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Epileptologie

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Ligue Suisse contre l'Epilepsie
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Swiss League Against Epilepsy

Richtlinien für die Autoren

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Was ist an die Redaktion einzureichen?

Alle Manuskripte sind inklusive Abbildungen und Tabellen in elektronischer Form einzureichen (MS Word).

Dr. med. Dr. sc. nat. Frédéric Zubler

Liebe Leserinnen, lieber Leser

In den meisten Fällen ermöglichen anfallsunterdrückende Medikamente Patienten ein Leben ohne epileptische Anfälle. Dennoch leiden circa 30% der Epilepsiepatienten trotz leitliniengerechter Behandlung weiterhin an epileptischen Anfällen – ein Zustand, der als pharmakoresistente Epilepsie bezeichnet wird.

Der erste Artikel fasst die Definition und zugrundeliegende Pathomechanismen einer pharmakoresistenten Epilepsie zusammen. Zukünftig könnte die Vorhersage epileptischer Anfälle zu neuen spezifischeren Behandlungen führen, wie im zweiten Artikel thematisiert.

In den Fällen, bei denen der fokale Anfallsursprung identifiziert werden kann und nicht in einem eloquenten kortikalen Areal liegt, kann eine chirurgische Entfernung dieses Areals zu Anfallsfreiheit führen. Die prächirurgische Diagnostik ist ein hoch spezialisiertes Verfahren. Ergänzend zu visuellen EEG-Auswertungen werden vermehrt computerbasierte Analyseverfahren in die klinische Praxis integriert – dies wird in zwei weiteren Artikeln thematisiert.

Zudem werden Fälle vorgestellt, in denen die Ursachen einer Epilepsie behandelt werden müssen, um Anfallsfreiheit herzustellen. Dies thematisiert der Fallbericht einer Autoimmunencephalitis im letzten Beitrag.

Pharmakoresistente Epilepsie ist ein faszinierendes Gebiet, in dem sich neue diagnostische und therapeutische Ansätze entwickeln. Ich hoffe, die folgenden Artikel werden das Interesse der Leser wecken. Schliesslich möchte ich den Mitautoren und dem Redaktionsteam für die Mitarbeit an der aktuellen Ausgabe von Epileptologie danken.

Frédéric Zubler

Dr. med. Dr. sc. nat. Frédéric Zubler

Chers lectrices, chers lecteurs

Dans la majorité des cas, les médicaments suppresseurs de crise[1] permettent au patient épileptique de ne plus avoir de crise. Malheureusement, il arrive dans environ 30% des cas que le traitement médicamenteux seul ne suffise pas – on parle alors d'épilepsie pharmacorésistante. Le premier article de ce numéro nous rappelle les définitions et mécanismes potentiels de la pharmacorésistance. Dans le futur, prédire l'occurrence des crises pourrait permettre un traitement plus ciblé, comme nous l'explique le second article.

En cas d'épilepsie structurelle – si l'origine des crises peut être identifiée et si le foyer ne se trouve pas dans une partie inopérable du cerveau – une résection peut alors permettre de supprimer les crises chez des patients ne répondant pas au traitement médicamenteux. Le bilan préchirurgical est une procédure hautement spécialisée pour laquelle, en plus de l'analyse visuelle, de nombreux algorithmes commencent à être intégrés en clinique – c'est le thème exploré par deux autres articles. Finalement, il arrive que la cause de l'épilepsie doive également être traitée pour permettre l'arrêt des crises. Un cas typique d'encéphalite auto-immune nous illustre ce principe dans le dernier article.

L'épilepsie pharmacorésistante est un domaine fascinant, pour l'analyse et traitement duquel de nouvelles approches sont annoncées. J'espère que les articles présentés ici sauront aiguiser la curiosité des lecteurs. En guise de conclusion – tant pour cet éditorial que pour ma collaboration à ce journal –, j'aimerais remercier les auteurs et les éditeurs qui ont œuvré à ce numéro d'Epileptologie.

Frédéric Zubler

1. *Contrairement à l'anglais et l'allemand, cette terminologie ne s'est pas encore répandue en français, langue dans laquelle l'on parle de médicaments anti-épiléptiques – ce qui est en principe inexacte puisque les médicaments actuels ne guérissent pas l'épilepsie.*

Dr. med. Dr. sc. nat. Frédéric Zubler

Dear readers

In most cases, seizure suppressive drugs allow patients to live seizure-free. However, about 30% of patients continue to have seizures despite best medical treatment – a condition called pharmacoresistant epilepsy. The first article summarises the definition and potential mechanisms of pharmacoresistance. In the future, seizure prediction might allow for more specific treatments, as discussed in the second article.

In those cases where a focal seizure onset can be identified (and does not lie in an eloquent cortical area), a surgical removal of this area can lead to seizure freedom. The pre-surgical evaluation is a highly specialised procedure. In addition to visual analysis, many computational algorithms start to be integrated into clinical practice – this topic is presented in two other articles. Finally, there are cases in which the cause of the epilepsy must also be treated to allow for seizures to stop. This principle is illustrated with a case report of autoimmune encephalitis in the last contribution.

Pharmacoresistent epilepsy is a fascinating field, for the analysis and treatment of which new approaches are emerging. I hope that the articles presented here will catch the reader's interest. As a conclusion (to this editorial and to my contribution to this Journal) I would like to thank all the authors and the editorial team who worked on this issue of Epileptologie.

Frédéric Zubler

Drug Resistance in Epilepsy

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Abstract

Around 20-30% of patients with epilepsy will not fully respond to medication, with potential consequences on quality of life, morbidity and premature mortality. Early identification of drug resistance is key to offer the patient other treatments alternative, such as surgery, neuro-modulation or ketogenic diet when the disease remains disabling. Drug resistance is defined by the number of medications having failed to fully control seizures. The International League Against Epilepsy (ILAE) defines drug resistance by the failure of two adequately chosen and dosed antiepileptic drugs (AED). More generally, with an increasing number of medications tried, the less likely is the next medication to be efficacious. Several factors are associated with drug resistance: high seizure frequency before treatment and some structural brain lesions (hippocampal sclerosis, tumors, focal cortical dysplasia for instance). There is an ongoing debate if drug resistance is caused or not by a specific mechanism across different epilepsy types. Two main mechanisms are postulated; either failure of the medication to reach the seizure onset zone(s) (because of expulsion due to drug transporters) or modifications (genetic?) of the treatments' binding site. At this time, there is conflicting evidence about these hypotheses and most of these experiments need to be replicated. More generally, drug resistant epilepsy could also well relate to the severity of the underlying condition.

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Keywords: Antiepileptic drug, surgery, prognosis, determinant

Pharmaco-résistance en épilepsie

Environ 20-30% des patients souffrant d'épilepsie ne vont pas répondre complètement au traitement médicamenteux, ceci avec des conséquences potentielles sur leur qualité de vie, une morbidité accrue et une mortalité prématurée. L'identification précoce de la pharmaco-résistance est importante pour offrir un traitement alternatif efficace à ces patients tels que la chirurgie, la neuromodulation ou la diète cétogène, quand l'épilepsie reste invalidante. La résistance au traitement est définie de manière pratique par un nombre de traitements qui a échoué à contrôler complètement les crises. La ligue internationale contre l'épilepsie (ILAE) définit la résistance au traitement comme l'échec de deux traitements adéquatement choisis et dosés. Plus généralement, la chance qu'un nouveau traitement soit efficace diminue avec chaque traitement essayé sans succès auparavant. Plusieurs facteurs sont associés avec la résistance au traitement, notamment la fréquence des crises avant le traitement et certaines causes structurelles (sclérose hippocampique, tumeurs, et dysplasie corticale focale par exemples). Il y a un débat pour savoir si la résistance au traitement est lié à un mécanisme spécifique que soit le type d'épilepsie. Deux mécanismes principaux sont postulés ; un défaut d'accès du médicament à la (les) régions(s) épileptogénique(s) (en raison de son expulsion par des transporteurs) ou une modification (génétique ?) des cibles des traitements. A ce stade, il y a des preuves contradictoires à propos de ces hypothèses et la plupart de ces experimentations nécessite encore d'être répliquées. Plus généralement, la résistance pourrait aussi être le fait d'une sévérité plus importante de la cause sous-jacente.

Mots-clés : médicament antiépileptique, chirurgie, prognostic, facteurs déterminants

Pharmakoresistenz in der Epilepsie

Ca. 20-30% der Patienten mit Epilepsie sprechen nicht gut auf anfallsunterdrückende Medikation an, mit möglichen Auswirkungen auf Lebensqualität, Morbidität und Lebenserwartung. Ein frühzeitiges Erkennen der Pharmakoresistenz ist wichtig, um den Patienten alternative Therapieoptionen wie Epilepsiechirurgie, Neurostimulation oder ketogene Diät anzubieten. Pharmakoresistenz wird definiert durch die Anzahl eingesetzter Medikamente mit Persistenz der Anfälle. Die Internationale Liga gegen Epilepsie (ILAE) definiert Pharmakoresistenz als fehlende Anfallsfreiheit trotz Einsatz von zwei adäquat ausgewählten und dosierten anfallsunterdrückenden Medikamenten (AED). Prinzipiell gilt, je mehr Medikamente bereits ohne Therapieerfolg eingesetzt wurden, desto kleiner ist die Wahrscheinlichkeit einer Wirkung eines weiteren Medikamentes. Es gibt mehrere Faktoren, die mit einer Pharmakoresistenz verbunden sind: insbesondere hohe Anfallsfrequenz vor Therapiebeginn und strukturelle Hirnläsionen (z.B. Hippocampussklerose, Tumoren, fokale kortikale Dysplasie). Es bleibt umstritten, ob Pharmakoresistenz durch spezifische Mechanismen bei verschiedenen Epilepsietypen entsteht oder nicht. Zwei Hauptmechanismen wurden postuliert: Einerseits fehlende Verfügbarkeit des Medikaments in der Anfallsursprungszone (in Folge einer Elimination durch Medikamententransporter) oder durch Modifikationen (genetisch bedingt?) der Wirkstoffbindungsstelle der Substanz. Zurzeit gibt es widersprüchliche Evidenz zu diesen Hypothesen – und die meisten Versuche müssen wiederholt werden. Generell könnte die Pharmakoresistenz vom Schweregrad der zugrunde liegenden Erkrankung abhängig sein.

Schlüsselwörter: Antiepileptika, Chirurgie, Prognose, Einflussfaktor

Introduction

Epilepsy is a common neurological disease, with a lifelong prevalence 1 in 26 in the general population [1]. Between 20-30% of patients with epilepsy develop drug-resistant epilepsy [2, 3]. This figure largely reflects the hospital setting of these studies. Considering epilepsy in the general population, drug resistance could be as low as 15% [4]. Drug resistance is a major determinant of epilepsy outcome, as it is associated with a higher risk of premature death, injuries, psychosocial difficulties and poor quality of life [2].

Based on epidemiological studies [5], the International League Against Epilepsy (ILAE) has defined drug resistant epilepsy as failure of adequate trials of two tolerated and appropriately chosen antiepileptic drugs (AED) (whether as monotherapies or in combination) to achieve sustained seizure freedom [6]. This definition can be applied for a period of time and it can vary in time; a patient can be drug resistant and drug responsive at different times in the course of the disease [6]. The ILAE guidelines recommend to use “the rule of three” to define seizure control: seizure freedom is considered after three times the longest pre-intervention inter-seizure interval in the previous year or twelve months for unique seizure [7]. This “the rule of three” has been validated statistically using aleatory (stochastic) models of events. This showed that after a period of seizure freedom lasting longer than 3 times the inter-seizure interval, the likelihood of recurrence is as low as 5% [7].

The diagnosis of drug-resistant epilepsy is usually straight forward, but a few pitfalls of pseudo-resistance should be avoided. For instance, the misdiagnosis of epilepsy is a common cause of pseudo-resistance because up to 25% of patients diagnosed of drug-resistant epilepsy suffer from psychogenic non epileptic seizures [8]. In case of disabling seemingly drug resistant epilepsy, an attempt to record seizures (ideally with video EEG) should be undertaken. Another rare reason is inadequate AED choice for the type of epilepsy syndrome, as well as a suboptimal dosage of AED prescribed, leading to insufficient control of seizures [2]. Other more common possible causes include patients’ lifestyle with poor treatment compliance and alcohol or drug abuse. Measuring AED plasma level after a recurrence is helpful to assess compliance. A 50% drop (or more) of plasma concentration (compared to a previous trough level) is considered as a sign of irregular medication intake [9].

Early identification of patients with drug-resistant epilepsy is important in order to offer alternative therapies, such as surgical treatments, neuromodulation therapy or ketogenic diet [2, 10]. There are evidences that earlier surgery is more likely to be successful [11, 12], although more difficult cases may also be referred later to presurgical work-up. A recent small prospective trial has indeed clearly shown the benefit of early surgery over medical management in drug resistant epilepsy [13]. This is furthermore supported by a recent European study comparing two periods of time (1997-1998 and 2012-2013), that showed that the results of epilepsy surgery tend to improve especially in MRI negative or complex cases [14].

Determinant factors of drug resistance

In two most notable studies of patients with epilepsy prospectively followed during 7 years [5] and 19 years [3], respectively, around 60% of patients were seizure free with the first or second tried AED. Several factors were associated with a poor prognosis in term of seizure control: large number of seizures before treatment (the main factor being high seizure frequency rather than the overall number) and a structural brain lesion. The nature of the lesion is also determinant in that respect [15]. Progressive lesions like tumors, hippocampal sclerosis (with continuous abnormal neuro-

genesis) and cortical development malformation (with early degenerative changes) are associated with a lower proportion of treatment responders [16]. Also, having dual pathologies (typically hippocampal sclerosis and focal cortical dysplasia) is often associated with a poor control of seizures [16].

On the other hand, a positive response to the first tried AED is understandingly a powerful prognostic factor of remission, as it has been shown in children with temporal lobe epilepsy [17]. Besides this, probability of controlling seizures decreases with each additional AED tried unsuccessfully [4, 5]. After 6 AED tried, chances to become seizure-free on medication are remote (down to a few percent) [4]. Patients with genetic generalized epilepsy usually have more chances to enter remission with AED than patients with focal structural epilepsy [5, 16, 17]. Patients diagnosed of epilepsy in adolescent or older ages seem also more likely to achieve remission with AED [2, 16, 17].

Possible mechanisms of drug-resistant epilepsy

There are different hypotheses about the cause of drug resistance in epilepsy that reflect our current lack of knowledge about the neurobiology of epilepsy. One underlying question is similar to the epilepsy mechanism in general: Is there a common additional mechanism of drug resistance that is not directly related to the pathogenesis of the epilepsy itself?

The other possibility is that there is no specific mechanism of resistance, but that pathogenesis of each epilepsy constellation can be particularly severe and lead to drug resistance; for instance, alterations in neuronal circuitry and neurotransmitter receptors seen in hippocampal sclerosis and cortical dysplasia, mutations in ion channels in some rare genetic epilepsy syndroms, or auto-immune mechanisms as in Rasmussen's encephalitis.

This debate, despite being seemingly remote from clinical practice, has potentially concrete implications. If there is indeed a specific mechanism of drug resistance, this would mean this mechanism may be amenable to a treatment.

Conversely, if drug resistance is the end result of multiple mechanisms, it is unlikely to be addressable as a whole. A fact arguing against a common mechanism is the role played by the underlying lesion in determining drug resistance. There have been, however, suggestions that a common mechanism might have a role irrespectively of the underlying cause of epilepsy [18].

Most research of a common mechanism of drug resistance has explored two aspects: Either the AED fail to reach the target because of drug transporters expelling it from the central nervous system, or the AED's cellular targets are altered, reducing the sensitivity to treatment [18, 19].

1. Drug-transporter hypothesis

AEDs need to cross the blood-brain barrier (BBB) to achieve their action in the brain parenchyma. P-glycoproteins (P-gp) are multidrug transporters located in the BBB that regulate the flow of different drugs in the brain. A gene family called MDR, with two subtypes of genes (MDR1 and MDR2) located on chromosome 7q21, expresses P-gp. Among these subtypes of genes, MDR1, also called ABCB1, expresses a multidrug-resistant transporter expressed in the brain [20].

This transporter has been well described in cancer drug resistance without establishing its exact mechanism [21], as well as in patients with HIV; its 3435 TT genotype is associated with lower nelfinavir and efivarenz plasma concentrations [22]. This drug transporter seems to regulate intraparenchymal AED concentrations in vivo in animal models [23], showing increased parenchymal carbamazepine (CBZ), phenytoin, lamotrigine concentrations once the drug transporter was inhibited [24]. P-gp expression was also shown to be increased in human epileptogenic tissues removed surgically and in post-mortem examination [25]. Increased activity of the P-gp drug transporter was also shown in vivo in patients with epilepsy using PET imaging of a transporter substrate, compared with free-seizure patients and healthy subjects [26].

There are also suggestions that P-gp genetic changes (CC-genotype compared to TT-genotype at ABCB1 C3435T polymorphism) would predispose for drug-resistant epilepsy [27]. These findings were however inconsistently replicated [28]. A more basic uncertainty about the relevance of the drug transporter hypothesis is whether AEDs are actually substrates of these transporters; experiments regarding CBZ and levetiracetam are controversial [19, 21, 29].

2. Change in AED target hypothesis

Genetic or functional modifications in the molecular drug targets can conceivably lead to a resistance to their ligands [30]. Most work in this perspective was done on sodium channels. Voltage-gated Na+ channels are formed by α and β subunits; AEDs modulating these channels mainly bind to α subunits [31]. SCN1A, SCN2A and SCN3A genes located on chromosome 2 encode several isoforms of α subunits of sodium channels. A relationship between the R19K polymorphism in SCN2A and resistance to sodium channels blocking AEDs was suggested [32].

Other changes were suggested to correlate with drug response [33]. SCN2A polymorphism IVS7-32A>G (rs2304016) was associated with resistance to sodium channels blocking AEDs, probably through splicing or gene expression as it is located in an intronic region. On the other hand, the SCN2A haplotype GCTGCGTATAAGA has been associated with a good response. On the

functional side of things, one study has shown that the carbamazepine mechanism of action – a use-dependent block of voltage-gated sodium channels – is lost in patients with a CBZ-resistant temporal lobe epilepsy in comparison with responder patients [30]. These findings were however not replicated.

To sum up, the mechanisms of drug resistance are to this day only hypotheses – most of them are still waiting to be replicated. Early identification of patients with drug resistant epilepsy remains key to improve the care of these patients.

