Autoimmune-associated epilepsy – a challenging concept

Nico Melzer and Felix Rosenow

Suggested Citation:
Melzer, N., & Rosenow, F. (2024). Autoimmune-associated epilepsy – a challenging concept. Seizure, 128, 20–23. https://doi.org/10.1016/j.seizure.2024.05.017

Seizure: European Journal of Epilepsy 128 (2025) 20–23

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Review

Autoimmune-associated epilepsy – a challenging concept

Nico Melzer [a,*], Felix Rosenow [b,c]

[a] Department of Neurology, Medical Faculty and University Hospital, Heinrich Heine University Düsseldorf, Moorenstraße 5, Düsseldorf 40225, Germany
[b] Goethe University Frankfurt, Epilepsy Center Frankfurt Rhine-Main, Department of Neurology, University Hospital Frankfurt, Frankfurt, Germany
[c] Goethe University Frankfurt, LOEWE Center for Personalized Translational Epilepsy Research (CePTER), Frankfurt, Germany

ARTICLE INFO

Keywords:
Autoimmune (limbic) encephalitis
Autoimmune-associated epilepsy
Focal seizures and epilepsy
Data-driven prediction

ABSTRACT

The current International League Against Epilepsy (ILAE) definition and classification guidelines for the first time introduced the category of immune-mediated focal epilepsy in addition to structural, genetic, infectious, and metabolic aetiologies. Moreover, the ILAE Autoimmunity and Inflammation Taskforce recently provided a conceptual framework for the distinction between acute "provoked" seizures in the acute phase of autoimmune encephalitis from chronic "unprovoked" seizures due to autoimmune-associated epilepsy. The first category predominately applies to those autoimmune encephalitis patients with autoantibodies against cell surface neural antigens, in whom autoantibodies are assumed to exert a direct ictogenic effect without overt structural damage. These patients do not exhibit enduring predisposition to seizures after the "acute phase" encephalitis, and thus do not fulfil the definition of epilepsy. The second category applies to those autoimmune encephalitis patients with autoantibodies against intracellular neural antigens and Rasmussen's encephalitis, in whom T cells are assumed to cause epileptogenic effects through immune-inflammation and overt structural damage. These patients do exhibit enduring predisposition to seizures after the "acute phase" of encephalitis and thus fulfil the definition of epilepsy. AAE may result from both, ongoing brain autoimmunity and associated structural brain damage according to the current ILAE definition and classification guideline. We here discuss the difficulties of this concept and suggest an unbiased translationally validated and data-driven approach to predict in an individual encephalitis patient the propensity to develop (or not) AAE and the cognitive and behavioural outcome.

1. Introduction

Seizures and epilepsy are a common clinical manifestation of autoimmune encephalitis (AIE; [1,2]) especially autoimmune limbic encephalitis (ALE; [3,4]), predominantly affecting mesial temporal structures such as the amygdala and the anterior part of the hippocampus.

In 2016 initial consensus criteria regarding the diagnosis of possible, probable, and definite AIE were established [1] and have recently been validated, independently [2]. In this framework, we suggested the restriction of MRI phenotypes to the mesial temporal lobe structures to define possible, probable, and definite ALE [3,4], especially to facilitate the investigation of neurocognitive symptoms of the disorder as well as seizure semiology and outcome [5]. Importantly, the diagnosis can be established also in the absence of distinct autoantibodies in serum and CSF [1,2] underlying the existence of seronegative probably T cell-mediated ALE [6-8]. Using these criteria, approximately 50 % of all patients in a tertiary epilepsy centre did not exhibit autoantibodies [3, 4], while presenting with a rather strong seizure phenotype with limited response to anti-seizure medication (ASM) and immunotherapy.

These and similar findings in other cohorts posed the question what factors may drive epileptogenesis i.e. the transition of the affected the neural network from acute immune-inflammation-driven to chronic immune-inflammation independent hyperexcitability and dysfunction in AIE and especially in ALE [9,10].

