interesting. Our review found some associations between the patients' clinical presentation and characteristic imaging changes for many of the encephalitis subtypes. Hence, considering only the patients with similar clinical presentations might lead to a more homogenous result in a meta-analysis of the patients' imaging data. The high across-study heterogeneity our analysis yielded might reflect the very variable manifestation of AIE. Similarly, the overall pooled heterogeneity value in Table 18 should be regarded with caution, as this corresponds to the pooling of different entities. As the entities are very diverse, a high heterogeneity across the studies is expected. Nonetheless, an overall pooled prevalence can provide an estimate for imaging changes across the different AIEs.

Considering our results, standard imaging alone is still insufficient for early diagnosis, and additional diagnostic methods are needed. Combining diagnostic measures such as neuroimaging and antibody testing, CSF analysis, or others can increase the overall specificity of the diagnostic tests. However, an evaluation of such combined effects is beyond the scope of our work.

A meta-analysis published recently and found later during our analysis evaluates the detection sensitivity of FDG-PET for the diagnosis of AIE.[1] As this study assesses AIE's neuroimaging, it is similar to our analysis. However, the study focuses on FDG-PET imaging, not reporting specific MRI changes for the AIE subtypes. In contrast to our study, data from only 17 studies are included, corresponding to 267 patients. Our meta-analysis had 177 studies with a total of 5050 patients. The detection sensitivity for changes on FDG-PET they found was 87 % (CI 80–92%). The heterogeneity index I^2 obtained for their data was 60 % ($p < 0.001$) when including all AIE subtypes. When only considering individual autoantibody-associated encephalitis subtypes, the heterogeneity index decreased to around 20 % ($p=0.33$). For the calculation of detection sensitivity on MRI, they obtained an I^2 of 73% ($p < 0.001$). Our heterogeneity index I^2 for calculating an overall pooled prevalence of imaging changes on MRI was higher, with 96 % ($p < 0.001$). The study[1] found an overall detection sensitivity for AIE with MRI of 56 % (CI 46–66%). We assume the detection sensitivity measure is equivalent to the prevalence of imaging changes. Our result for the overall pooled prevalence of MRI changes across all encephalitis subtypes was 57 %. Thus, our results are very similar, even though the study size in [1] is much smaller (267 vs. 5050 patients). The higher value for heterogeneity across our included studies may have been caused by assessing more subtypes of AIE. Although we investigated partly different antibody-associated encephalitides, we obtained very similar results. This is most likely attributable to the much larger number of anti-NMDAR encephalitis patients compared to other subtypes included in both studies. Hence, the result for an overall pooled prevalence in both studies mainly reflects the prevalence of imaging changes for anti-NMDAR encephalitis. Overall, the study by Bordonne et al. [1] finds that the detection sensitivity of changes in brain imaging is higher on FDG-PET images than on MRIs. This is similar to the results obtained in our systematic overview.

In our complementary subgroup analysis, we evaluated MRI data of the post-acute disease stage. Here, our analysis yielded rather unexpected results. For anti-NMDA encephalitis patients, we anticipated the frequency of MRI changes to increase due to frequent, predominantly frontotemporal atrophy. However, our systematic overview already revealed a slight trend toward a decrease in MRI changes in the post-acute disease stage. The discrepancy between the obtained results and our expectations might be due to the low number of cases we could include for the post-acute analysis. With such a limited number of patients, it is difficult to obtain reliable data. A single study can significantly change the whole outcome. In our analysis, four studies[61,65,68,232] all show similar prevalences for post-acute MRI changes with around 40 % to 50 %. However, one larger study[35] reports a prevalence of 23 % for post-acute MRI alterations. As this is the second largest study in our subgroup analysis, it greatly affects the resulting pooled prevalence and the I^2 representing heterogeneity. The highest prevalence was found in the study by Finke et al.[79] (58 %). As this study compared standard clinical MRIs to high-resolution structural imaging, a higher prevalence for identified imaging changes was anticipated.