References

1. *Hesdorffer DC et al. Estimating risk for developing epilepsy: a population-based study in Rochester, Minnesota. Neurology 2011; 76(1): 23-7*
2. *Kwan P, Schachter SC and Brodie MJ. Drug-resistant epilepsy. N Engl J Med 2011; 365(10): 919-26*
3. *Mohanraj R and Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. Eur J Neurol 2006; 13(3): 277-82*
4. *Picot MC et al. The prevalence of epilepsy and pharmacoresistant epilepsy in adults: a population-based study in a Western European country. Epilepsia 2008; 49(7): 1230-8*
5. *Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000; 342: 315-319*
6. *Kwan P et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010; 51(6): 1069-77*
7. *Westover MB et al. Revising the "Rule of Three" for inferring seizure freedom. Epilepsia 2012.; 53(2): 368-76*
8. *Smith D, Defalla BA and Chadwick DW. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. QJM 1999; 92(1): 15-23*
9. *Specht U et al. Postictal serum levels of antiepileptic drugs for detection of noncompliance. Epilepsy Behav 2003; 4(5): 487-95*
10. *Schmidt D, Löscher W. New developments in antiepileptic drug resistance: an integrative view. Epilepsy Curr 2009; 9: 46-52*
11. *Simasathien T et al. Improved outcomes with earlier surgery for intractable frontal lobe epilepsy. Ann Neurol 2013; 73(5): 646-654*
12. *Edelvik A et al. Long-term outcomes of epilepsy surgery in Sweden. A national prospective and longitudinal study. Neurology 2013; 81(14): 1244-1251*
13. *Engel J et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: A randomized trial. JAMA 2012; 307(9): 922-930*
14. *Baud MO et al. European trends in epilepsy surgery. Neurology 2018; 91(2): e96-e106*
15. *Asadi-Pooya AA et al. Prevalence and Incidence of Drug-Resistant Mesial Temporal Lobe Epilepsy in the United States. World Neurosurg 2017; 99: 662-666*
16. *Semah F et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998; 51: 1256-1262*
17. *Dlugos DJ, Sammel MD, Strom BL, Farrar JT. Response to first drug trial predicts outcome in childhood temporal lobe epilepsy. Neurology 2001; 57: 2259-2264*
18. *Remy S and Beck H. Molecular and cellular mechanisms of pharmacoresistance in epilepsy. Brain 2006; 129(Pt 1): 18-35*
19. *Schmidt D, Löscher W. Drug resistance in epilepsy: putative neurobiologic and clinical mechanism. Epilepsia 2005; 46(6): 858-877*
20. *Kwan P, Brodie MJ. Potential Role of Drug Transporters in the Pathogenesis of Medically Intractable Epilepsy. Epilepsia 2005; 46(2): 224-235*
21. *Baltes S et al. Differences in the transport of the antiepileptic drugs phenytoin, levetiracetam and carbamazepine by human and mouse P-glycoprotein. Neuropharmacology 2007; 52(2): 333-46*
22. *Fellay J et al. Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. Lancet 2002; 359(9300): 30-6*
23. *Löscher W and Potschka H. Drug resistance in brain diseases and the role of drug efflux transporters. Nat Rev Neurosci 2005; 6(8): 591-602*
24. *Liu JY et al. Neuropathology of the blood-brain barrier and pharmacoresistance in human epilepsy. Brain 2012; 135(Pt 10): 3115-33*
25. *Sisodiya SM et al. Drug resistance in epilepsy: expression of drug resistance proteins in common causes of refractory epilepsy. Brain 2002; 125: 22-31*
26. *Fieldmann M et al. P-glycoprotein expression and function in patients with temporal lobe epilepsy: a case-control study. Lancet Neurol 2013; 12: 777-85*
27. *Siddiqui A et al. Association of multidrug resistance in epilepsy with a polymorphism in the Drug-Transporter gene ABCB1. New Engl J Med 2003; 348: 1442-8*
28. *Tan NCK et al. Failure to comfirm association of polymorphism in ABCB1 with multidrug resistant epilepsy. Neurology 2004; 63: 1090-1092*
29. *Sisodiya SM, Goldstein DB. Drug resistance in epilepsy: More twists in the tale. Epilepsia 2007; 48(12): 2369-2370*
30. *Remy S et al. A novel mechanism underlying drug resistance in chronic epilepsy. Ann Neurol 2003; 53: 469-479*
31. *Ferraro TN and Buono RJ. The relationship between the pharmacology of antiepileptic drugs and human gene variation: an overview. Epilepsy Behav 2005; 7(1): 18-36*
32. *Leschziner GD et al. ABCB1 genotype and PGP expression, function and therapeutic drug response: a critical review and recommendations for future research. Pharmacogenomics J 2007; 7(3): 154-79*
33. *Kwan P et al. Multidrug resistance in epilepsy and polymorphisms in the voltage-gated sodium channel genes SCN1A, SCN2A, and SCN3A: correlation among phenotype, genotype, and mRNA expression. Pharmacogenet Genomics 2008; 18(11): 989-98*

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Forecasting Seizures: Not Unthinkable Anymore

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"Prediction is very difficult, especially about the future."

Niels Bohr, Nobel Prize in Physics in 1922

Summary

Epilepsy is a cyclical brain disorder par excellence: Single or clusters of spontaneous seizures recur with relatively fixed symptom-free intervals. This temporal structure of epilepsy is a fascinating phenomenon that likely has an endogenous basis. Over the past decades, seizure prediction has been a niche endeavor for a few epileptologists and scientists acquainted with non-linear systems and equipped with the necessary statistical background. Today with the rapid development of wearables and implantable devices, the idea is gaining terrain in the clinical epileptology community. Aided by synergetic developments in machine learning and the accumulation of massive amounts of epilepsy data, the field can transform this once vague idea into a practical tool for the broader drug-resistant epilepsy population. We make the prediction that forecasting seizures is soon-to-be a reality.

Epileptologie 2018; 35: 156 – 161

Keywords: Seizure prediction, chronobiology, circadian rhythm, multidien rhythms

La prédiction des crises d'épilepsie n'est plus impensable

L'épilepsie est une maladie cyclique par excellence : des crises spontanées isolées ou en grappe surviennent à intervalles relativement fixe. Cette structure temporelle de l'épilepsie est un phénomène fascinant qui a probablement une base endogène. Au cours des décennies passées, les tentatives de prédiction de crises ont été le terrain de jeux de quelques épileptologues et scientifiques connaissant bien les systèmes non-linéaires et les outils statistiques. Aujourd'hui, avec le développement rapide des appareils « wearable » et implantables, l'idée gagne du terrain au sein de la communauté épileptologique. Avec l'aide de développements en « machine-learning » et l'accumulation de quantités de données sur l'épilepsie, notre branche peut transformer cette idée autrefois vague en un outil pratique pour le bénéfice des patients. Nous prédisons que la prédiction des crises est une réalité à venir.

Mots-clés : prédiction des crises, chronobiologie, rythme circadien, rythmes multidien

Anfallsvorhersage: Nicht mehr undenkbar

Epilepsie kann als typisches Beispiel einer „zyklischen Hirnerkrankung" betrachtet werden: Einzelne Anfälle oder Gruppen von Anfällen wechseln sich mit erstaunlich konstanten anfallsfreien Zeitperioden ab. Dieses faszinierende Phänomen hat mit hoher Wahrscheinlichkeit endogene Ursachen. Während der letzten Jahrzehnte hat die Anfallsvorhersage ein Nischendasein gefristet, hauptsächlich betrieben von einer Gruppe von Epileptologen und Naturwissenschaftlern, die über das notwendige anspruchsvolle Wissen über nichtlineare Systeme und statistische Methoden verfügten. Mit der heutigen raschen Entwicklung von

trag- oder sogar implantierbaren Geräten stösst die Idee der Anfallsvorhersage nun aber auf zunehmend breiteres Interesse und Akzeptanz in der klinischen Epileptologie. Unterstützt durch die synergetische Entwicklung des maschinellen Lernens und die Entstehung umfassender Datenmengen, generiert durch zunehmend mobilere Epilepsiediagnosegeräte, besteht erstmals die Möglichkeit, die einst noch unscharfe Vision einer Anfallsvorhersage in die Praxis umzusetzen, zum Nutzen aller Patienten mit pharmakoresistenter Epilepsie. Wir sagen voraus, dass die Vorhersage von Anfällen schon bald Realität sein wird.

Schlüsselwörter: Anfallsvorhersage, Chronobiologie, circadianer Rhythmus, Multidien-Rhythmen

Introduction

Epilepsy is characterized by the seemingly random occurrence of spontaneous seizures. Yet, any neurologist has been confronted with individual patients' seizure diary revealing striking regularity (**Figure 1**). Over the course of history, this regularity in seizures has been attributed to devil intervention, phases of the moon – epilepsy patients were once called "lunatics" in reference to their behaviors influenced by the moon – or other obscure forces. Centuries of observation have only formally identified a handful of triggers (**Table 1**) for epileptic seizures, and none that is considered causal of the disorder. An underexplored endogenous modulation may be underlying rhythmicity in epilepsy.

Historical aspects

In the 19th century, Gowers already recognized groups of epilepsy patients having exclusively nocturnal (22%) or diurnal (45%) episodes or a mix of both (33%) [1]. At the beginning of the 20th century, colonies for epilepsy patients were organized, motivated by the rationale that work in the fields was beneficial for their health. One such example is the Lingfield colony, in the London countryside, where more than 100 boys and men were living in community. Through constant surveillance, and meticulous charting of the time and date of seizure occurrence, a number of facts regarding rhythmicity in epilepsy were established. In the 1920s, Langdon-Down and Brain [2] showed the circadian modulation beyond vigilance stages of 2'524 major seizures (mostly convulsive). A decade later, this was confirmed by Griffith and Fox [3] in extended analyses based on no less than 39'929 seizure occurrences. They showed that seizures tended to recur at the same time of the day across patients, with preferential times being 6 a.m., noon and midnight. They also showed that seizures are interspersed with relatively constant seizure-free intervals in given patients. The duration of this interval varied from patient to patient, for example weekly, bi-weekly, monthly or longer, including rare examples of seasonal epilepsy. Their landmark paper points to a patient-specific endogenous multidien (multi-day) rhythmicity in epileptic activity that is key to determining seizure timing.

As epilepsy patients regained their status of community dwellers, access to that information was partially lost, due to the pervasive inaccuracy of self-reported events. Nevertheless, Bercel [4] published in the 1960s a series of 1105 male and females cases of which 10% displayed regular cycles of 2 weeks, 4 weeks, or several months. He also made the comment that "The

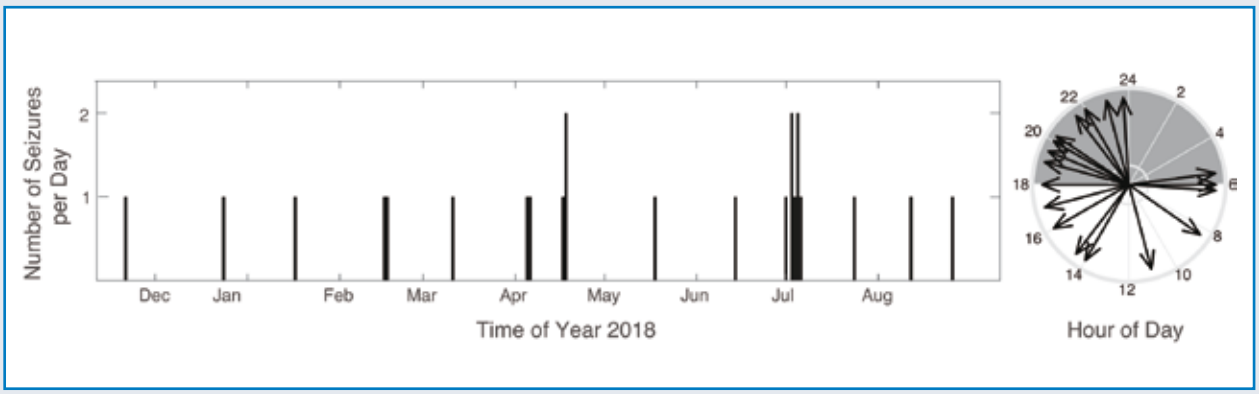

Figure 1: Example of a seizure diary kept during about a year by a patient followed at the University Hospital of Bern (Inselspital, courtesy of PD Dr. med. Heidemarie Gast). Left: note the striking regularity with which single seizures or clusters occur. Yet, the average periodicity of 23 days is slightly variable. In July, seven seizures occurred over the course of 5 days, representing a prolonged cluster.
Right: Each arrow represents one seizure and is pointing to its time of occurrence on the 24-hour clock. Note a tendency for seizure to occur in the afternoon and evening, with a second smaller cluster around six o'clock. Without access to continuous recordings of interictal epileptiform activity, rhythmicity is apparent, but only partially characterized.

Table 1: Factors influencing the timing of seizures

Triggers	Cyclical modulation
Medication non-compliance	Circadian cycle (time of day)
Alcohol or drugs	Sleep-wake cycle (brain states)
Stress	Multidien cycles (multiple days)
Sleep deprivation	Hormonal cycles (for example: menstrual)
Fatigue	Unknown modulating factors
Flashing lights (rarely)	
Reflex seizures (rarely)	

time structure of epileptic rhythms has not yet been studied by means of computer technics, which leaves a good many male epileptics with 28-day periodicity still staring at the moon for an answer". Although the study of seizure timing by means of computer technics has advanced our statistical understanding of the phenomenon, the biological explanation for these rhythms is still lacking entirely and an influence of lunar cycles has not formally been excluded. One fact is established: Rhythmicity in epilepsy is to be found in women, men and children alike.

Temporal structure in epilepsy

Historical knowledge on temporal patterns of seizure recurrence has been rediscovered over the past few years through the lens of technology. Data from chronic EEG (i.e. many months) in ambulatory patients represent an invaluable source of information to broaden our knowledge on the topic. Electrographic documentation is one objective measurement of seizure timing that can fully supplant patient-based seizure calendars, notorious for being unreliable and inaccurate in many cases [5].

To this day, two datasets of chronic EEG recordings have been investigated: the *NeuroVista* and the *NeuroPace* data. The *NeuroVista* data comes from a trial of an implanted seizure warning system in 15 patients over three years (see below) and represents to date the only continuous raw EEG data recorded over many months. The *NeuroPace* data comes from a responsive neurostimulation device implanted, to this date, in more than 1500 patients for therapeutic purposes in the US. As opposed to the *NeuroVista* data, the *NeuroPace* data does not provide access to continuous raw EEG but instead counts of detected epileptiform events. Despite this limitation, data accumulated for up to 10 years provides an important source of information.

In a recent study [6], epileptic activity was shown to be regulated at multiple temporal scales. First, the sleep-wake and circadian cycles were shown to influence the rate of interictal epileptiform discharges. Second, the study unraveled that ictal and interictal activity was modulated in multidien cycles with periodicity of several days specific to each patient. This observation positions the interictal epileptiform activity as an excellent biomarker to monitor epileptic brain activity over time. Indeed, interictal epileptiform activity can be used to "partition" time into periods of low and high risk for epileptic seizures [7].

The pro- and pre-ictal states

The feasibility of seizure forecasting crucially relies on the existence of two pathophysiological phenomena that are known to clinicians: a pro-ictal state on the scale of days and a pre-ictal state on the scale of minutes to hours. The pro-ictal state relates closely to the circadian and multidien rhythms described in the previous paragraph. Due to pro-ictal states lasting a few days, seizures tend to occur in clusters during these recurring periods of high seizure risk (**Figure 2**). Clinical evidence for a pre-ictal state is to be found in some patients (~6%) who feel "something building up" as non-specific premonitory symptoms (that are different from an aura), minutes to hours before the occurrence of a

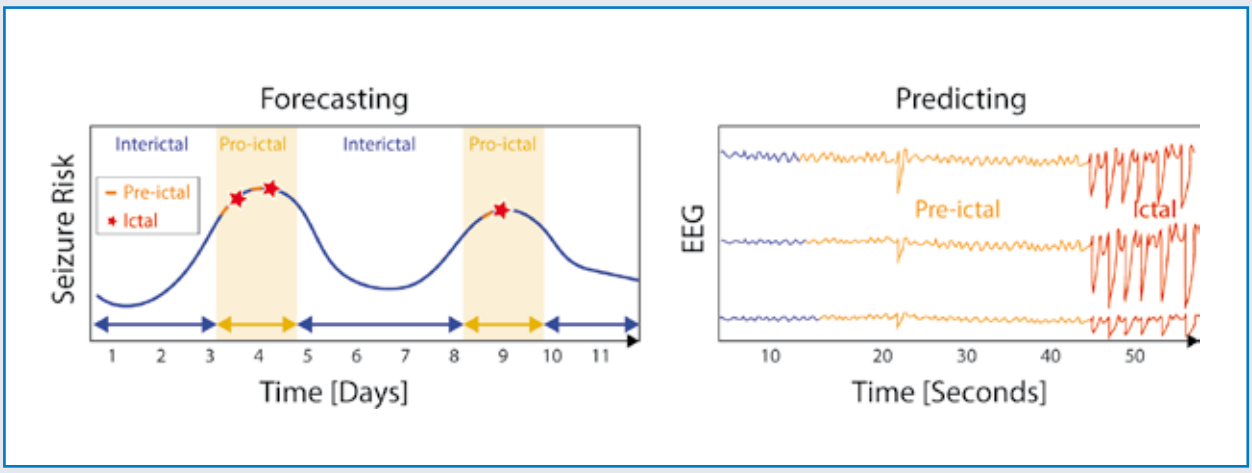

Figure 2: Depiction of the different states of the epileptic brain over time.
Left: Seizures happen for the most part during pro-ictal states and can be forecasted by extrapolating the expected next cycle.
Right: Seizure prediction seconds or minutes before seizure onset, based on the detection of a pre-ictal state in the EEG. Future algorithms for the anticipation of seizures will combine information at both temporal scales for improved performance.

seizure, including restlessness, malaise and headaches [8]. There is also mounting electrophysiological and neuroimaging [9] evidence that changes in the brain are detectable, minutes before the onset of seizures.

While a consensus definition is lacking, the field usually refers to seizure prediction in the sense of warnings of impending seizures based on the detection of a pre-ictal state. Based on recent understanding of the temporal structure of epilepsy, we propose that seizure-risk forecasting can be defined as establishing the probabilistic forecast of seizures over the course of a few days, akin to weather forecasting. These two concepts are not antagonist but complementary and reflect the multiple timescales (days vs. minutes) at which epilepsy operates. In a Bayesian approach, knowing the seizure risk on a given day or hour will help refine the performance of seizure prediction algorithms [10]. An alert (pro-ictal) could be given a few days in advance and confirmed (or not) by a warning of imminent seizure (pre-ictal) a few minutes in advance.

Past trials of seizure prediction

With the development of chaos theory and non-linear system theory in the 1980s, physicists became interested in applying their tools to EEG time series, aiming at understanding the dynamics of the brain switching from one state (normal) to another (seizure). Using intracranial EEG from inpatient epilepsy work-ups, early papers described peri-ictal changes of chaoticity measures, and proposed that the methods from non-linear dynamics could help anticipate seizures [11]. However, the initial enthusiasm was slowed down by several studies reporting negative results or questioning the validity of the methods applied (for an overview see [12]). During the first few international workshops on seizure prediction (Bonn, 2002, Freiburg 2007), none of the participants was able to predict seizures above chance on a dataset available during the meeting.