2. Acute provoked seizures and chronic unprovoked seizures in autoimmune (limbic) encephalitis

Following the introduction of the concept by experts in the field [11], the current International League Against Epilepsy (ILAE) definition and classification guidelines for the first time introduced the category of immune-mediated focal epilepsy in addition to structural, genetic, infectious, and metabolic aetiologies [12,13]. Moreover, the ILAE Autoimmunity and Inflammation Taskforce recently provided a conceptual framework for the distinction between acute "provoked" seizures in the

* Corresponding author.
E-mail address: nico.melzer@med.uni-duesseldorf.de (N. Melzer).

https://doi.org/10.1016/j.seizure.2024.05.017
Received 25 March 2024; Received in revised form 24 May 2024; Accepted 25 May 2024
Available online 27 May 2024

acute phase of AIE/ALE from chronic "unprovoked" seizures due to autoimmune-associated epilepsy (AAE) [14]. The first category predominately applies to those AIE/ALE patients with autoantibodies against cell surface neural antigens, in whom autoantibodies are assumed to exert a direct ictogenic effect without overt structural damage. These patients do not exhibit *enduring* predisposition to seizures after the "acute phase of AIE/ALE", and thus do not fulfil the definition of epilepsy [15]. The second category applies to those AIE/ALE patients with autoantibodies against intracellular neural antigens and Rasmussen's encephalitis (RE, [16]), in whom T cells are assumed to cause epileptogenic effects through immune-inflammation and overt structural damage. These patients do exhibit *enduring* predisposition to seizures after the "acute phase of AIE/ALE/RE" and thus fulfil the definition of epilepsy [15]. The authors point out that AAE may result from both, ongoing brain autoimmunity and associated structural brain damage according to the current ILAE definition and classification guideline [12-14].

First of all, it is important to distinguish acute provoked seizures due to autoimmune encephalitis from chronic unprovoked seizures due to autoimmune-associated epilepsy. However, the current concept confers several difficulties with strong consequences for clinical counselling and treatment of affected patients:

(i) It is still unclear – especially in an individual ALE patient with seizures originating from affected mesial temporal lobe structures – whether assumed clinical seizure freedom indeed corresponds also to electroencephalographic seizure freedom (seizure underreporting; [17]). Thus, the *enduring* predisposition to seizures *per se* is hard to assess reliably due to clinical seizure underreporting [17]. Moreover, restrictions in recording duration and invasiveness of current EEG techniques pose another source of inaccuracy to reliably assess seizure outcomes [17]. Regular use of long-term (video-)EEG recording during the disease course would aid to improve the diagnostic accuracy.

(ii) The time course of the "acute phase of AIE/ALE/RE" is very poorly or even undefined [14], and there are no reliable biomarkers for this period. Moreover, while an acute phase may be clinically recognized in RE and AIE/ALE with autoantibodies against cell surface neural antigens such as anti-NMDAR, anti--LGI1, or anti-CASPR2 encephalitis, it may virtually be absent in patients with anti-GAD65 AIE/ALE.

(iii) Nothing is said about the large number of patients with seronegative AIE/ALE [3,4]. Giving the histopathological evidence for a T cell-mediated pathology in these cases [6-8], they may have a higher likelihood of developing AAE but are not covered by the proposed conceptual definitions [14].

(iv) There are also AIE/ALE patients with autoantibodies against cell surface neural antigens, who also exhibit strong parenchymal T cell responses [18-21], rendering their predisposition of AAE fully unclear according to the proposed conceptual definitions [14].

(v) A large proportion of AIE/ALE patients with autoantibodies against cell surface neural antigens develop persistent brain atrophy i.e. structural brain damage even when immune-inflammation appears to have resolved [22].