For anti-LGI1 encephalitis, we expected the pooled prevalence of MRI changes in the post-acute disease stage to increase according to the trend of the articles yielded by our literature search. This was in line with the result of our statistical evaluation. However, the patients reported with anti-LGI1 encephalitis were usually in later adulthood. Therefore, the increase of brain MRI changes in later disease stages or after recovery could have also been associated with age-related degeneration. Furthermore, the persisting high heterogeneity across the studies in our subgroup analysis could have been related to the retrospective nature of many included studies. The articles were mainly reporting cases of hospitalized patients with severe clinical symptoms. Moreover, most descriptions only included patients with LE. Until 2016, with the publication of Graus and colleagues[15], there was no clear definition for definite autoimmune LE. According to Graus' definition, imaging changes must be present for a diagnosis of LE. However, all but one article[93] we included in this analysis were published until 2017. Therefore, we do not expect that imaging changes were obligatory for the diagnosis of LE in those articles. Still, the prevalence of MRI changes in these studies was comparatively high.[94]

In contrast, the study by Navarro and colleagues[94] focused on patients with FBDS. Only 55.8 % of the examined patients presented with memory impairment at disease onset. Accordingly, the prevalence of MRI changes at the onset was remarkably low for the anti-LGI1 encephalitis patients, with only 34.7 %. In the post-acute disease stage, the prevalence of MRI changes increased to 65 %, which was still the lowest of all studies we found for LGI1 encephalitis patients in the post-acute disease stage. The two other studies[39,233] with comparatively low prevalence rates (68 %, 71 %), both recruited their patients from databases of national antibody testing laboratories. These patients were not necessarily hospitalized or severely symptomatic.

Overall, it is essential to note that no diagnostic test can be 100 % sensitive and provide complete certainty. Even advanced imaging methods are not able to detect all neuroimaging changes.[188] Wagner and colleagues[188] evaluated an automated MRI post-processing method in autoimmune LE patients. The authors compared the computerized approach, quantifying FLAIR signal intensities and volume changes, to the visual assessment of brain images by experienced neuroradiologists. The comparison showed that the LE detection rate of the automated approach was significantly superior to the visual inspection of the images. In contrast, no significant difference in detecting hippocampal sclerosis was found. Considering this, it should be kept in mind that the prevalence of detected changes in neuroimaging still has a strong observer-dependent component for some abnormalities.

5 Conclusions

Our results confirm findings of prior, smaller meta-analyses. In terms of pooled prevalence for image alterations on MRI, the statistical findings of our meta-analysis are in excellent agreement with the results in studies most recently published.[1] However, our results further enhance the prior results in several directions: (1) the number of studies considered is much larger (2) likewise, the total number of patients included is much larger (3) the type and number of autoantibodies explored (4) distinction between cell surface and intracellular antibodies.

The encephalitis subtype where we found the most significant result was anti-$GABA_b$ encephalitis. Here we detected a high prevalence of MRI changes associated with a low heterogeneity while including a larger number of studies.

6 Literature

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7 Appendix

7.1 Eidesstattliche Versicherung

„Ich, Marie Schweikard, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Imaging alterations in autoimmune encephalitis: systematic review and meta-analysis, Bildgebende Veränderungen bei Autoimmunenzephalitis: systematischer Review und Meta-Analyse selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

_____ _____

Datum Unterschrift

7.2 Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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7.4 Statistics certificate

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Bescheinigung

Hiermit bescheinige ich, dass Frau Marie Schweikard innerhalb der Service Unit Biometrie des Instituts für Biometrie und Klinische Epidemiologie (iBikE) bei mir eine statistische Beratung zu einem Promotionsvorhaben wahrgenommen hat. Folgende Beratungstermine wurden wahrgenommen:

- Termin 1: 28.02.2022

Folgende wesentliche Ratschläge hinsichtlich einer sinnvollen Auswertung und Interpretation der Daten wurden während der Beratung erteilt:

- Die Durchführung des Systematic Reviews anhand des PRISMA Statements ist zu empfehlen.
- Random Effects Modelle für die Meta-Analyse, sowie Forest-, Funnel- und Doi-Plots zur Visualisierung für die Studienergebnisse basierend auf den einzelnen Autoantikörpern sollten zur Analyse, Visualisierung und Interpretation verwendet werden.
- Eine sehr hohe Heterogenität zwischen den Studienergebnissen (im Forestplot sichtbar oder anhand von I^2 geschätzt) spricht dagegen diese in einem Prävalenzschätzer zusammenzufassen. Es wird daher dringend angeraten Subgruppenanalysen zu machen, um die Quelle der Heterogenität zu erfassen.

Diese Bescheinigung garantiert weder die richtige Umsetzung der in der Beratung gemachten Vorschläge, die korrekte Durchführung der empfohlenen statistischen Verfahren noch die richtige Darstellung und Interpretation der Ergebnisse. Die Verantwortung hierfür obliegt allein dem Promovierenden. Das Institut für Biometrie und Klinische Epidemiologie übernimmt hierfür keine Haftung.

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