One consequence of the raising skepticism was that researchers took “one step back” and started to re-investigate and better define the events to be predicted, i.e. the seizures [13]. A better understanding of epileptic seizures can help identify states promoting or impairing their occurrence and ultimately improve prediction. Over the past two decades, the understanding of seizure dynamics, i.e. how seizures begin, how they propagate and how they terminate [14,15], has improved with the use of advanced analytical methods [16 - 20]. Yet, no single biomarker of the preictal state has been identified to date.

As a consequence, in the 2010s the field has turned to multi-variate measures and machine-learning as the default approach to personalizing predictive algorithms on a patient-specific basis. A number of standards were established for the statistical testing of algorithm performance [12]. These developments have been led by contributive efforts of the machine-learning community through competitions open to the public (www.kaggle.com). Rigorous methodology was imposed including training algorithms on a subset of data and testing them on a separate subset of data from the same patients that was not available to the participants [21, 22]. Overall, the results were above chance and very encouraging when based on long-term recordings. The initial issue of low specificity of prediction was overcome. This is key as false warnings can lead to increased stress for patients. Yet, this approach does not help us understand the pathophysiology of epilepsy, as the algorithms typically rely on a number of EEG input features that are difficult to synthesize into one coherent explanation.

First prospective trial of seizure prediction

After a few prospective trials based on inpatient EEG recordings, researchers soon realized that changes in medication and sleep deprivation could confuse the picture. There are clear benefits in attempting seizure prediction in ambulatory patients, on stable medication, in their natural environment. The *NeuroVista* trial is to date the only prospective trial of ambulatory seizure prediction. It took place in Melbourne between 2010 and 2012, enrolling 15 participants. This study relied on chronic intracranial EEG using 16 electrodes, directly in contact with one brain hemisphere. A subclavicular implant was communicating to an external hand-held unit. The system enabled data processing in real time and issued warnings in the form of colored lights: blinking red for impending seizure, white for indeterminate and blue for safe. Across patients, results were mixed, but for a subset of patients (N=9) above-chance warnings could be issued. Interestingly, the blue light (safe) was as valuable as the red light and contributed to decrease stress. Once the study concluded, the *NeuroVista* system was never commercialized due to a lack of investment.

From this trial a number of points were clear: Prediction algorithms need to be patient-specific and require a great amount of data to be trained. Success of prediction also seemed to heavily depend on finding the right algorithm. Even in patients with seizures that were difficult to predict during the trial, offline analysis and algorithm development after the closure of the trial enabled great improvement in predictions, once the correct method was found. This indicates that aside from hardware development (i.e. a recording device), optimization of software is also needed. This pioneering study established that seizure prediction was feasible prospectively, and useful for these patients. This represents a revolution for our field.

Upcoming trials

Enriched by evidence accumulated with chronic EEG, new clinical trials are in preparation. The American Epilepsy Foundation attributed a 3 million dollar grant to a team of scientists to develop a system for seizure forecasting (www.epilepsy.com). Other trials in Europe (Radar-CNS, www.radar-cns.org) have also invested in wearables to better understand epilepsy at a large scale. Yet the most reliable biomarker to date remains brain activity; and in addition to intracranial systems, sub-scalp minimally invasive EEG could be used for similar purposes.

Future of chrono-epileptology

In the coming years, miniaturization of electronics, development of connected devices (« Internet of Things ») and rapid development of know-how in neuro-engineering will continue. Technology will play a major role in neurology in general and in epileptology in particular. EEG is the only established portable technique for investigating the brain in its natural environment. It is far superior to MRI in its applicability to continuous chronic recordings.

It is thus natural to think that the advent of chronic EEG will improve the care for chronic neurological disorders. Today, it is conceivable that patients with epilepsy will track their disease activity and titrate their anti-epileptic drugs, just like patients with diabetes track their glucose and adjust their insulin. Seizure forecasting is not unthinkable anymore [23, 24].

References

1. *Gowers WR. Epilepsy and other chronic convulsive diseases: their causes, symptoms & treatment. London: Churchill, 1881*
2. *Langdon-Down M, Russell Brain W. Time of day in relation to convulsions in epilepsy. Lancet 1929; 213: 1029–32*
3. *Griffiths GM, Fox JT. Rhythm in epilepsy. Lancet 1938; 232: 409–16*
4. *Bercel N. The periodic features of some seizure states. Ann N Y Acad Sci 1964; 1–8.*
5. *Elger CE, Hoppe C. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. Lancet Neurol 2018; 17: 279–88*
6. *Baud MO, Kleen JK, Mirro EA et al. Multi-day rhythms modulate seizure risk in epilepsy. Nat Commun 2018; 9: 88*
7. *Baud MO, Rao VR. Gauging Seizure Risk. Neurology. 2018; 1–24*
8. *Schulze-Bonhage A, Kurth C, Carius A et al. Seizure anticipation by patients with focal and generalized epilepsy: A multicentre assessment of premonitory symptoms. Epilepsy Res 2006; 70: 83–8*
9. *Federico P, Abbott DF, Briellmann RS et al. Functional MRI of the pre-ictal state. Brain 2005; 128: 1811–7*
10. *Karoly PJ, Ung H, Grayden DB et al. The circadian profile of epilepsy improves seizure forecasting. Brain 2017; 140: 2169–82*
11. *Iasemidis LD, Sackellares JC, Zaveri HP, et al. Phase space topography and the Lyapunov exponent of electrocorticograms in partial seizures. Brain Topogr 1990; 2: 187–201*
12. *Mormann F, Andrzejak RG, Elger CE et al. Seizure prediction: the long and winding road. Brain 2007; 130: 314–33*
13. *Gotman J. A few thoughts on "What is a seizure?" Epilepsy Behav 2011; 22: S2–S3*
14. *Jiruska P, de Curtis M, Jefferys JGR et al. Synchronization and desynchronization in epilepsy: controversies and hypotheses. J Physiol 2013; 591: 787–97*
15. *Jirsa VK, Stacey WC, Quilichini PP et al. On the nature of seizure dynamics. Brain 2014; 137: 2210–30*
16. *Schindler K, Gast H, Goodfellow M et al. On seeing the trees and the forest: Single-signal and multisignal analysis of periictal intracranial EEG. Epilepsia 2012; 53: 1658–68*

17. *Schindler KA, Bialonski S, Horstmann M-T et al. Evolving functional network properties and synchronizability during human epileptic seizures. Chaos 2008; 18: 033119–6*
18. *Kramer MA, Eden UT, Kolaczyk ED, et al. Coalescence and Fragmentation of Cortical Networks during Focal Seizures. J Neurosci 2010; 30: 10076–85*
19. *Ponten SC, Bartolomei F, Stam CJ. Small-world networks and epilepsy: Graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. Clin Neurophysiol 2007; 118: 918–27*
20. *Horstmann M-T, Bialonski S, Noennig N et al. State dependent properties of epileptic brain networks: Comparative graph–theoretical analyses of simultaneously recorded EEG and MEG. Clin Neurophysiol 2010; 121: 172–85*
21. *Brinkmann BH, Wagenaar J, Abbot D et al. Crowdsourcing reproducible seizure forecasting in human and canine epilepsy. Brain 2016; 139: 1713–22*
22 *Kuhlmann L, Karoly P, Freestone DR et al. Epilepsyecosystem.org: crowdsourcing reproducible seizure prediction with long-term human intracranial EEG. Brain 2018; 112: 172–12*
23. *Kuhlmann L, Lehnertz K, Richardson MP et al. Seizure prediction — ready for a new era. Nat Rev Neurol 2018; 1–13*
24. *Stacey WC. Seizure Prediction Is Possible – Now Let's Make It Practical. EBioMedicine 2018; 1–2*

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Virtual Resection for Predicting the Outcome of Epilepsy Surgery

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Summary

The identification of effective targets for resection is a crucial requirement for the surgical treatment of epilepsy. Quantitative methods have the potential to provide beneficial information in this regard and might in the future reduce the necessary time and effort for physicians.

The approach described here uses a distributional clustering framework for the modeling of multivariate time series to predict the efficacy of arbitrary resections. This novel approach allows simulating the resection of any combination of channels and assigns them a collective value indicating the likelihood of the model's ictal state. When simulated, the majority of resections that rendered patients seizure free in reality (Engel class I) considerably decrease the probability of the ictal state compared to the situation of no resection. The same is not the case for most actually performed but ineffective resections (Engel class IV) and most random simulated resections.

The presented method enables physicians to test planned resections in silico for their efficacy before surgery. Further validation could help to establish this method in the clinical routine and thereby not only disburden physicians from a cumbersome and error prone task but also introduce objectivity into it and eventually increase the success rate in epilepsy surgery.

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Keywords: Epilepsy, quantitative EEG, resective surgery, predictive modeling

Computerbasierte Vorhersage der Wirkung von Epilepsiechirurgie

Bei der chirurgischen Behandlung von Epilepsie ist es entscheidend, Gewebe zu identifizieren, dessen Resektion einen positiven Effekt für den Patienten hat. Quantitative Methoden können diesbezüglich hilfreiche Informationen bereitstellen und somit den Arbeits- und Zeitaufwand für Ärzte verringern. Bis heute werden quantitative Methoden im routinemässigen Arbeitsablauf jedoch kaum verwendet und die zu resezierenden Hirnareale werden nach wie vor fast ausschliesslich von Experten durch visuelle Analyse bestimmt.

Die hier beschriebene Methode modelliert die zeitliche Entwicklung von intrakraniellen EEG-Ableitungen, um die Wirksamkeit hypothetischer Resektionen vorherzusagen. Das Modell berechnet dazu die Wahrscheinlichkeit iktaler Zustände für die simulierte Resektion beliebiger Kombinationen von EEG-Kanälen. Verglichen mit dem Ausgangszustand führt die Simulation von tatsächlich durchgeführten Resektionen, unter welchen die Patienten anfallsfrei wurden (Engel-Klasse I) im Modell mehrheitlich zu einer erheblich tieferen Wahrscheinlichkeit iktaler Zustände. Bei den meisten Resektionen, die keinen vorteilhaften Effekt für den Patienten hatten (Engel-Klasse IV) und den meisten zufälligen simulierten Resektionen ist keine vergleichbare Wahrscheinlichkeitsabnahme zu beobachten.

Dieser neuartige Ansatz ermöglicht es Ärzten, geplante Resektionen zuerst am Computer auf ihre vermutliche Wirksamkeit zu prüfen. Eine umfangreichere Validierung könnte diese Methode im klinischen Alltag etablieren und dadurch Ärzte von mühsamen und fehleranfälligen Arbeiten entlasten, ein erhöhtes Mass an Objektivität in den prächirurgischen Arbeitsprozess

bringen und voraussichtlich die Erfolgsrate in der Epilepsiechirurgie erhöhen.

Schlüsselwörter: Epilepsie, quantitative EEG-Analyse, Epilepsiechirurgie, prädiktive Simulation

Résection virtuelle pour simuler la chirurgie de l'épilepsie

Dans la chirurgie de l'épilepsie, il est crucial d'identifier avec précision la zone à réséquer. Les méthodes quantitatives peuvent y contribuer, et vont potentiellement faciliter les investigations pré-chirurgicales. A ce jour les approches quantitatives n'ont cependant pas encore été intégrées dans la décision clinique, et l'identification des cibles de la chirurgie est faite par examen visuel. L'approche que nous décrivons ici utilise des méthodes de partitionnement de données («clustering» en anglais) appliquées aux séries temporelles pour prédire l'effet de différentes résections. Cette nouvelle approche nous permet de simuler la résection d'un groupe de canaux, et d'attribuer à la configuration restante une probabilité d'entrer ou non dans un état ictal. Lorsque nous simulons la résection effectuée chez les patients sans crises après l'intervention (Engel 1), notre model prédit une probabilité plus faible pour la résurgence d'un état ictal. Par contre, si nous simulons la résection effectuée chez des patients avec persistance de crises après l'opération, ou des résections au hasard, on note que cette probabilité n'est pas diminuée.

La méthode que nous présentons permet donc aux cliniciens de tester des résections in silico avant de les réaliser. La validation clinique de notre méthode pourrait aider le clinicien, en introduisant une méthode objective dans la bilan pré-chirurgical de l'épilepsie.

Mots-clés : épilepsie, EEG quantitatif, chirurgie résective, prédiction

Introduction

Epileptic seizures heavily decrease patients' quality of life. To render patients seizure free is thus the main goal of epilepsy treatment. Using pharmaceuticals, this is not achieved in around one third of all epilepsy patients [1-4]. For those suffering from pharmacoresistant focal onset epilepsies, surgical treatment can be considered. Surgical treatment aims to remove the tissue that is necessary and sufficient for the generation of epileptic seizures, termed the epileptogenic zone (EZ) [5, 6]. Since this zone is a theoretical concept, there is no technique to directly identify it by any current imaging or electrophysiological technique and clinicians are forced to use approximations.

One proxy that is often used in practice is the seizure onset zone (SOZ) which is defined by the channels of an EEG recording first showing continuous epileptiform activity. The SOZ is thought to overlap with the EZ but its exact boundaries and the actual extent of overlap with the EZ remain unknown [5]. Nowadays, the determination of the SOZ is still mainly done visually by human experts, as no automated method has found its way into clinical routine. However, the visual analysis has several disadvantages: It requires time and lacks objectivity. Also the success rate of the current practice leaves room for improvement – long-term seizure freedom is achieved in up to 2/3 of patients [7-10].

Computational analysis of intracranial EEG (iEEG) data could help to improve on all these issues and thus has evoked large interest and extensive research. A variety of techniques based on different mathematical and physical concepts has been applied to iEEG to identify tissue for surgical resection. Signals can be analyzed individually (univariate) or by their interrelations with other signals (bivariate and multivariate), whereas the latter can be further divided into symmetric relations (undirected) and causal relations (directed). Furthermore, such techniques can be linear or non-linear and they can be applied in signal space or in frequency space. For a comprehensive survey the interested reader may refer, for example, to [11].

Functional network analysis has been used to identify critical channels as potential targets for surgical removal. Typically, each channel constitutes a node and connections between nodes are determined by some pairwise dependency measure. Using graph theory nodes can be characterized and selected by their position or influence in the network regarding connectivity, centrality or similar. Several studies have shown relations between such salient nodes and the resected brain tissue and its related post-surgical outcome [12-16]. A limitation of these approaches is their descriptive nature, i.e. they cannot make predictions about the system under modifications; also, the pairwise construction of node relations does not capture statistical dependencies of higher order.

Few studies presented computational models to simulate and assess resective surgery targets in silico. Hutchings et al. combined a nonlinear computational model with subject-specific diffusion tensor imaging data [17]. Sinha et al. set up patient-specific dynamical network models using network connectivity derived from interictal ECoG data [18, 19]. Goodfellow et al. used the first half of seizures from iEEG data to derive patient-specific functional networks of neural mass models which then allow to test alternative resection strategies [20]. Using various periictal segments of the same patients' data, Lopes et al. set up a mathematical model to examine the contribution of brain regions

to seizure generation and thereby make recommendations for resection [21]. All these models have shown to capture crucial features of the data and to provide additional clinically relevant information.

Here we present some illustrative examples of a further method recently developed at the Inselspital [22] that sets up a probabilistic model that, after a learning procedure, can be used to simulate the effects of the removal of tissue beneath the electrodes of the EEG. In particular, it allows making predictions about seizure likelihood after selective elimination of input signals (EEG channels). The method has been shown to predict a clear decrease in seizure likelihood when resections are simulated that rendered the corresponding patients seizure free in reality. Vice versa, resections which did not have any beneficial effect for the patients in reality do generally not decrease the predicted seizure likelihood when simulated [22].

A soft clustering method

In the following, a brief description is provided how a model is derived from an iEEG recording (left half of **Fig. 1**) and how this model is used to make predictions about the efficacy of resections (right half of **Fig. 1**). For a detailed mathematical description and an in-depth understanding of the process please refer to the method's original publication [22].

At the beginning a model is generated using the data of all channels of a periictal segment, containing the complete seizure and the immediately preceding 180 second (s) preictal period. This allows the model to learn both, ictal and non-ictal activity. Afterwards the model is used with the data of all channels, but only from the preictal segment. This constitutes the situation when no resection is simulated. Then, the data of an arbitrary set of channels is removed for the entire recording which simulates the resection of this set. The difference between this situation and the situation where no resection was simulated yields the model's prediction about the efficacy of the specific resection. The actual set of channels recording from tissue that

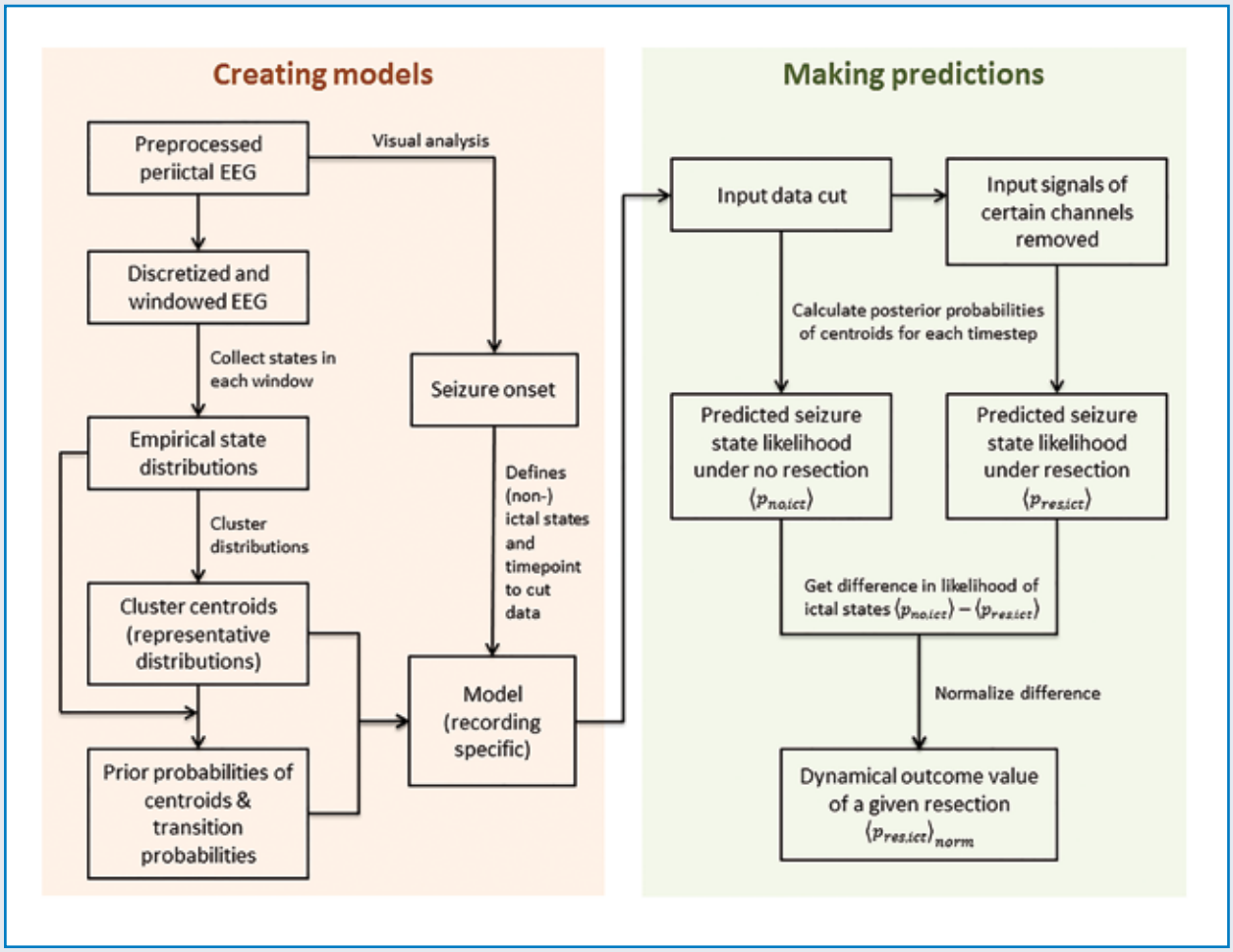

Figure 1: The course of actions to generate a model from an intracranial EEG recording (left half) and to make a prediction for an arbitrary resection using the model (right half). Further explanations can be found in the text.

was later resected is subsequently referred to as the *actual resection* (determined using coregistered pre- and post-operative MR images and post-implantation CT images [15]).