(vi) As pointed out above, in AAE immune effector mechanisms may still be present, while immune-mediated structural brain damage already occurred that may or may not be visible on MRI [14] i.e. there is no MRI criterion to reliably distinguish seizures from epilepsy in AIE/ALE.

(vii) Uncontrolled seizures in the acute phase of AIE/ALE (and not the cellular localization of the target antigen of autoantibodies) have recently been identified as a major risk factor of developing AAE [23,24].

(viii) Moreover, it is fully unclear whether parenchymal immune-inflammation is ever fully resolved given the persistence of tissue resident memory T cells and activated microglia also for decades of pharmacoresistant focal epilepsy [25]. These cells have been shown to drive compartmentalized parenchymal immune-inflammation in the brain [26,27].

(ix) Moreover, the criterion of cessation of seizures following immunotherapy as an idicator of their acute provoked origin and the absence of structural brain damage as opposed to their chronic unprovoked nature due to structural brain damage does not seem to be appropriate given the fact that there are no drugs licensed based on larger phase III randomized controlled trials to treat AIE/ALE/RE. So, a lack of a clinical response to immunotherapy is not a suitable indicator of resolution of immune-inflammation given the unknown efficacy of currently used drugs and compartmentalized immune-inflammation in the brain.

Current concepts of epileptogenesis refer to the fact that a previously normal neural network after or during a certain pathological stimulus that may or may not by itself induce acute symptomatic seizures (such as stroke, brain tumours, traumatic brain injury, or encephalitis) becomes persistently hyperexcitable independent of the continuous impact of the precipitating pathogenic factor [9,10]. This is likely an active process of neural network adaptation, and it is likely not the structural damage itself that drives seizures and epilepsy [9,10].

These concepts of epileptogenesis can be experimentally tested in suitable animal models and then be transferred to humans. We recently established a model of primary T cell-driven ALE resulting in hippocampal sclerosis (HS) [7,8]. This model goes along with early activated astrogliosis and microglia activation and acute high-frequency seizures that turns into hippocampal sclerosis (HS) with astrogliosis and microglia activation with persisting chronic low-frequency seizures [7,8]. This model is well suited to study T cell-driven epileptogenesis experimentally and provide hints how to identify and monitor this process in patients.

3. Conclusion

Currently, it is hardly possible in an individual AIE/ALE/RE patient to separate acute provoked seizures from chronic unprovoked seizures (epilepsy) due to limitations in determining seizure outcomes, unclear time courses, potential causal interactions between both seizure origins, compartmentalized immune-inflammation and a lack of licensed drugs to resolve immune-inflammation in the brain parenchyma. This makes it hard to decide when to terminate ASMs and to counsel the individual patient regarding driving abilities and other behavioural restrictions and recommendations.

Thus, studies are urgently needed to define clinical and paraclinical (MRI [28-30], EEG [31-35], serum or cerebrospinal fluid (CSF) [36,37]) biomarkers in a hypothesis-free data-driven approach reliably predicting (or not) the development of AAE and the cognitive and behavioural outcome in the due cause of an individual patient́s disease [28-30]. These studies should be experimentally validated in suitable animal models.

Funding

N. M. was funded by the German Federal Ministry of Science and Education (Comprehensive, Orchestrated, National Network to Explain, Categorize and Treat autoimmune encephalitis and allied diseases within the German NEtwork for Research on AuToimmune Encephalitis – CONNECT GENERATE 2.0; 01GM2208A).

Declaration of competing interest

N. M. has received honoraria for lecturing and travel expenses for attending meetings from Biogen Idec, GlaxoSmith Kline, Teva, Novartis Pharma, Bayer Healthcare, Genzyme, Alexion Pharmaceuticals,

Fresenius Medical Care, Diamed, UCB Pharma, AngeliniPharma, BIAL and Sanofi-Aventis, has received royalties for consulting from UCB Pharma, Alexion Pharmaceuticals and Sanofi-Aventis and has received financial research support from Euroimmun, Fresenius Medical Care, Diamed, Alexion Pharmaceuticals, and Novartis Pharma.