Initially the periictal iEEG data of a recording (panel 1 in **figures 2-4**) is preprocessed (filtered and normalized channel-wise), discretized to 7 values and time windowed (window length = 1.25s). The discretized values of all channels inside a window constitute a distribution and all these empirical distributions are clustered to get 6 representative distributions (the cluster centroids, in the following called the model's states). It can now be determined for each time step which state best represents the data in that window (panel 2 in **figures 2-4**). This is the model's description of the full data. Using this description one can define the probabilities of all states when no further information is provided (prior probabilities) and the transition probabilities between states. The time point of seizure onset (visually identified by an experienced epileptologist) separates the recording into a preictal phase and an ictal phase. If a state is occurring mainly during the preictal phase it is considered a non-ictal state, by contrast states mainly occurring in the ictal phase are considered ictal states.

The seizure onset also determines the time point after which no iEEG data is provided to the model when making predictions (following referred to as cutting the data). In these simulations, the probability distribution of the states before seizure onset and the transition probabilities induce the states' temporal dynamics in the ictal phase. When the data is cut (panel 3 in **figures 2-4**) one calculates the probabilities of each state at each time step (posterior probabilities). The summed probability of all ictal states in the ictal phase determines the predicted likelihood of a seizure occurring.

Repeating this process, but with the input data of some channels removed over the whole recording (panel 4 and 5 in **figures 2-4**), simulates the resection. The resulting likelihood of a seizure occurring in contrast to the situation where no resection is simulated determines the predicted efficacy of this resection to hinder the development of seizures. We call this predicted efficacy dynamical outcome which is 1 for complete seizure abatement, between 0 and 1 for lower predicted benefit or below 0 if the resection is even expected to worsen the situation.

Example cases

We now show three examples of the procedure described above. In all cases the periictal iEEG time series is shown in the first panel with the clinically determined seizure onset at 180s. The second panel shows the corresponding temporal evolution of the state probabilities when the full iEEG data is fed to the model. This determines the ictal states (the states predominantly active after 180s) and the time point to cut the input data for the subsequent simulations. If the input data is cut, the state probabilities develop according to the model afterwards which is shown in the third panel. The fourth and the fifth panel show situations when additionally the input data of certain channels is removed completely, for the actual resection (panel 4) and an equally sized random set of channels (panel 5).

The first case is of a patient with Engel class I (i.e. the patient was seizure free after resection). After the seizure onset, different states become probable that have not been probable before. In both cases where the full data is provided (panel 2 of **Fig. 2**) and with the data cut after seizure onset (panel 3 of **Fig. 2**), the transitions to state 4 and then to states 2 and 5 remain similar. According to the second panel, the states 1-2 and 4-5 are classified as the ictal states. When simulating the patient's actual resection, the probabilities of the ictal states largely vanish and the non-ictal state 6 becomes highly probable. This indicates that the removal of these channels is expected to prevent the development of seizures (panel 4 of **Fig. 2**).

Since this patient became seizure free after surgery, this is what one would expect from the corresponding simulation. A majority of tested random resections containing the same number of channels as the actual resection have no such effect. This indicates they would not help to reduce seizure occurrence as one would expect from arbitrary resections (one example shown in panel 5 of **Fig. 2**). Accordingly, this patient counts as a true positive case in the summary statistics (see below).

The second case is from an Engel class IV patient (i.e. no improvement at all after surgery). The succession of states in the ictal part of the recording does not change when no input data is provided in this part (panel 2 and 3 of **Fig. 3**). In patients without any reduction of seizure occurrence in reality, one would obviously want the model to predict the same. However, in this case the simulation of the actual resection extensively lowers the probability of the ictal states (2-6) (panel 4 of **Fig. 3**). This can typically not be observed for random resections (panel 5 of **Fig. 3**). The patient thus counts as a false positive.

The third case is again from a class IV patient. The initial order of states becoming active in the ictal part (panel 2 of **Fig. 4**) is not observable after the data is cut at seizure onset (panel 3 of **Fig. 4**). This time the simulation of the actual resection correctly predicts it to have no beneficial effect for the patient (no decrease of the probabilities of the ictal states 2-5) (panel 4 of **Fig. 4**). The same is the case for most random resections and some, as the one displayed in panel 5, are also predicted to be more beneficial for the patient than the actual resection (lower probability of the ictal states). This patient counts as a true negative.

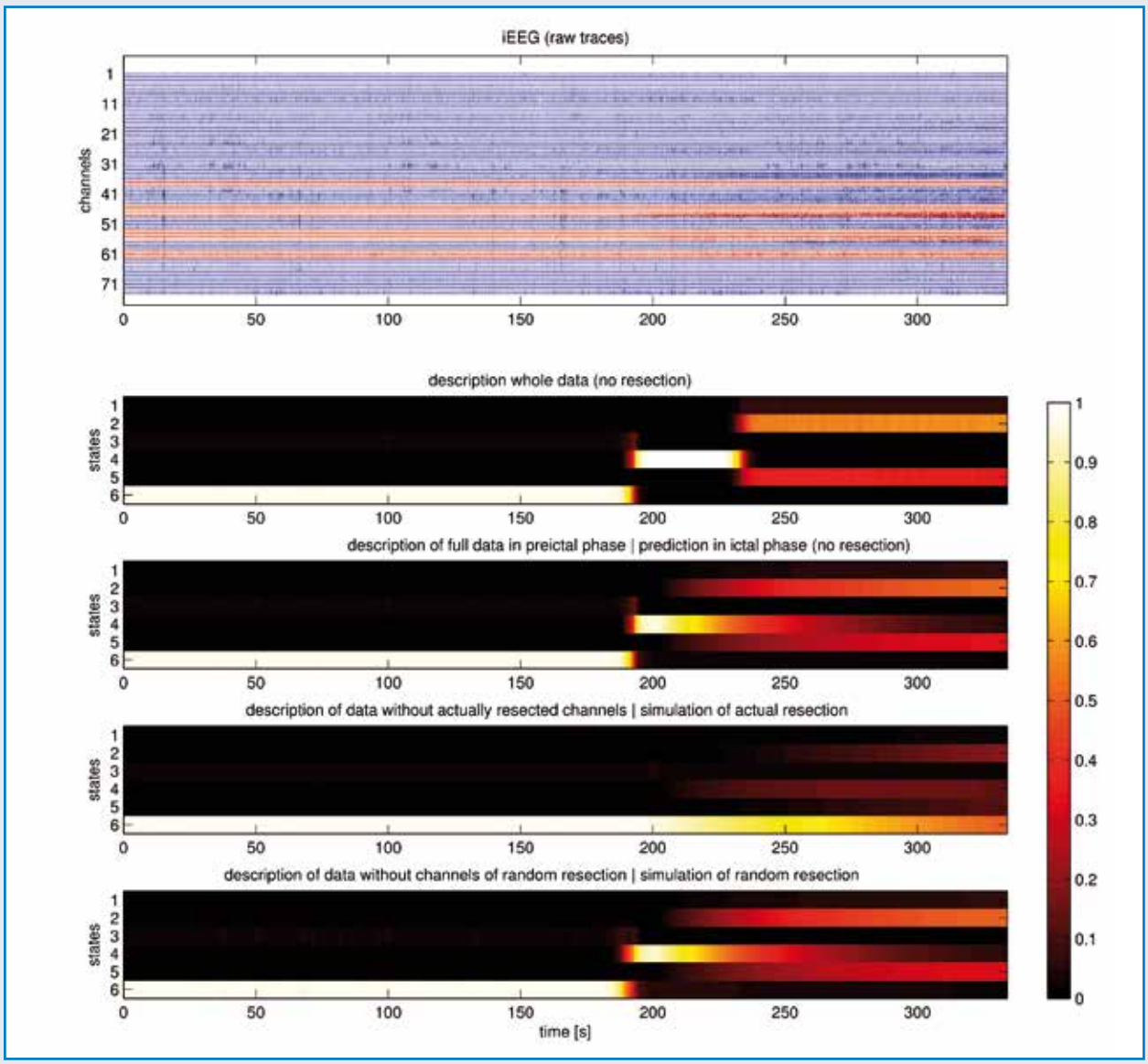

Figure 2: Panel 1 shows the segment of the intracranial EEG recording of a class I patient (4) that was used to create the model which then correctly predicts the efficacy of the actual resection (dynamical outcome = 0.955). The clinically determined seizure onset is at 180s and channels recording from brain tissue that was subsequently resected are in red. Panels 2-5 show for different situations the probabilities (color coded) of the model's states (y-axis) over time (x-axis). Panel 2: full iEEG data is provided to the model for the preictal and the ictal phase. Based on this analysis states 1-2 and 4-5 are defined as ictal states because they are mainly probable during the seizure. Panel 3: iEEG data of all channels until the seizure onset is provided whereas the dynamics in the ictal phase are determined by the model only. Still, they strongly resemble the dynamics in panel 2. Panel 4: iEEG data of all but the actually resected channels until the seizure onset is provided. The model predicts a high probability of a non-ictal state (state 6) throughout. Panel 5: iEEG data of all but a random selection of channels until the seizure onset is provided. The model predicts an ictal dynamic.

Summary statistics

In former publications this method was applied to groups of pharmacoresistant epilepsy patients that had resective surgery with known outcome and a follow-up of at least one year [22, 23]. We here show the summary results for 20 patients (see [23] for details on the patients). Only patients free from seizures and auras after surgery (Engel class I) and patients for whom the surgery had no beneficial effect (Engel class IV) were included.

We generated a model for the first artifact-free recording of each patient and assessed the effectiveness of different simulated resections to prevent a developing seizure. For each model we simulated the resection of the channels that recorded from tissue that got afterwards resected during surgery (the actual resection). In addition, we tested for each patient's model a set of

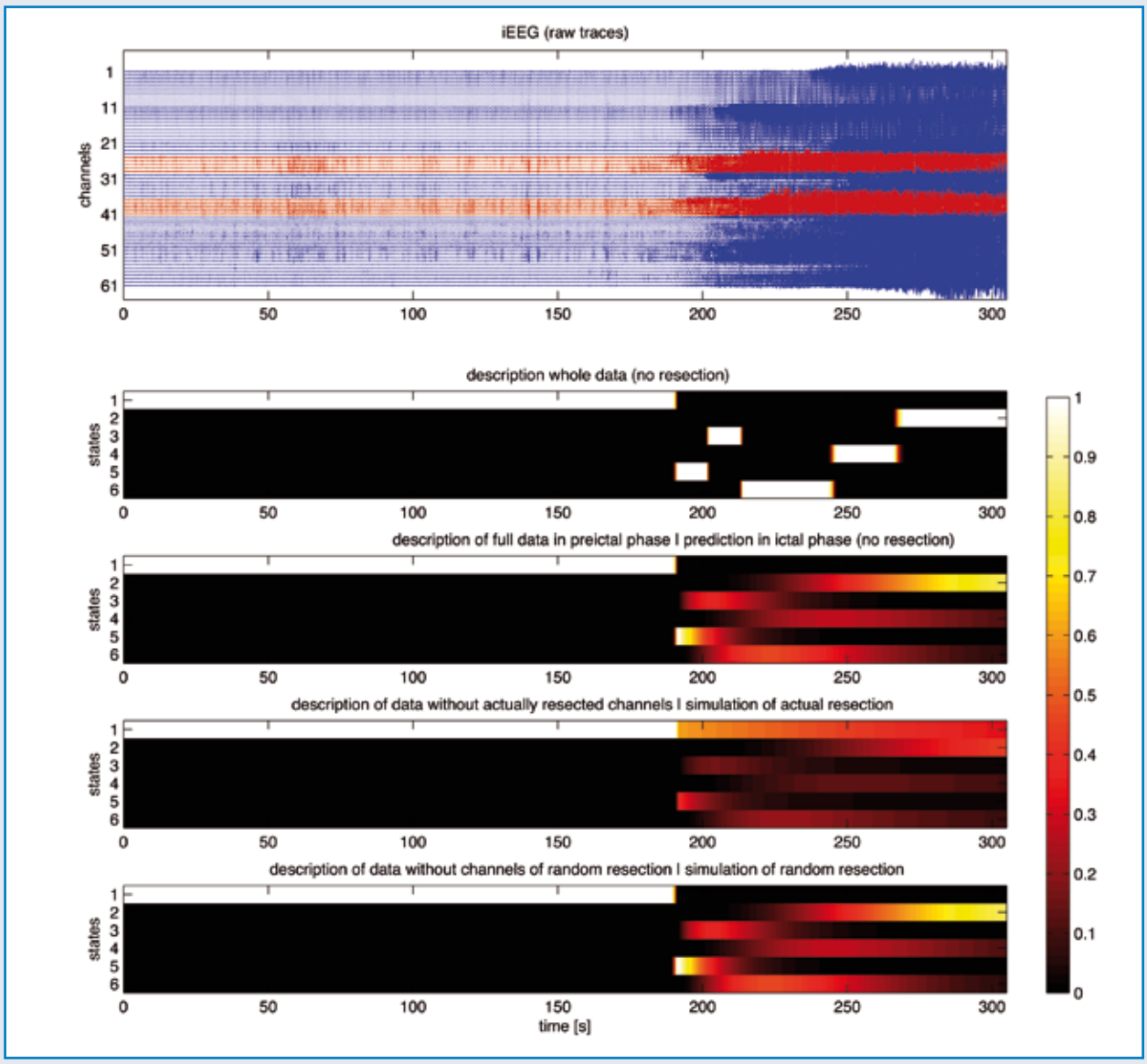

Figure 3: The same displays and depictions as in Fig. 2 for a class IV patient (15) where the model falsely predicts considerable benefit for the patient from the actual resection (dynamical outcome = 0.896). The ictal states are in this case states 2-6.

3000 random resections. The number of channels in these random resections was constrained to the number of actually resected channels of the respective patient, and the channels of the actual resection were excluded from becoming part of the random resections.

This procedure was performed for all models and the results are collected in Figure 5. The sorted dynamical outcomes of all simulated resections are shown as the cumulative distribution by the black line. From all random resections (~60'000) a large portion has a very low dynamical outcome indicating their inefficiency.

Discussion

We applied a dynamic soft clustering approach for multivariate time series to intracranial EEG data of epilepsy patients to predict the effectiveness of (virtual) resections to prohibit seizures. The probability of automatically determined ictal model states was used as an outcome performance measure, called the dynamical outcome.

When simulating the resections actually performed in the patients, we found a considerable decrease in dynamical outcome in most Engel class I patients correctly predicting the benefit of the actual resection. Given the vast numbers of possible models and channel resection protocols, it is extremely unlikely to get these results by chance. In the Engel class IV patients, we found in most cases no considerable decrease of dynamical outcome

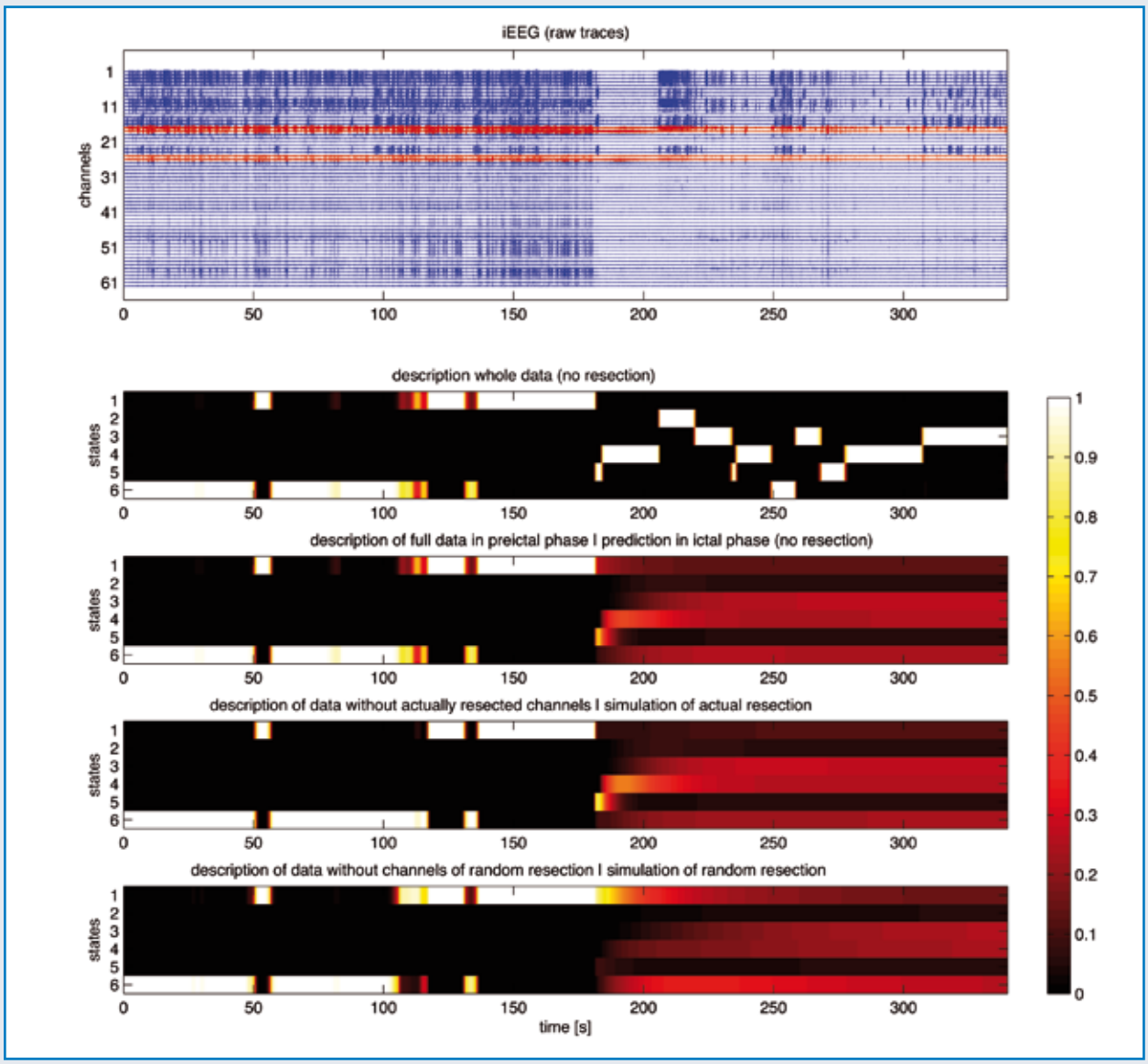

Figure 4: The same displays and depictions as in Fig. 2 for a class IV patient (17) where the model correctly predicts no improvement by the actual resection (dynamical outcome = 0.0). The ictal states are in this case states 2-5.

when simulating the actual resections. In this case the interpretation of the results is ambiguous as the negative prediction may also be caused by the model's failure to capture crucial features of the time series. When simulating arbitrary resections, in all cases the majority of resections are predicted to have no considerable beneficial effect. This verifies that the method is specific and does not predict high benefit for a disproportional number of resections.

These results suggest that the presented approach is capable of extracting key features of epileptic iEEG time series and, based on that, predicting the seizure-preventing efficacy of different resection protocols. Visual analysis typically focuses on searching suspicious patterns as spike-waves or low-amplitude, fast oscillations. This univariate view may be too simplistic for some forms of epileptic activity. Multivariate measures including complex interactions of multiple subparts of the epileptic brain could provide new and helpful information. It will be the object of future work to identify these crucial features.

So far, most of these approaches share the limitation that they can currently only make assessments of previously selected resections and are not able to provide the resection(s) predicted to be most beneficial. To find the best resection in the huge number of possible resections is a combinatorial optimization problem. In the case of nonlinear methods, there is (currently) no algorithm to solve this problem exactly in feasible time. Approximate algorithms like e.g. metaheuristic procedures would be a possibility to extend such approaches to include that capability in the future.

To bring these technologies closer to clinical understanding and finally acceptance, one needs to inves-

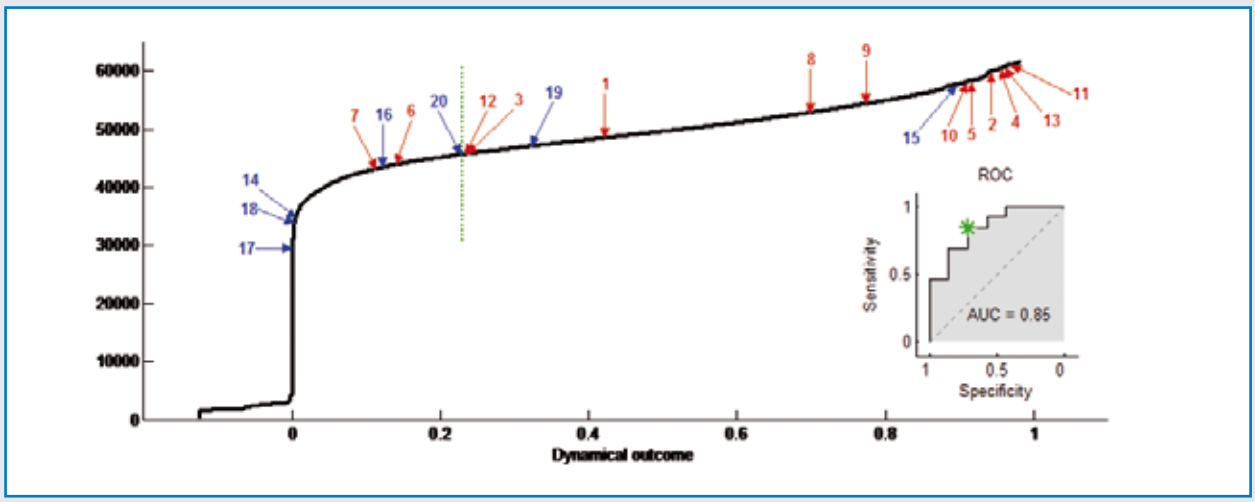

Figure 5: Conjoint dynamical outcomes of 20 patients. All simulated resections of all patients are depicted as cumulative distribution by the black line. The actual resections are denoted by the colored arrows and patient identifiers, red for Engel class I patients (1-13) and blue for Engel class IV patients (14-20). The ROC-curve displays the method's performance as binary classifier with the green asterisk as the point with minimal distance to perfect performance. The green dotted line is the corresponding optimal threshold.

tigate the meaning of the cluster centers displayed in Figures 2-4. Are these clusters indicating the appearance of certain wave-forms or wave-form distributions among iEEG channels?

Numerous approaches including the one presented here can be used to assess the efficacy of distinct and clinically preselected channel resections. In their visual analyses epileptologists focus on suspicious patterns such as spike-waves or low amplitude, fast oscillations, thus univariate signal characteristics. Suboptimal outcomes suggest that at least some cases require more elaborated considerations like multivariate techniques incorporating complex interactions of different subparts. This assumption is supported by the growing perception of epilepsy as a network phenomenon [13, 15, 16, 24-30]. Computational models such as the clustering procedure presented in this study could provide assistance to grasp such complex interactions and thus have the potential to improve the surgical treatment of epilepsy.

References

1. *Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000; 342(5): 314-319*
2. *Jacobs J, Zijlmans M, Zelmann R et al. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. Ann Neurol 2010; 67(2): 209-220*
3. *Schuele SU, Lüders HO. Intractable epilepsy: management and therapeutic alternatives. Lancet Neurol 2008; 7(6): 514-524*
4. *Wiebe S, Jette N. Pharmacoresistance and the role of surgery in difficult to treat epilepsy. Nat Rev Neurol 2012; 8(12): 669-677*
5. *Rosenow F, Lüders H. Presurgical evaluation of epilepsy. Brain 2001; 24(9): 1683-1700*
6. *Lüders HO, Najm I, Nair D et al. The epileptogenic zone: general principles. Epileptic Disord 2006; 8(Suppl 2): S1-9*
7. *Wiebe S, Blume WT, Girvin JP et al. randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001; 345(5): 311-318*
8. *Téllez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 2005; 128(5): 1188-1198*
9. *de Tisi J, Bell GS, Peacock JL et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet 2011; 378(9800): 1388-1395*
10. *Engel JJ, McDermott MP, Wiebe S et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. Jama 2012; 307(9): 922-930*
11. *Rummel C, Andrzejak RG, Schindler K. Quantitative analysis of peri-ictal multi-channel EEG. Epileptologie 2012; 29: 99-113*
12. *Jung YJ, Kang HC, Choi KO et al. Localization of ictal onset zones in Lennox-Gastaut syndrome using directional connectivity analysis of intracranial electroencephalography. Seizure 2011; 20(6): 449-457*
13. *Wilke C, Worrell G, He B. Graph analysis of epileptogenic networks in human partial epilepsy. Epilepsia 2011; 52(1): 84-93*
14. *van Mierlo P, Carrette E, Hallez H et al. Ictal-onset localization through connectivity analysis of intracranial EEG signals in patients with refractory epilepsy. Epilepsia 2013; 54(8): 1409-1418*
15. *Rummel C, Abela E, Andrzejak RG et al. Resected brain tissue, seizure onset zone and quantitative EEG measures: Towards prediction of post-surgical seizure control. PLoS One 2015; 10(10): 0141023*
16. *Zubler F, Gast H, Abela E et al. Detecting functional hubs of ictogenic networks. Brain Topogr 2015; 28(2): 305-317*
17. *Hutchings F, Han CE, Keller SS et al. Predicting surgery targets in temporal lobe epilepsy through structural connectome based simulations. PLoS Comput Biol 2015; 11(12): e1004642*
18. *Sinha N, Dauwels J, Wang Y et al. An in silico approach for pre-surgical evaluation of an epileptic cortex. Conf Proc IEEE Eng Med Biol Soc 2014; 4884-4887*

19. Sinha N, Dauwels J, Kaiser M et al. Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling. Brain 2016; 140(2): 319-332
20. Goodfellow M, Rummel C, Abela E et al. Estimation of brain network ictogenicity predicts outcome from epilepsy surgery. Sci Rep 2016; 6: 29215
21. Lopes MA, Richardson MP, Abela E et al. An optimal strategy for epilepsy surgery: Disruption of the rich-club? PLoS Comput Biol 2017; 13(8): e1005637
22. Steimer A, Müller M, Schindler K. Predictive modeling of EEG time series for evaluating surgery targets in epilepsy patients. Hum Brain Mapp 2017; 38(5): 2509-2531
23. Müller M, Schindler K, Goodfellow M et al. Evaluating resective surgery targets in epilepsy patients: A comparison of quantitative EEG methods. J Neurosci Methods 2018; 305: 54-66
24. Ponten SC, Bartolomei F, Stam CJ. Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. Clin Neurophysiol 2007; 118(4): 918-927
25. Schindler K, Bialonski S, Horstmann MT et al. Evolving functional network properties and synchronizability during human epileptic seizures. Chaos 2008; 18(3): 033119
26. Kramer MA, Kolaczyk ED, Kirsch HE. Emergent network topology at seizure onset in humans. Epilepsy Res 2008; 79(2-3): 173: 186
27. Richardson MP. Large scale brain models of epilepsy: dynamics meets connectomics. J Neurol Neurosurg Psychiatry 2012; 83(12): 1238-1248
28. Engel JJ, Thompson PM, Stern JM et al. Connectomics and epilepsy. Curr Opin Neurol 2013; 26(2): 186-194
29. van Diessen E, Diederen SJH, Braun KPJ et al. Functional and structural brain networks in epilepsy: what have we learned? Epilepsia 2013; 54(11): 1855-1865
30. Bialonski S, Lehnertz K. Assortative mixing in functional brain networks during epileptic seizures. Chaos 2013; 23(3): 033139

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Combining Visual and Computational Approaches in Pre-surgical Evaluation for Pharmaco-resistant Epilepsy: a Case-based Presentation

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Summary

About thirty percent of patients with focal epilepsy continue to have seizures despite best possible treatment with seizure suppressive drugs. For these patients, epilepsy surgery is currently the best chance to attain seizure freedom. Pre-surgical evaluation is a highly specialized task, and aims at a) delineating the brain area responsible for seizure generation and to b) assess whether this brain area may be surgically removed without neurological sequelae. Pre-surgical evaluation requires an integrated analysis of clinical, electrophysiological and neuroradiological findings. Here we present the case of a patient with MR-negative focal epilepsy who underwent pre-surgical evaluation at the Berne University Hospital. We describe sequentially the different steps of the evaluation and novel quantitative EEG and MRI analysis methods that may contribute to clinical decision making.

Epileptologie 2018; 35: 171 – 180

Keywords: EEG, Stereo EEG, MRI, temporal lobe epilepsy, epilepsy surgery, quantitative analysis

Visuelle und quantitative Analyse in der prächirurgischen Abklärung der Epilepsie: eine Fallvorstellung

Etwa dreissig Prozent der Patienten mit fokalen Epilepsien haben trotz bestmöglicher Behandlung mit anfallsunterdrückenden Medikamenten weiterhin Anfälle. Für diese Patienten bietet Epilepsiechirurgie die derzeit beste Chance, Anfallsfreiheit zu erreichen. Die prächirurgische Abklärung ist ein hochspezialisiertes Verfahren und zielt darauf ab, a) das für die Anfallsentstehung verantwortliche Hirnareal abzugrenzen und b) abzuschätzen, ob dieses Hirnareal ohne neurologische Folgeschäden chirurgisch entfernt werden kann. Die prächirurgische Abklärung benötigt eine integrierte Analyse klinischer, elektrophysiologischer und neuroradiologischer Befunde. Wir stellen hier den Fall eines Patienten mit MR-negativer fokaler Epilepsie vor, der sich der prächirurgischen Abklärung am Berner Universitätsspital unterzogen hat. Wir beschreiben der Reihe nach die verschiedenen Abklärungsschritte sowie neue quantitative Methoden zur Auswertung von EEG und MRT, die zur klinischen Entscheidungsfindung beitragen können.

Schlüsselwörter: EEG, Stereo-EEG, MRT, Temporallappenepilepsie, Epilepsiechirurgie, quantitative Analyse

Convergence des méthodes d'analyse visuelle et computationelle dans l'évaluation préchirurgicale de l'épilepsie: présentation d'un cas

Trente pour-cent des patients avec une épilepsie focale continuent d'avoir des crises épileptiques malgré le meilleur traitement médicamenteux possible. Pour ces patients, la meilleure chance de ne plus avoir de crises est la chirurgie de l'épilepsie. L'évaluation pré-chirurgicale de l'épilepsie est une procédure hautement spécialisée, dont le but est a) d'identifier la région du cerveau responsable de la génération des crises, et b) d'évaluer si cette région peut être réséquée chirurgicalement sans déficit neurologique. L'évaluation pré-chirurgicale requiert l'analyse combinée des données cliniques, electrophysiologiques et neuroradiologiques. Nous présentons le cas d'un patient qui a participé à une évaluation pré-chirurgicale à l'Hôpital Universitaire de Berne (Inselspital). Nous décrivons les différentes étapes de cette évaluation, en présentant aussi de nouvelles méthodes d'analyse quantitative de l'EEG et de l'IRM.

Mots-clés : EEG, Stereo-EEG, IRM, épilepsie du lobe temporal, chirurgie de l'épilepsie, analyse quantitative

Introduction

Epilepsy can be devastating. In particular the seemingly unpredictable occurrence of seizures often leads to dramatic psychological and social consequences. Patients start to renounce social events and are impaired to perform several professional or

leisure activities such as driving or swimming. Many studies have shown that persistence of seizures – and not epilepsy per se – is associated with higher risk of depression [1]. The primary goal of epilepsy therapy is seizure freedom.

In two-thirds of patients this can be achieved with seizure suppressive drugs. However, the remaining patients continue to have seizures albeit best medical treatment [2]. For many of these patients, surgical removal of the seizure-generating brain region is currently the best method to achieve seizure control [3]. If resective epilepsy surgery is not possible, neuromodulatory approaches such as electric stimulation of the thalamus or the vagal nerve may be considered (also see Epileptologie 1/2017 on brain stimulation).

Epilepsy surgery aims at resecting the brain area responsible for the generation and/or propagation of epileptic seizures. The two most important conditions to render resection possible are: 1) that one particular brain region can be delineated as causing the seizures (often referred to as the "epileptogenic zone", EZ), and 2) that this brain region can be resected without severe neurological sequelae, such as speech impairment.

The EZ has been defined as "the minimal region that has to be removed in order to provide seizure freedom"[4]. Delineating this area directly is not possible with current methods, but the EZ can be approximated by considering the location of a radiologically detectable structural pathology ("epileptogenic lesion"), the brain area where the seizures start ("seizure onset zone", SOZ) and propagate, and where interictal epileptiform EEG signals are recorded ("irritative zone")[4].

Pre-surgical evaluation is a highly specialized procedure, conducted by multidisciplinary teams of neurologists, neurosurgeons, neuroradiologists, psychologists, psychiatrists, physicists and engineers. This diversity reflects the versatility of techniques invoked. The three most important modalities are 1) seizure semiology, namely the clinical description of seizures, 2) magnetic resonance imaging (MRI) and 3) the electroencephalogram (EEG).

EEG can be recorded with extracranial or with intracranial electrodes, the latter either with grid and strip electrodes placed onto the cortex (Electrocorticogram) or with depth electrodes stereotactically inserted into the brain (Stereo-EEG). The advantage of intra- compared to extracranial EEG is a much higher sensitivity (signal to noise ratio) and better spatial resolution than standard EEG. Disadvantages are that the procedure is invasive and spatial coverage is restricted, requiring an excellent a priori hypothesis about the location of the seizure onset zone before implantation.

In many cases, pre-surgical evaluation is straightforward, if the findings of the different modalities are consistent. For instance for patients with hippocampal sclerosis of the non-dominant cerebral hemisphere, an EEG with intracranial electrodes is not mandatory, if seizure semiology, MRI findings, and the extracranial EEG match [5]. However, the situation turns more complex if the different non-invasive modalities fail to identify clearly the putative EZ, or even give conflicting results. Another difficult situation arises when the putative EZ is localized within or at the border of a highly eloquent brain region, which cannot be resected without causing severe deficits.

Here we present the case of a patient who underwent epilepsy surgery at the University Hospital Bern / Inselspital. This case illustrates the investigations carried out sequentially during pre-surgical evaluation, first with extracranial EEG ("Phase 1"), then with intracranial EEG ("Phase 2"). We present several quantitative tools – some of them developed at our institution – that we apply to MRI and intracranial EEG.

Case presentation

This 32-year old male has been having seizures for more than 10 years. The semiology of his seizures was stereotypical. At seizure onset he experienced a strange feeling of "perceiving the world as memories", he then heard voices without being able to understand the meaning of what they said; after about 20 seconds the voices would fade within a few seconds, and he would then feel extremely tired. Family members described that while having his seizures the patient was whining, and would only faintly react when talked to. For a short period after the seizure he could only reply with "yes" or "no".

The MRI was normal, all standard extracranial EEGs were normal or revealed only discrete slowing over both temporal regions. Over the past 10 years the patient had been treated with valproic acid, carbamazepine, oxcarbazepine, levetiracetam, and lamotrigine (in various combinations) without attaining seizure freedom. Based on the seizure semiology and interictal EEG findings, a temporal lobe epilepsy was suspected.

Phase 1

As a first diagnostic step the patient was hospitalized for several days for continuous EEG-video monitoring with extracranial electrodes ("Phase 1"). The interictal EEG during wakefulness was normal (**Figure 1A**). During light sleep, however, we observed focal slowing on the left hemisphere, as well as isolated epileptic spikes fronto-temporal left (**Figure 1B**). Two seizures were recorded (after reducing the seizure suppressive drugs). Both seizures occurred during light sleep (stage non-REM 1). The ictal EEG showed epileptiform signals on the temporal left derivations at seizure onset, followed by rapid propagation to the contralateral hemisphere (**Figure 1C**).