F. R. has received honoraria for lecturing, scientific advice and travel expenses from Angelini Pharma, Desitin Pharma, Eisai GmbH, Jazz Pharma, Roche Pharma and UCB Pharma. He has received financial research support from Eisai GmbH, Kanso Dr. Schär, Milupa, the LOEWE Programm of the Federal state of Hessen, the Dr. Senckebergische Foundation, the Kassel Foundation, The Detlev-Wrobel Fonds for Epilepsy Research, The Chaja Foundation and the Ernst-Max von Grunelius Foundation.

Acknowledgments

N. M. would like to thank Helga Seiwert for writing and editing of the manuscript.

References

[1] Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Hoftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Pruss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostasy K, Saiz A, Venkatesan A, Vincent A, Wandinger KP, Waters P, Dalmau J. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15:391–404.

[2] Van Steenhoven RW, de Vries JM, Bruijstens AL, Paunovic M, Nagtzaam MM, Franken SC, Bastiaansen AE, De Bruijn MA, Van Sonderen A, Schreurs MWJ, Gardeniers M, Verdijk RM, Balvers RK, Sillevis Smitt PA, Neuteboom RF, Titulaer MJ. Mimics of autoimmune encephalitis: validation of the 2016 clinical autoimmune encephalitis criteria. Neurol Neuroimmunol Neuroinflamm 2023;10.

[3] Mueller C, Langenbruch L, Rau JMH, Brix T, Strippel C, Dik A, Golombeck KS, Monig C, Johnen A, Rauber S, Wiendl H, Meuth SG, Bolte J, Kovac S, Melzer N. Neuropsychological performance in autoimmune limbic encephalitis: evidence from an immunotherapy-naive cohort. Arch Clin Neuropsychol 2022;37:738–52.

[4] Mueller C, Langenbruch LM, Rau JMH, Brix T, Strippel C, Dik A, Golombeck KS, Moenig C, Raeuber SJ, Kovac S, Wiendl H, Meuth SG, Bolte J, Johnen A, Melzer N. Determinants of cognition in autoimmune limbic encephalitis- a retrospective cohort study. Hippocampus 2021;31:1092–103.

[5] Kaaden T, Madlener M, Angstwurm K, Bien CG, Bogarin Y, Doppler K, Finke A, Gerner ST, Reimann G, Hausler M, Handreka R, Hellwig K, Kaufmann M, Kellinghaus C, Koertvelyessy P, Kraft A, Lewerenz J, Menge T, Paliantonis A, von Podewils F, Pruss H, Rauer S, Ringelstein M, Rostasy K, Schirotzek I, Schwabe J, Sokolowski P, Suesse M, Suhs KW, Surges R, Tauber SC, Thaler F, Bergh FT, Urbanek C, Wandinger KP, Wildemann B, Mues S, Zettl U, Leypoldt F, Melzer N, Geis C, Malter M, Kunze A. Seizure semiology in antibody-associated autoimmune encephalitis. Neurol Neuroimmunol Neuroinflamm 2022;9.

[6] Graus F, Escudero D, Oleaga L, Bruna J, Villarejo-Galende A, Ballabriga J, Barcelo MI, Gilo F, Popkirov S, Stourac P, Dalmau J. Syndrome and outcome of antibody-negative limbic encephalitis. Eur J Neurol 2018;25:1011–6.

[7] Gallus M, Roll W, Dik A, Barca C, Zinnhardt B, Hicking G, Mueller C, Naik VN, Anstotz M, Kramer J, Rolfes L, Wachsmuth L, Pitsch J, van Loo KMJ, Rauber S, Okada H, Wimberley C, Strippel C, Golombeck KS, Johnen A, Kovac S, Gross CC, Backhaus P, Seifert R, Lewerenz J, Surges R, Elger CE, Wiendl H, Ruck T, Becker AJ, Faber C, Jacobs AH, Bauer J, Meuth SG, Schafers M, Melzer N. Translational imaging of TSPO reveals pronounced innate inflammation in human and murine CD8 T cell-mediated limbic encephalitis. Sci Adv 2023;9:eabq7595.

[8] Pitsch J, van Loo KMJ, Gallus M, Dik A, Kamalizade D, Baumgart AK, Gnatkovsky V, Muller JA, Opitz T, Hicking G, Naik VN, Wachsmuth L, Faber C, Surges R, Kurts C, Schoch S, Melzer N, Becker AJ. CD8(+) T-lymphocyte-driven limbic encephalitis results in temporal lobe epilepsy. Ann Neurol 2021;89:666–85.

[9] Simonato M, Agoston DV, Brooks-Kayal A, Dulla C, Fureman B, Henshall DC, Pitkanen A, Theodore WH, Twyman RE, Kobeissy FH, Wang KK, Whittemore V, Wilcox KS. Identification of clinically relevant biomarkers of epileptogenesis - a strategic roadmap. Nat Rev Neurol 2021;17:231–42.

[10] Pitkanen A, Lukasiuk K. Mechanisms of epileptogenesis and potential treatment targets. Lancet Neurol 2011;10:173–86.

[11] Geis C, Planaguma J, Carreno M, Graus F, Dalmau J. Autoimmune seizures and epilepsy. J Clin Invest 2019;129:926–40.

[12] Rosenow F, Akamatsu N, Bast T, Bauer S, Baumgartner C, Benbadis S, Bermeo-Ovalle A, Beyenburg S, Bleasel A, Bozorgi A, Brazdil M, Carreno M, Delanty N, Devereaux M, Duncan J, Fernandez-Baca Vaca G, Francione S, Garcia Losarcos N, Ghanma L, Gil-Nagel A, Hamer H, Holthausen H, Omidi SJ, Kahane P, Kalamangalam G, Kanner A, Knake S, Kovac S, Krakow K, Kramer G, Kurlemann G, Lacuey N, Landazuri P, Lim SH, Londono LV, LoRusso G, Luders H, Mani J, Matsumoto R, Miller J, Noachtar S, O'Dwyer R, Palmini A, Park J, Reif PS, Remi J, Sakamoto AC, Schmitz B, Schubert-Bast S, Schuele S, Shahid A, Steinhoff B, Strzelczyk A, Szabo CA, Tandon N, Terada K, Toledo M, van Emde Boas W, Walker M, Widdess-Walsh P. Could the 2017 ILAE and the four-dimensional epilepsy classifications be merged to a new "Integrated Epilepsy Classification"? Seizure 2020;78:31–7.

[13] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshe SL, Nordli DR, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58:512–21.

[14] Steriade C, Britton J, Dale RC, Gadoth A, Irani SR, Linnoila J, McKeon A, Shao XQ, Venegas V, Bien CG. Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: conceptual definitions. Epilepsia 2020;61:1341–51.

[15] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel Jr J, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshe SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475–82.

[16] Varadkar S, Bien CG, Kruse CA, Jensen FE, Bauer J, Pardo CA, Vincent A, Mathern GW, Cross JH. Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. Lancet Neurol 2014;13:195–205.

[17] Elger CE, Hoppe C. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. Lancet Neurol 2018;17:279–88.

[18] Golombeck KS, Bonte K, Monig C, van Loo KM, Hartwig M, Schwindt W, Widman G, Lindenau M, Becker AJ, Glatzel M, Elger CE, Wiendl H, Meuth SG, Lohmann H, Gross CC, Melzer N. Evidence of a pathogenic role for CD8(+) T cells in anti-GABAB receptor limbic encephalitis. Neurol Neuroimmunol Neuroinflamm 2016;3:e232.