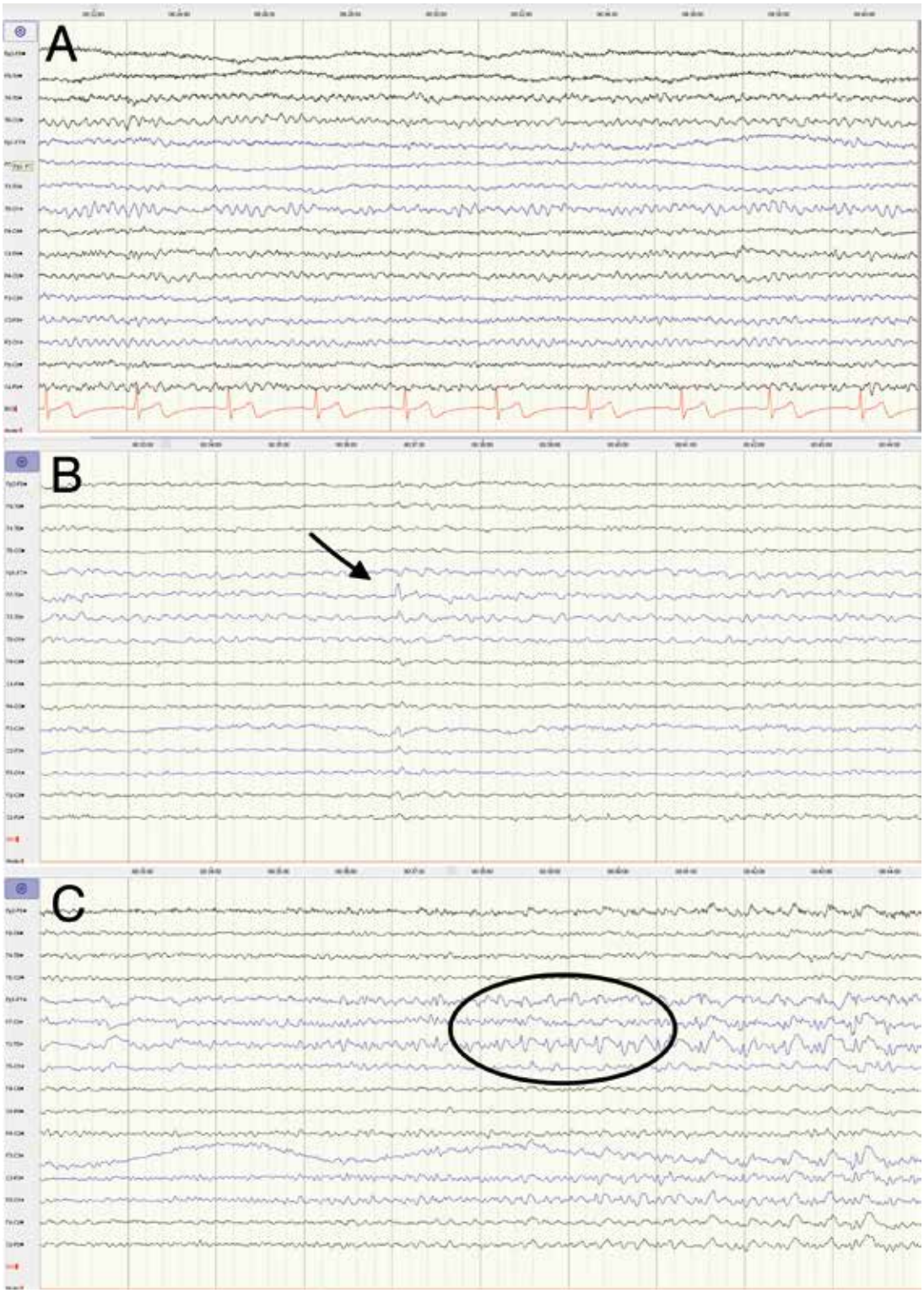

Figure 1: Extracranial EEG during phase 1 pre-surgical evaluation; bipolar longitudinal montage, 10-second epochs.
(A) The interictal EEG in wakefulness was normal with a posterior dominant rhythm at 9-10 Hz, without clear focal slowing or epileptiform signals.
(B) During light sleep (here sleep stage NREM1) appearance of a focal slowing on the left hemisphere, with isolated focal interictal spikes frontotemporal (black arrow).
(C) The EEG at seizure onset shows an evolving pattern starting from the temporal derivations with an increase in amplitude, a decrease in frequency and a propagation to the ipsi-lateral parasagittal regions and to the vertex. We also note the appearance of rhythmic spike waves temporal left (black oval) The interictal and ictal EEG suggest a left temporal lobe epilepsy.

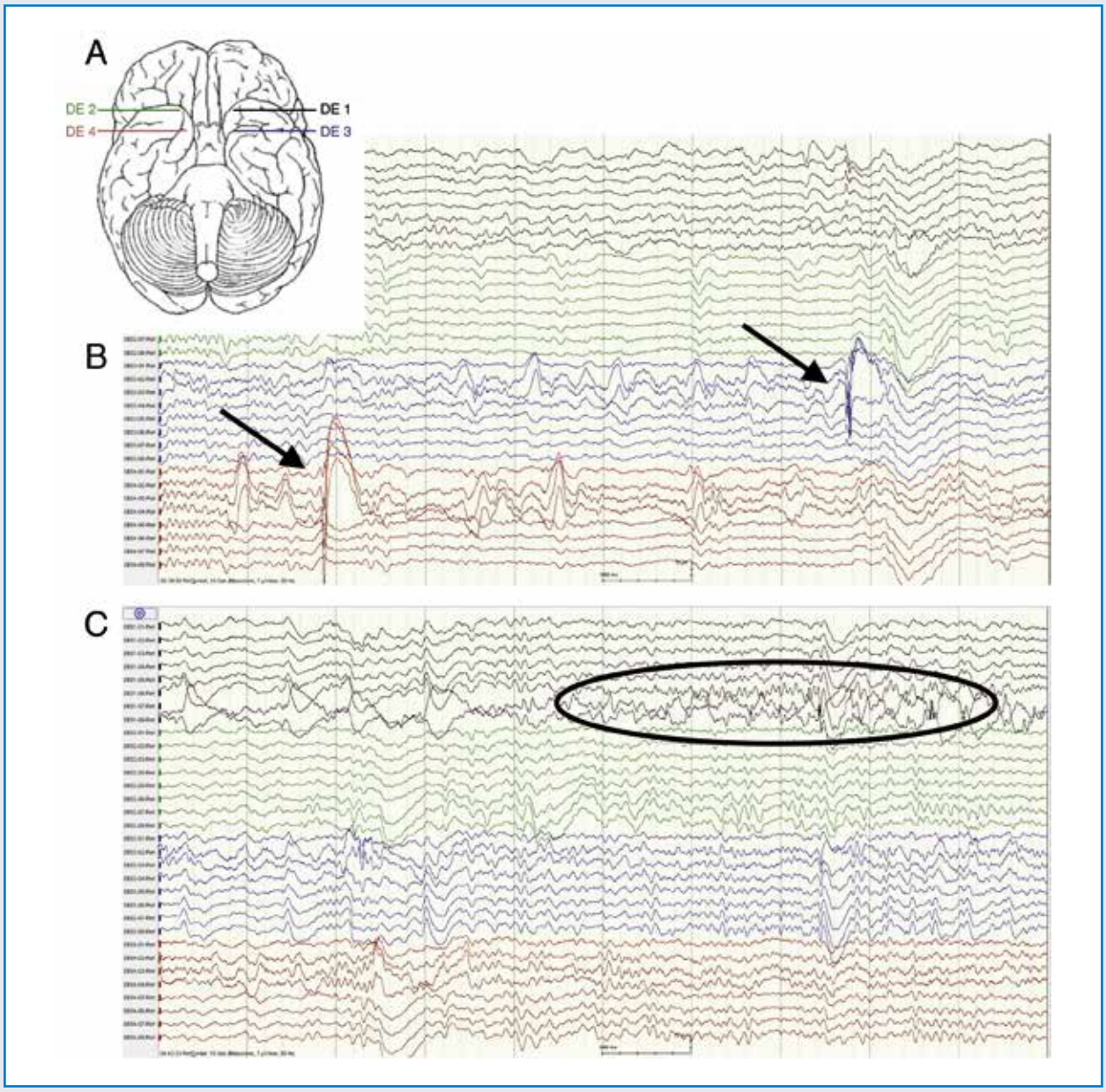

Figure 2: Intracranial EEG during phase 2; monopolar montage, 10-second epochs.
(A) Schematic of electrode placement. Four depth electrodes (DE) were inserted in the temporal lobes: DE1 in the left uncus (anterior temporal lobe), DE2 in the right uncus, DE3 in the left hippocampus, DE4 in the right hippocampus.
(B) The interictal recordings showed isolated and asynchronous interictal spikes in both hippocampi.
(C) At seizure onset the EEG showed a few spikes followed by low amplitude fast activity in the last contacts of electrode DE1 (black oval), localizing the seizure onset zone in the lateral part of the left temporal pole.

Another MRI followed the video EEG. It showed swelling of the left hippocampus, which had not been detectable on the previous MRI, and was therefore interpreted as post-ictal oedema (and not as an epileptogenic structural lesion).

At that point the hypothesis of an involvement of the left temporal lobe was confirmed, however in absence of a persistent lesion on the MRI, the extent of the epileptogenic zone could not be estimated. Thus it was decided to proceed to phase 2 investigations with intracerebral EEG (Stereo-EEG).

Phase 2

Two depth electrodes ("DE") were implanted on each side in the temporal lobes, each with several contacts (**Figure 2A, 5A**). The hypothesis to be confirmed by the phase 2 investigation was a seizure onset zone in the left mesiotemporal lobe. Bitemporal implantation was necessary to rule out seizure onsets in the right temporal lobe (undetected by extracranial EEG) and to measure the time of propagation from the left to right temporal lobe, which is an important prognostic factor in regard to post-surgical seizure control [6].

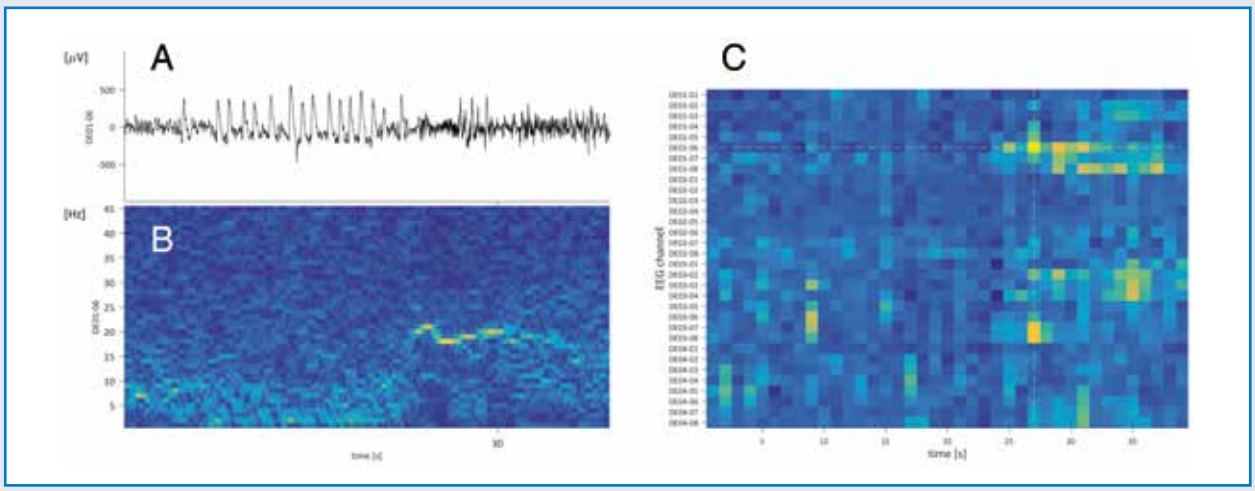

Figure 3: Quantitative analysis of low amplitude fast oscillations (LAFOs).
(A) Intracranial EEG signal recorded at the 6th contact of the left anterior depth electrode (channel DE1-06) at seizure onset (40 seconds); LAFO are visible in the second half of the trace.
(B): JSPECT algorithm applied to this EEG channel; the algorithm quantifies the sustained oscillations at different frequencies and different time windows. For this particular channel we observe a transitory appearance of oscillations at 20Hz (in yellow).
(C) JSPECT applied to all channels in order to identify which channels produce the most LAFOs.

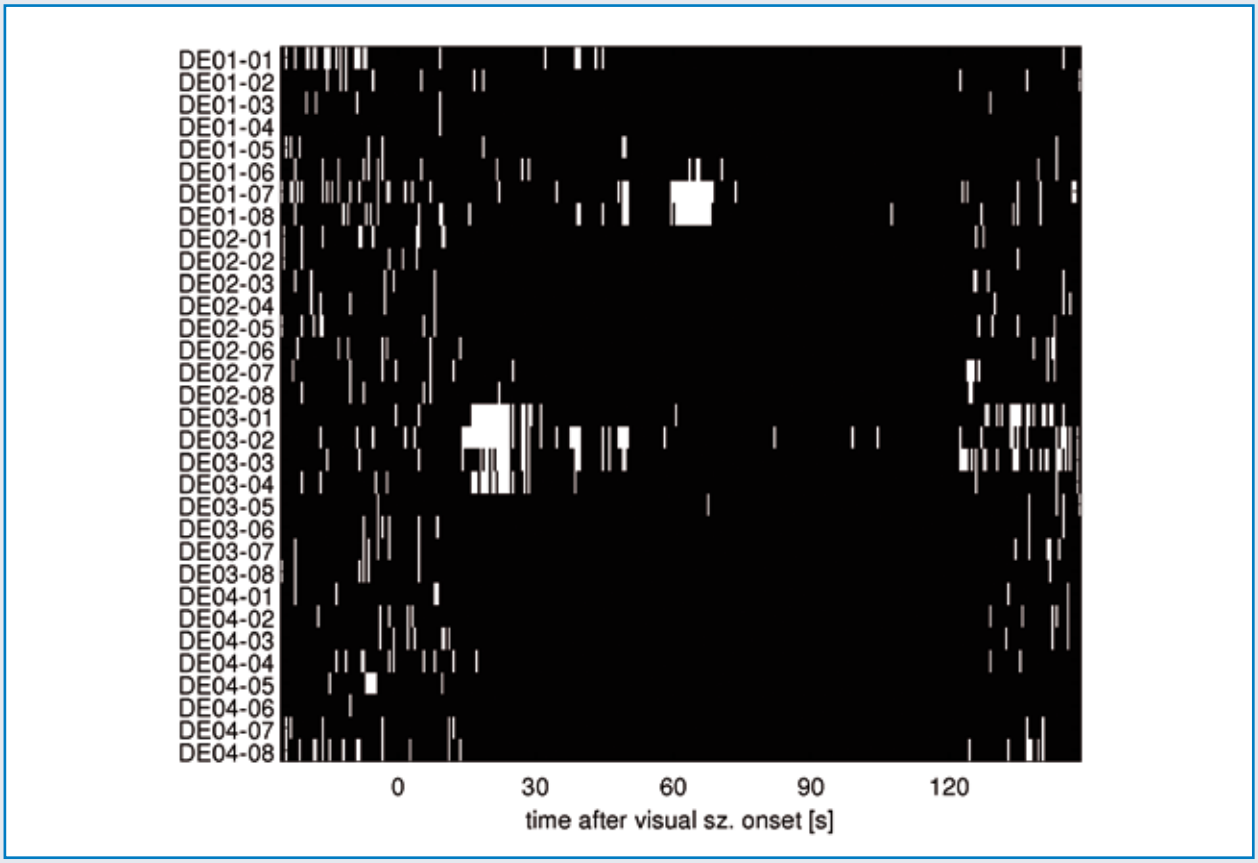

Figure 4: Quantitative analysis of non-linear signal interactions during the first seizure of phase 2. Channels exhibiting extraordinarily high nonlinear interactions are shown in white, those within the normal range in black. Seizure onset is at t = 0 and termination at t = 120s.

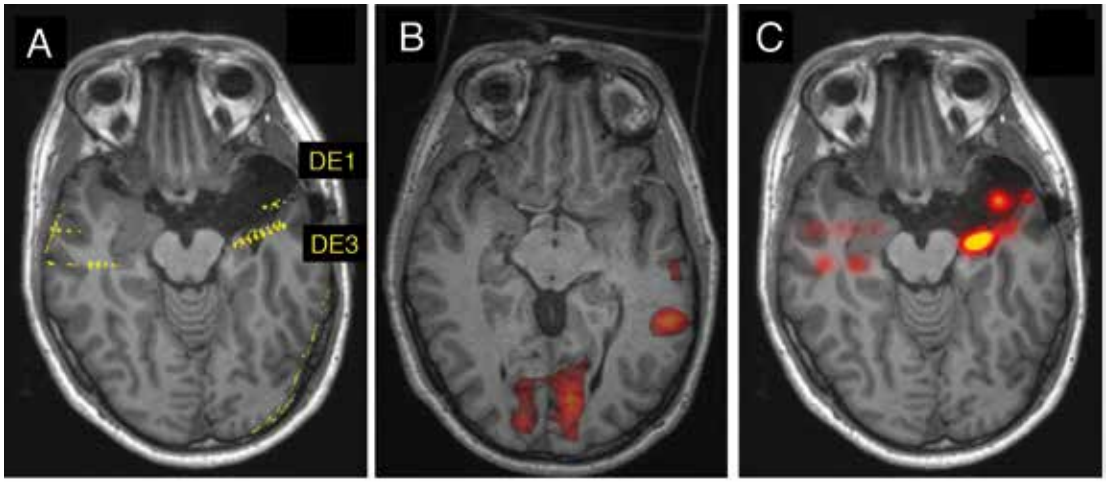

Figure 5: Neuroradiology
(A) Fusion of the computer tomogram during implantation of the electrodes with the postoperative MRI, highlighting the localization of each contact with respect to the resection area. The contacts on DE1 have been removed, the ones on DE3 not completely.
(B) Functional MRI (fMRI) used to identify the eloquent cortex. In a visual and verbal paradigm for syntax recognition, we observed an involvement of the temporal lobe left, just posterior to the seizure onset zone.
(C) Spatial mapping of nonlinear signal interactions (Figure 4) onto the postoperative MRI. The channels with high nonlinear interactions on DE3 have not been resected.
(All 3 figures with radiologic convention: the left hemisphere is represented on the right and vice-versa.)