[19] Bracher A, Alcala C, Ferrer J, Melzer N, Hohlfeld R, Casanova B, Beltran E, Dornmair K. An expanded parenchymal CD8+ T cell clone in GABA(A) receptor encephalitis. Ann Clin Transl Neurol 2020;7:239–44.

[20] Brandle SM, Cerina M, Weber S, Held K, Menke AF, Alcala C, Gebert D, Herrmann AM, Pellkofer H, Gerdes LA, Bittner S, Leypoldt F, Teegen B, Komorowski L, Kumpfel T, Hohlfeld R, Meuth SG, Casanova B, Melzer N, Beltran E, Dornmair K. Cross-reactivity of a pathogenic autoantibody to a tumor antigen in GABA(A) receptor encephalitis. Proc Natl Acad Sci U S A 2021;118.

[21] Pitsch J, Kamalizade D, Braun A, Kuehn JC, Gulakova PE, Ruber T, Lubec G, Dietrich D, von Wrede R, Helmstaedter C, Surges R, Elger CE, Hattingen E, Vatter H, Schoch S, Becker AJ. Drebrin autoantibodies in patients with seizures and suspected encephalitis. Ann Neurol 2020;87:869–84.

[22] Finke C, Pruss H, Heine J, Reuter S, Kopp UA, Wegner F, Then Bergh F, Koch S, Jansen O, Munte T, Deuschl G, Ruprecht K, Stocker W, Wandinger KP, Paul F, Bartsch T. Evaluation of cognitive deficits and structural hippocampal damage in encephalitis with leucine-rich, glioma-inactivated 1 antibodies. JAMA Neurol 2017;74:50–9.

[23] Matricardi S, Casciato S, Bozzetti S, Mariotto S, Stabile A, Freri E, Deleo F, Sartori S, Nosadini M, Pappalardo I, Meletti S, Giovannini G, Zucchi E, Di Bonaventura C, Di Gennaro G, Ferrari S, Zuliani L, Zoccarato M, Vogrig A, Lattanzi S, Michelucci R, Gambardella A, Ferlazzo E, Fusco L, Granata T, Villani F. Immune Epilepsies Study Group of the Italian League Against, E. Epileptic phenotypes in autoimmune encephalitis: from acute symptomatic seizures to autoimmune-associated epilepsy. J Neurol Neurosurg Psychiatry 2022.

[24] Smith KM, Britton JW, Thakolwiboon S, Chia NH, Gupta P, Flanagan EP, Zekeridou A, Lopez Chiriboga AS, Valencia Sanchez C, McKeon A, Pittock SJ, Dubey D. Seizure characteristics and outcomes in patients with neurological conditions related to high-risk paraneoplastic antibodies. Epilepsia 2023;64:2385–98.

[25] Merkler D, Vincenti I, Masson F, Liblau RS. Tissue-resident CD8 T cells in central nervous system inflammatory diseases: present at the crime scene and ...guilty. Curr Opin Immunol 2022;77:102211.

[26] Frieser D, Pignata A, Khajavi L, Shlesinger D, Gonzalez-Fierro C, Nguyen XH, Yermanos A, Merkler D, Hoftberger R, Desestret V, Mair KM, Bauer J, Masson F, Liblau RS. Tissue-resident CD8(+) T cells drive compartmentalized and chronic autoimmune damage against CNS neurons. Sci Transl Med 2022;14:eabl6157.

[27] Vincenti I, Page N, Steinbach K, Yermanos A, Lemeille S, Nunez N, Kreutzfeldt M, Klimek B, Di Liberto G, Egervari K, Piccinno M, Shammas G, Mariotte A, Fonta N, Liaudet N, Shlesinger D, Liuzzi AR, Wagner I, Saadi C, Stadelmann C, Reddy S, Becher B, Merkler D. Tissue-resident memory CD8(+) T cells cooperate with CD4(+) T cells to drive compartmentalized immunopathology in the CNS. Sci Transl Med 2022;14:eabl6058.