Box 1: Nonlinear signal interactions in intracranial EEG

If signals recorded from different brain regions show similar dynamics, this may indicate a relationship between these regions (exchange of information is needed to coordinate the firing of extended groups of neurons). Signal interactions may be linear or nonlinear (see Epileptologie 2/2012). In the context of intracranial EEG, Andrzejak et al. [13] found that focal EEG differed from non-focal EEG by higher stationarity, higher non-randomness and higher nonlinear signal interaction. Pearson's correlation coefficient is a powerful and noise-robust measure for assessing linear relationships, but fails to detect certain kinds of nonlinear relationships. In contrast, mutual information is a more general interrelation measure and sensitive to any kind of signal relationships (linear and nonlinear).

To disentangle both kinds of signal interactions, Rummel et al. [14] introduced a framework using linear and nonlinear interrelation measures together with different types of surrogate signals. Surrogates are randomized signal copies that selectively conserve certain signal properties. This allowed to quantify linear signal interaction in excess to random effects for a given power spectrum as well as nonlinear interaction in excess to linear effects in a unified approach. In another paper by Rummel et al. [11] it was found that groups of epilepsy surgery patients with good (Engel classes I and II) and unfavorable (Engel class IV) post-surgical seizure control significantly differed in the extent of resected channels showing nonlinear signal interactions ($p = 0.014$).

The interictal stereo EEG revealed independent epileptic spikes in the deeper contacts of both posterior electrodes (DE3 and DE4), corresponding to the left and right hippocampus (**Figure 2B**). In other words, we found a bitemporal "irritative zone". However, the irritative zone often is spatially more extended than the epileptogenic zone. The ictal recordings demonstrated that the first EEG changes occurred in the lateral contacts of the most anterior electrode on the left hemisphere (DE1), corresponding to the left lateral temporal pole (**Figure 2C**), with rapid propagation into the hippocampus.

Quantitative EEG analysis

Low amplitude fast oscillations (LAFOs) at seizure onset are one of the most reliable markers of the EZ [7]. One way to detect LAFOs is by visual inspection, for instance by setting a high-pass filter with a relatively high cut-off (>5-10Hz) and to use high temporal resolution (i.e. display only 2-5s per screen). In addition, one can use quantitative methods such as frequency analysis.

Instead of using FFT (Fast Fourier Transform, a standard procedure used for frequency analysis) on the EEG signal directly, we have been using an algorithm called JSPECT [8]. In essence, with JSPECT two different transformations are applied to the EEG signal before performing the FFT. This procedure compensates for the lower amplitude of LAFOs, and removes the broadband spectral contamination due to epileptic spikes. An example of such an analysis is shown in **Figure 3**. Note that the smaller the neuronal-glial network generating the oscillation [9] and the closer the electrode, the faster the recorded oscillations will be.

The peri-ictal intracranial EEG of our patient was not only analysed to delineate channels with LAFOs, but also to identify channels with significant nonlinear interactions (see method description in **Box 1**). Figure 5 shows the temporal evolution of EEG channels exhibiting excess nonlinear signal interactions with other brain regions. About 15 seconds after seizure onset, the channels DE3-1 to DE3-4 located on the mesial part of the posterior left depth electrode started to show strong nonlinear interactions. Later on (about 60 seconds after seizure onset) excess nonlinear interactions have propagated to the channels DE1-7 and DE1-8 located on the lateral and temporo-polar part of the more anterior left depth electrode.

Quantitative MRI analysis

To complement the visual analysis by neuroradiologists, the MRI was in addition evaluated statistically (see method description in **Box 2**). The volume of the left hippocampus was 4.9 ± 0.2 ml, confirming enlargement compared to the age and sex adjusted expectation (3.6-4.3 ml, $p = 0.001$). However, also the right hippocampus was enlarged (5.1 ± 0.2 ml, expected 3.6-4.4 ml, $p = 0.002$). In consequence, hippocampal volumetry did not contribute to lateralization.

By contrast, the cortical morphometry supported lateralisation. It yielded extended alterations on both hemispheres (**see Figure 6A**). The highest statistical significance was obtained in the left temporal pole and parahippocampal gyrus ($p < 10^{-5}$). Further alterations were detected in the bilateral precuneus and cingulate gyrus, the left precentral and right postcentral gyrus, the right superior frontal gyrus and the left rostral middle-frontal gyrus. This pattern of widespread cortical alterations was similar to the pattern of thickness reductions that were recently found in patients with left mesio-temporal epilepsy (**Figure 6B**). In contrast,

Box 2: Morphometric analysis

For morphometric analysis, the shape of the brain is expressed in terms of real numbers, which then enable statistical evaluation. For group comparison a variety of commercial or free morphometry software toolboxes are available. The largest morphometric group comparison so far was undertaken in epilepsy patients with temporal lobe epilepsies and left mesio-temporal sclerosis (N = 415). It showed a cortical thickness reduction in the left temporal pole, parahippocampal, entorhinal and superior temporal gyrus as well as in the bilateral superior frontal, precentral and paracentral gyrus and precuneus, compared to N = 1,727 healthy controls (see Figure 6B). In contrast, in TLE patients with right mesio-temporal sclerosis (N = 339) cortical thickness reductions were less extensive and confined to the bilateral precentral and paracentral gyrus.

Despite these important findings, current morphometry tools are not particularly suited for comparison of an individual patient with a group of healthy controls. To close this gap, we have developed an automated morphometric analysis pipeline and statistical evaluation concept for individual patients [15, 16]. In brief, freely available software packages are used to calculate a multitude of regional morphometric parameters from T1-weighted MRI (i.e. global and regional volumes of grey matter, white matter and cerebro-spinal fluid as well as regional estimates of cortical thickness, cortical surface area, cortical curvature and cortical grey-white contrast). These estimates are then statistically compared to a large anonymized database of healthy controls, who have participated in earlier studies at our hospital (N = 422). In addition, asymmetry indices and a regional summary classifier are calculated, the latter indicating where on the cortex any of the morphometric parameters deviate from the age and sex adjusted expectation.

Using a group of patients with temporal lobe epilepsies, we have recently shown that this automated morphometric analysis concept in general yielded high accuracy (diagnostic odds ratio) when comparing regions classified as statistical anomalies with the assessment by human experts [15].

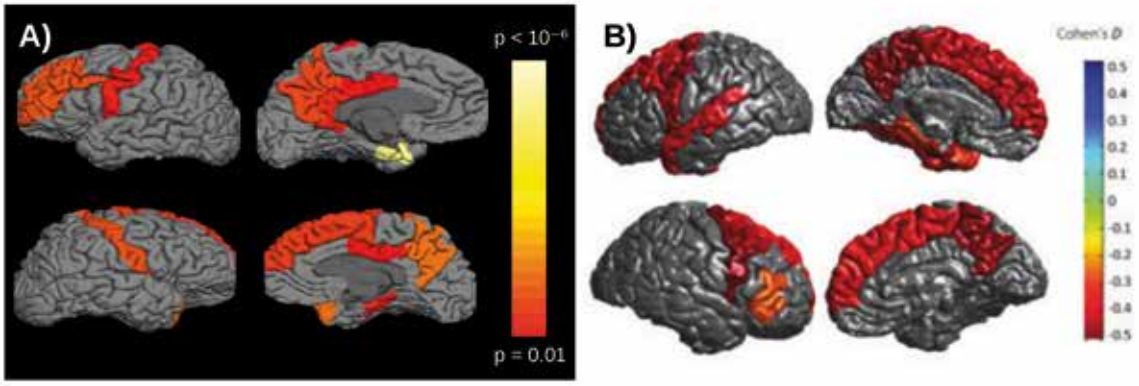

Figure 6: Morphometry
(A) Summary classifier of cortical anomalies in our patient.
(B) Group finding of cortical thickness reduction in temporal lobe epilepsy with left mesio-temporal sclerosis according to the ENIGMA epilepsy study (reproduced with permission from [10]). Note the similarities of the pattern shown in both panels.

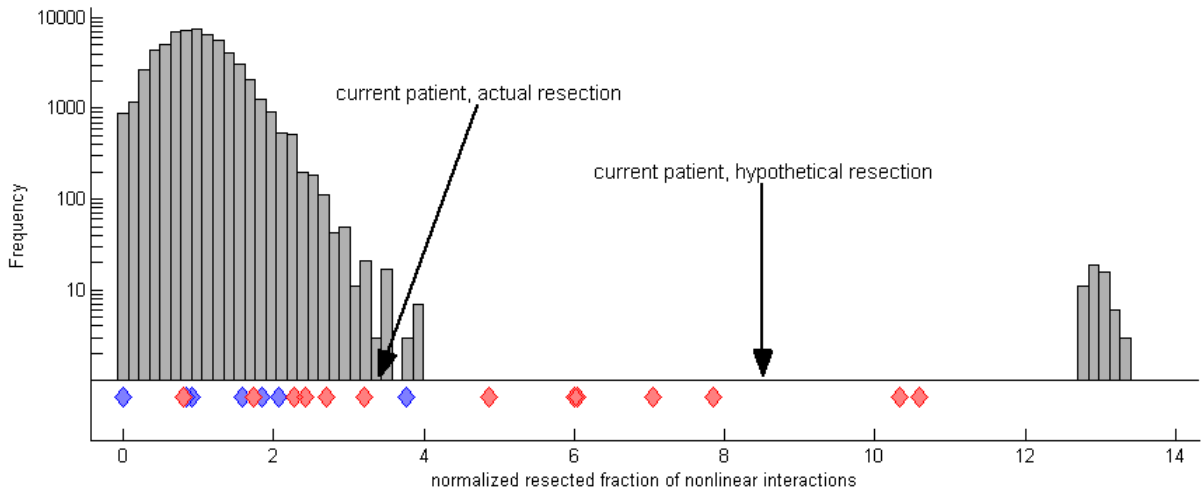

Figure 7: Normalized nonlinearity fraction of random (histogram) and actual resections in 13 patients with Engel class I (red diamonds) and 7 patients with Engel class IV (blue diamonds) [12]. A value of one indicates that the fraction is as large as the average fraction removed under random resections. The values obtained for the patient studied in the present article are indicated by arrows. According to the model, extending the resection to include tissue monitored by DE3-1 and DE3-2 would dramatically increase the probability of a good outcome.

patients with right mesio-temporal epilepsy have different and more localized characteristics [10].

Defining the resection area

In summary, the work-up indicated that the SOZ was in the lateral part of the left anterior temporal lobe, in a region closer to DE1 than to DE3. On the other hand, interictal spikes were visible on the mesial part of DE3, and the ictal activity (judged visually) propagated fast to these contacts. Moreover, the first increase in non-linear interaction was visible on these contacts. This raised the question of the posterior boundary of the resection area. More specifically: Should (and could) the brain area where DE3 was implanted be completely resected? And what about the left hippocampus? Naturally, the more extensive the resection, the higher the chances to remove the epileptogenic zone. On the other hand, a larger resection area increases the risk of neuropsychological deficits.

To help answer this essential question, a functional MRI (fMRI) was performed. This examination confirmed that in this patient, the language was located in the left hemisphere. As shown in **Figure 5B**, the fMRI indicated that part of the comprehension and syntactic function of language was processed in a brain area corresponding to the region where the external contacts of DE3 were located. In addition, other neuropsychological tests showed that the function of the left hippocampus (essential for verbal memory) was intact.

Because of his demanding professional activity, the patient could not afford to suffer verbal memory impairment or even aphasia. Therefore, the decision was taken to remove the temporal pole as well as the amygdala, but only the very anterior part of the hippocampus and temporal lobe ("temporal polectomy with amygdalectomy and anterior hippocampectomy"). The brain area corresponding to the lateral part monitored by DE3 was not resected (**Figure 5A**).

Post operative assessment

Surgery was performed without complications and histology showed subcortical gliosis and a few ectopic neurons. Complete seizure control was not achieved. However, the seizures occurred at a significantly reduced rate, and were less intense than before the surgery (corresponding to Engel class 3, "worthwhile improvement"). Moreover the seizures occurred now mainly immediately before sleep onset. Despite the restricted resection, the patient first had verbal memory deficits, which almost completely resolved over the course of the first year and did not impair his professional activities.

Our clinical assessment was corroborated by the findings of quantitative EEG analysis. **Figure 5C** shows a heat map of the nonlinear interaction effects. The area corresponding to the location of the EEG channels showing the largest nonlinear signal interactions (hippocampus left) were not resected.

Interestingly, it was recently demonstrated that the extent of resection of channels with large nonlinear signal interactions can be used to discriminate Engel class I ("complete seizure freedom") from Engel class IV ("no improvement") [11], [12]. **Figure 7** shows a histogram of the normalized fraction of nonlinear signal interactions that would be removed if resection schemes were sampled randomly. The red and blue diamonds indicate the actual resections in class I and class IV patients, respectively. The mean resected fraction of nonlinear interactions was significantly larger in class I patients than in class IV patients ($p < 10^{-3}$ [12]).

Adding the actually performed resection of our patient to this plot, the normalized fraction of resected nonlinearities assumes a value of 3.4. If we designed a hypothetical resection that included the actual resection and the two additional channels DE3-1 and DE3-2, which also exhibited large nonlinear signal interaction (**see Fig. 4C**), this value would increase to 8.5, suggesting class I outcome (**Figure 6**). However, the risk of neuropsychological deficits prohibited this more extensive resection and the effect of it will thus remain speculative.

Discussion

We have presented the case of a patient who underwent pre-surgical investigations, and then epilepsy surgery leading to improved seizure control. Even though the patient was not completely seizure free, this case is interesting for several reasons. First, it illustrates the use of several quantitative methods, which we apply as complementary diagnostics to patients with pharmacoresistent epilepsy. The non-invasive technique of morphometric MRI analysis revealed a pattern of statistical anomalies, highly suggestive for left rather than right mesial temporal lobe epilepsy (**Figure 6**). Such findings may in the future help to optimize planning of invasive EEG in selected patients.

Intracranial EEG may also benefit from quantitative analysis, either for a more precise characterisation of visually detectable features (e.g. LAFOs), or for identifying properties of the signal that are not easily perceived by visual inspection (e.g. the relative importance of linear and nonlinear effects). We have also discussed how the effect of various resection areas on EEG dynamics can be simulated in advance (see also the article by Müller et al. in this issue).

Finally, the present case demonstrates that the identification of the EZ is only one aspect of the pre-

surgical evaluation, and that other considerations such as post-operative neuropsychological deficits have to be taken into account when evaluating therapeutical options.

References

1. *Devinsky O, Barr WB, Vickrey BG et al. Changes in depression and anxiety after resective surgery for epilepsy. Neurology 2005; 65: 1744–1749*
2. *Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000; 342: 314–319*
3. *Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. Lancet Neurol 2014; 13: 1114–1126*
4. *Rosenow, F., Lüders, H. Presurgical evaluation of epilepsy. Brain 2001: 124; 1683–1700*
5. *Diehl B, Lüders HO. Temporal lobe epilepsy: when are invasive recordings needed? Epilepsia 2000; 41 Suppl 3: 61–74*
6. *Wieser HG, Siegel AM. Analysis of Foramen Ovale Electrode-Recorded Seizures and Correlation with Outcome Following Amygdalohippocampectomy. Epilepsia 1991; 32; 838–850*
7. *Modur PN, Zhang S, Vitaz TW. Ictal high-frequency oscillations in neocortical epilepsy: implications for seizure localization and surgical resection. Epilepsia 2011; 52: 1792–1801*
8. *Niederhauser JJ, Esteller R, Echauz J et al. Detection of seizure precursors from depth-EEG using a sign periodogram transform. IEEE Trans Biomed Eng 2003; 50: 449–458*
9. *Buzsáki G, Draguhn A. Neuronal oscillations in cortical networks. Science 2014; 304: 1926–1929*
10. *Whelan CD, Altman A, Botia JA et al. Structural brain abnormalities in the common epilepsies assessed in a worldwide ENIGMA study. Brain 2018; 141: 391–408*
11. *Rummel C, Abela E, Andrzejak RG et al. Resected Brain Tissue, Seizure Onset Zone and Quantitative EEG Measures: Towards Prediction of Post-Surgical Seizure Control. PLoS One 2015; 10: e0141023*
12. *Müller M, Schindler K, Goodfellow M et al. Evaluating resective surgery targets in epilepsy patients: A comparison of quantitative EEG methods. J Neurosci Methods 2018; 305: 54-66*
13. *Andrzejak RG, Schindler K, Rummel C. Nonrandomness, nonlinear dependence, and nonstationarity of electroencephalographic recordings from epilepsy patients. Phys Rev E 2012; 86: 046206*
14. *Rummel C, Abela E, Müller M et al. Uniform approach to linear and nonlinear interrelation patterns in multivariate time series. Phys Rev E 2011; 83: 066215*
15. *Rummel C, Slavova N, Seiler A et al. Personalized structural image analysis in patients with temporal lobe epilepsy. Scientific Reports 2017; 7: 10883*
16. *Rummel C, Aschwanden F, McKinley R, et al. A fully automated pipeline for normative atrophy in patients with neurodegenerative disease. Front Neurol 2017; 8: 727*

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Ein Fall von limbischer Autoimmunenzephalitis mit seriellen Anfällen

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Zusammenfassung

Die limbische Autoimmunenzephalitis ist oftmals von epileptischen Anfällen begleitet und tritt als paraneoplastisches Syndrom, aber auch rein als Autoimmunerkrankung ohne obligatorische Assoziation mit einem Tumor auf. Die Diagnosestellung ist aufgrund der Vielfalt der klinischen Primärpräsentation schwierig und erfolgt häufig verzögert, was mit einem schlechteren klinischen Outcome assoziiert sein kann. Hinsichtlich der Therapie fehlen derzeit noch grössere kontrollierte klinische Studien. Empfohlen wird eine Immuntherapie und – sofern vorhanden und möglich – eine Behandlung der assoziierten Tumorerkrankung. Begleitende epileptische Anfälle zeigen häufig ein unzureichendes Ansprechen auf anfallsunterdrückende Medikamente. Wir präsentieren den Fall einer klassischen paraneoplastischen limbischen Enzephalitis, die sich mit schwierig zu therapierenden epileptischen Anfällen manifestierte.

Epileptologie 2018; 35: 181 – 185

Schlüsselwörter: EEG, serielle Anfälle, Autoimmunenzephalitis, paraneoplastisches Syndrom, Anti-Hu-Antikörper, Anti-SOX-1-Antikörper

A case of autoimmune limbic encephalitis with serial epileptic seizures

Autoimmune limbic encephalitis is often accompanied by epileptic seizures. It can occur as a paraneoplastic syndrome as well as an autoimmune disease without associated tumour. Its diagnosis can be challenging due to the variety of clinical symptoms. This often leads to a delayed begin of therapy, which can be associated with an unfavourable outcome. In absence of controlled clinical studies, treatment guidelines are based on experts' opinion and retrospective case series. The current therapy consists of immunotherapy and – if required – treatment of the underlying tumour. Concomitant epileptic seizures frequently show an incomplete response to seizure suppressive drugs alone. Here we present the case of a patient with classic paraneoplastic limbic encephalitis, which manifested with epileptic seizures that were difficult to treat.