[28] Genon S, Bernhardt BC, La Joie R, Amunts K, Eickhoff SB. The many dimensions of human hippocampal organization and (dys)function. Trends Neurosci 2021;44:977–89.

[29] Genon S, Eickhoff SB, Kharabian S. Linking interindividual variability in brain structure to behaviour. Nat Rev Neurosci 2022;23:307–18.

[30] Wu J, Li J, Eickhoff SB, Scheinost D, Genon S. The challenges and prospects of brain-based prediction of behaviour. Nat Hum Behav 2023;7:1255–64.

[31] Omidvarnia A, Pedersen M, Vaughan DN, Walz JM, Abbott DF, Zalesky A, Jackson GD. Dynamic coupling between fMRI local connectivity and interictal EEG in focal epilepsy: a wavelet analysis approach. Hum Brain Mapp 2017;38:5356–74.

[32] Omidvarnia A, Kowalczyk MA, Pedersen M, Jackson GD. Towards fast and reliable simultaneous EEG-fMRI analysis of epilepsy with automatic spike detection. Clin Neurophysiol 2019;130:368–78.

[33] Lu D, Bauer S, Neubert V, Costard LS, Rosenow F, Triesch J. Towards early diagnosis of epilepsy from EEG Data. *Computational biology and health informatics*. In: Proceedings of the 5th Machine Learning for Healthcare Conference; 2020. p. 80–96.

[34] Lu D, Bauer S, Neubert V, Costard LS, Rosenow F, Triesch J. Staging epileptogenesis with deep neural networks. *Computational biology and health*

informatics. In: Proceedings of the 11th ACM International Conference on Bioinformatics; 2020. p. 1–10.

[35] Farahat A, Lu D, Bauer S, Neubert V, Costard LS, Rosenow F, Triesch J. Diagnosing epileptogenesis with deep anomaly detection. *Proceedings of machine learning research*. In: Proceedings of the 7th Machine Learning for Healthcare Conference; 2022. p. 325–42.

[36] Strippel C, Herrera-Rivero M, Wendorff M, Tietz AK, Degenhardt F, Witten A, Schroeter C, Nelke C, Golombeck KS, Madlener M, Ruber T, Ernst L, Racz A, Baumgartner T, Widman G, Doppler K, Thaler F, Siebenbrodt K, Dik A, Kerin C, Rauber S, Gallus M, Kovac S, Grauer OM, Grimm A, Pruss H, Wickel J, Geis C, Lewerenz J, Goebels N, Ringelstein M, Menge T, Tackenberg B, Kellinghaus C, Bien CG, Kraft A, Zettl U, Ismail FS, Ayzenberg I, Urbanek C, Suhs KW, Tauber SC, Mues S, Kortvelyessy P, Markewitz R, Paliantonis A, Elger CE, Surges R, Sommer C, Kumpfel T, Gross CC, Lerche H, Wellmer J, Quesada CM, Then Bergh F, Wandinger KP, Becker AJ, Kunz WS, Meyer Zu Horste G, Malter MP, Rosenow F, Wiendl H, Kuhlenbaumer G, Leypoldt F, Lieb W, Franke A, Meuth SG, Stoll M, Melzer N. German network for research on autoimmune, E. A genome-wide association study in autoimmune neurological syndromes with anti-GAD65 autoantibodies. Brain 2023;146:977–90.

[37] Rauber S, Schroeter CB, Strippel C, Nelke C, Ruland T, Dik A, Golombeck KS, Regner-Nelke L, Paunovic M, Esser D, Munch C, Rosenow F, van Duijn M, Henes A, Ruck T, Amit I, Leypoldt F, Titulaer MJ, Wiendl H, Meuth SG, Meyer Zu Horste G, Melzer N. Cerebrospinal fluid proteomics indicates immune dysregulation and neuronal dysfunction in antibody associated autoimmune encephalitis. J Autoimmun 2023;135:102985.