Keywords: EEG, repetitive seizures, autoimmune encephalitis, paraneoplastic syndrome, anti-Hu antibodies, anti-SOX1 antibodies

Un cas d'encéphalite limbique autoimmune associée à des crises sérielles

L'encéphalite limbique autoimmune est souvent associée à des crises épileptiques. Elle peut être d'origine paranéoplastique ou autoimmune sans association tumorale. Le diagnostic peut être difficile en raison de la variété des présentations possibles, ce qui peut retarder le début du traitement et péjorer le pronostic. En l'absence de larges études contrôlées, les recommandations concernant le traitement se fondent sur les opinions d'experts et sur des séries rétrospectives. La thérapie comporte un volet immunologique (cortisone ou immunoglobulines) et – en cas de tumeur – une prise en charge oncologique. Les crises ne répondent que partiellement au traitement anti-épileptique. Nous présentons ici un cas typique d'encéphalite limbique paranéoplastique associée à des crises sérielles difficiles à contrôler.

Mots-clés : EEG, crises sérielles, encéphalite autoimmune, syndrome paranéoplastique, anticorps anti-HU, anticorps anti-SOX-1

Klinische Präsentation

Die notfallmässige Zuweisung der bis anhin gesunden 51-jährigen Patientin erfolgte aufgrund eines erstmaligen sekundär generalisierten tonisch-klonischen Anfalls. Bereits seit drei Tagen waren der Patientin stereotype Episoden mit Schwindel, Nausea, okzipitalen Kopfschmerzen sowie passagerer Desorientiertheit aufgefallen. Darüber hinaus bestanden keine körperlichen Beschwerden, insbesondere Fieber, Nachtschweiss oder Gewichtsverlust wurden verneint. Keine regelmässige Medikamenteneinnahme, aktiver Tabakkonsum.

In der klinisch-neurologischen Untersuchung bei Aufnahme fand sich eine leichte Aphasie bei ansonsten normalen Befunden.

Im initialen EEG auf der Notfallstation (**Abb. 1**) zeigten sich links temporal periodische steile Signale (lateralized periodic discharges, L-PDs [1]) mit rezidivierenden epileptischen Anfällen. Das MRI des Schädels zeigte den in **Abb. 2** dargestellten Befund. In der MR-Angiographie der supraaortalen Gefässe fiel in der miterfassten apikalen Lunge eine spikulierte noduläre, primär tumorsuspekte Raumforderung im rechten Oberlappen auf. Im Labor fand sich eine leichte Hyponatriämie von 128 mmol/L (Referenz 136-145 mmol/L). Die Lumbalpunktion zeigte eine isolierte Proteinerhöhung von 0.55 g/L (Referenz 0.20-0.40 g/L).

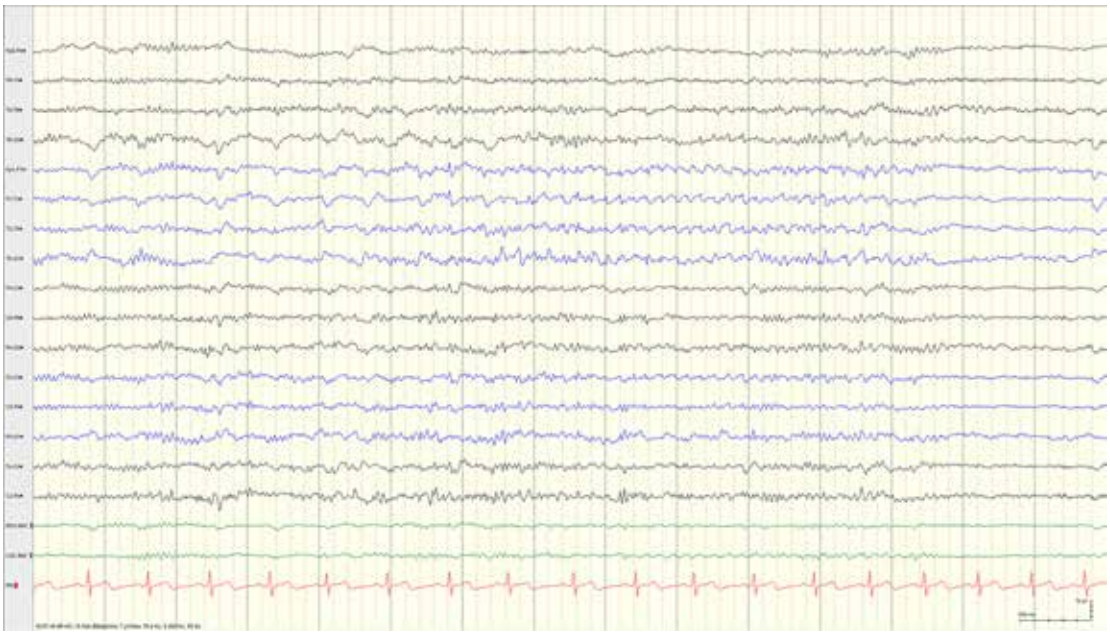

Abbildung 1: ***Initiales EEG*** **(bipolare Montage, 15 Sekunden). Initial links temporal periodische steile Signale um 1 Hz (L-PDs; [1]), welche dann in eine monomorphe, rhythmische Theta-Aktivität um 5 Hz übergehen. Dieses Muster zeigt sich wiederholt während der Ableitung, teilweise auch mit räumlicher Ausbreitung nach posterior und kontralateral.**

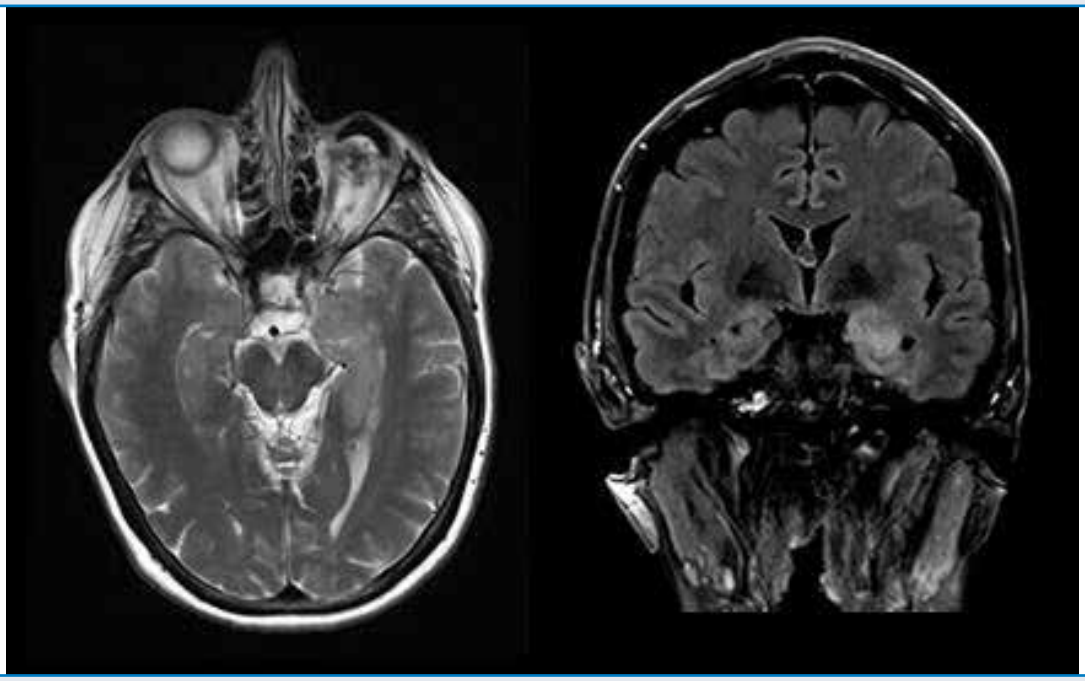

Abbildung 2: ***MR Schädel; links: axiale T2w; rechts: koronare FLAIR mit Fettsaturation nach Kontrastmittelapplikation*****. Es zeigt sich eine deutlich ödematös aufgetriebene und hyperintens signalalterierte Hippokampusformation links ohne Enhancement nach Kontrastapplikation. Das übrige Hirnparenchym stellt sich unauffällig dar; nebenbefundlich zeigt sich ein Status nach Enukleation links mit Bulbusprothese.**

Therapie und Verlauf

Eine intravenöse anfallsunterdrückende Therapie mit Levetiracetam und Clonazepam wurde auf der Notfallstation begonnen. Bei Persistenz der epileptischen Abläufe im Langzeit-EEG erfolgte einige Stunden später zusätzlich eine Aufsättigung mit Phenytoin. Bei hochgradigem klinischem und radiologischem Verdacht auf eine Autoimmunenzephalitis (a.e. paraneoplastisch aufgrund der primär tumorsuspekten Raumforderung im rechten Lungenoberlappen und der Hyponatriämie) wurde zusätzlich eine Kortison-Stosstherapie (1g Methylprednisolon für 5 Tage) begonnen.

Die Differentialdiagnose einer viralen Enzephalitis war aufgrund der normalen Zellzahl im Liquor nach dreitägiger Symptomatik und des in seiner räumlichen Ausbreitung begrenzten, nicht kontrastmittelanreichernden MRI-Befundes zwar weniger wahrscheinlich, jedoch initial nicht ausgeschlossen, weswegen pragmatisch eine Therapie mit Aciclovir bis zum Erhalt einer negativen Herpes-simplex-Virus -PCR begonnen wurde.

Die weitere Abklärung der Raumforderung mittels CT-Thorax und Biopsie erbrachte die Diagnose eines kleinzelligen Bronchialkarzinoms. Bei positiven Anti-Hu- und SOX-1 Antikörpern im Serum wurde die Diagnose einer paraneoplastischen Enzephalitis bestätigt. Die weiteren Antikörper für eine Autoimmunenzephalitis waren negativ.

Während der ersten drei Tage zeigte sich trotz Ausbau der anfallsunterdrückenden Therapie (bis hin zu einer passageren Fünffach-Therapie mit Levetiracetam, Phenytoin, Lacosamid, Topiramat und Clonazepam) keine Befundverbesserung im Langzeit-EEG (**Abb. 3A**). Klinisch dominierte eine Orientierungs- sowie Kurzzeitgedächtnisstörung. Nach Beginn einer zusätzlichen intravenösen Immunglobulingabe verbesserte sich das EEG-Muster zunehmend (**Abb. 3B und C**). Bei einer sich zeitgleich einstellenden klinischen Verbesserung wurde auf eine weitere Eskalation der anfallsunterdrückenden Therapie mit therapeutischem Burst-Suppression verzichtet.

Ein Verlaufs-EEG nach dem ersten Zyklus Chemotherapie zeigte den in **Abb. 4** dargestellten Befund ohne LPDs oder iktale Aktivität, aber noch mit linkshemisphärischer Verlangsamung. Die anfallsunterdrückende Therapie konnte im Verlauf langsam reduziert

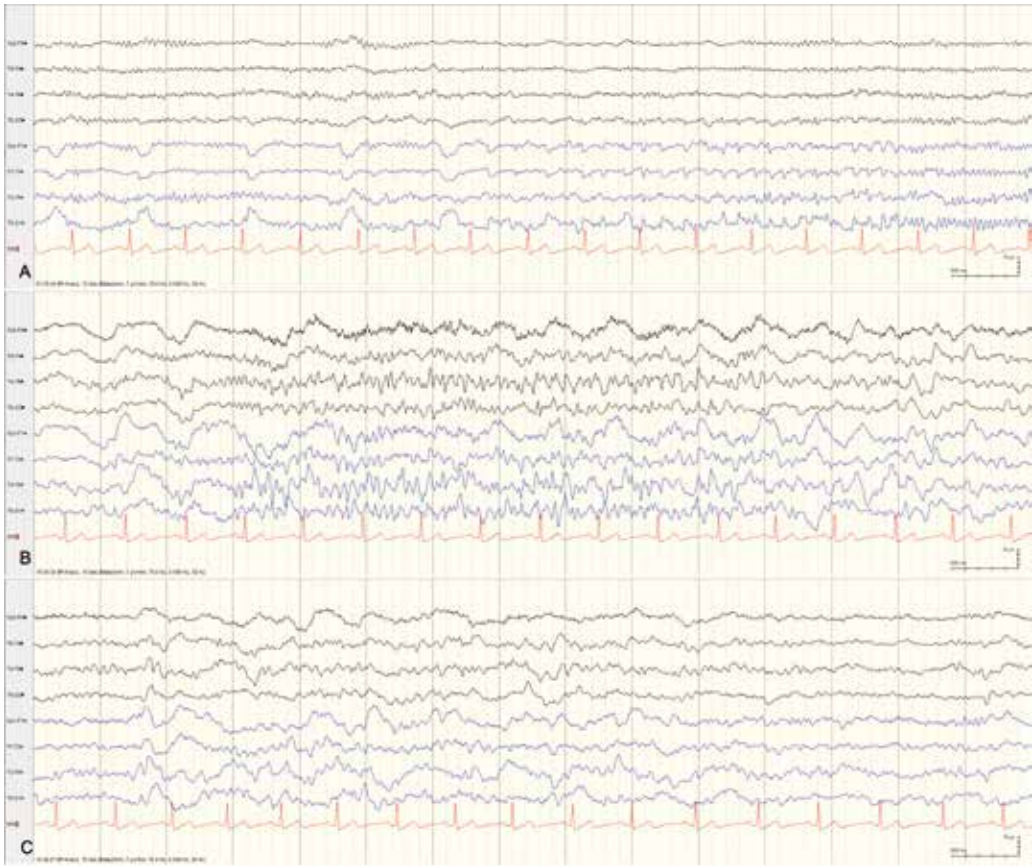

Abbildung 3: ***Abschnitte der kontinuierlichen Ableitung (bitemporale Reihe, bipolare Ableitung, 15 Sekunden).*** **Initial lateralized periodic discharges (LPDs) links mit fokalem Anfall links temporal (A: erster Tag), im Verlauf v.a. im Schlaf weiterhin Strecken rhythmischer Aktivität mit jedoch graduellem Verlust der LPDs und der Evolution (in Frequenz, Amplitude und räumlicher Ausbreitung), so dass wir diese – auch in Zusammenschau mit der sich einstellenden klinischen Besserung – nicht mehr als sicheres Anfallsäquivalent interpretierten (B: 3. Tag; C: 5. Tag).**

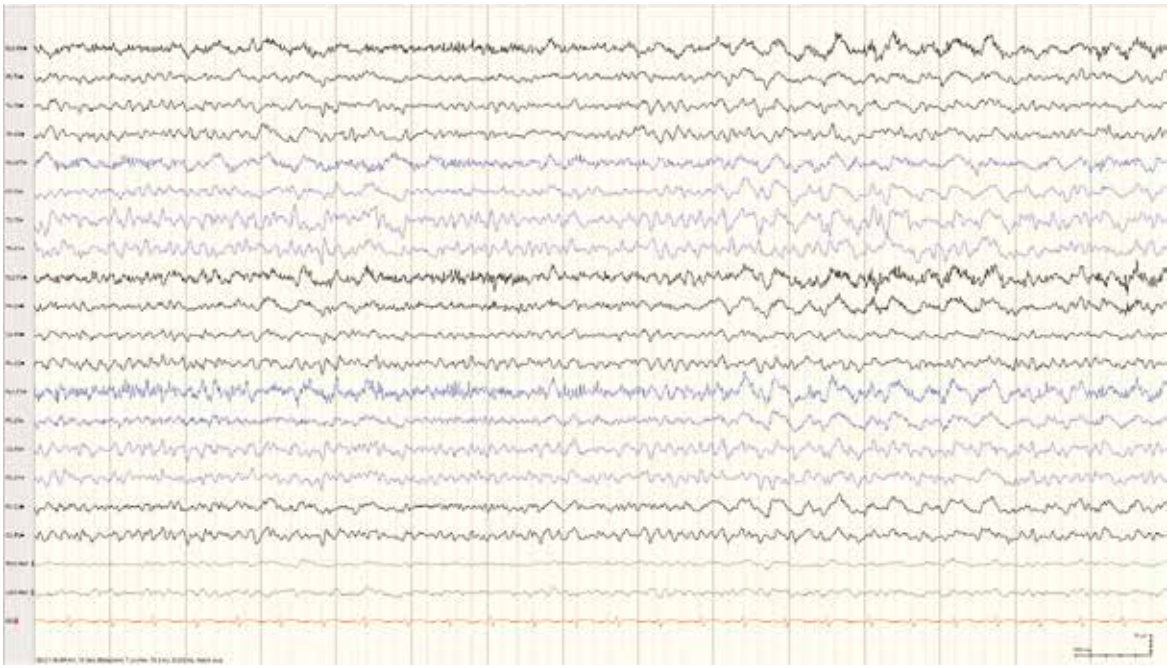

Abbildung 4: ***Bildausschnitt über 15 Sekunden, bipolare Montage*****. Leichte Allgemeinveränderung mit linkstemporalem Verlangsamungsherd und intermittierend generalisierter rhythmischer Delta-Aktivität (G-RDA; [1]).**

werden, ohne dass es zu weiteren epileptischen Anfällen oder einer Verschlechterung im EEG kam.

Diskussion

Die Autoimmunenzephalitis ist eine immunvermittelte Erkrankung, die typischerweise die mesiotemporalen (limbischen) Strukturen betrifft, es sind jedoch Lokalisationen entlang der gesamten Neuroachse möglich. Sie kann – wie im vorliegenden Fall – paraneoplastisch bedingt sein und ist dann häufig mit den klassischen onkoneuronalen, intrazellulären Antikörpern (z.B. Anti-Hu, Anti-Yo, Anti-Ri-AK) vergesellschaftet.

Neben der paraneoplastischen Form der limbischen Enzephalitis gibt es auch Erkrankungsformen, die rein autoimmun ohne Assoziation mit einem Malignom auftreten oder nur in einem Teil der Fälle mit einem Malignom assoziiert sind. Diese Erkrankungsformen wurden in den letzten Jahren als eine Ursache von neu auftretenden Temporallappenepilepsien im Erwachsenenalter identifiziert [2] und seit nun etwas mehr als einer Dekade wurden verschiedene, überwiegend extrazelluläre Antikörper gegen synaptische Rezeptoren, Ionenkanäle und andere Zelloberflächenproteine charakterisiert, welche mit diesen Erkrankungen verbunden sind [3]. Diese extrazellulären Antikörper spielen in der Pathophysiologie der nur fakultativ paraneoplastischen Enzephalitiden eine direkte Rolle, indem sie die Struktur und Funktion des Zielproteins und/oder -rezeptors verändern und damit zu einer reversiblen neuronalen Schädigung führen.

Gewisse Antikörper konnten mit einem charakteristischen klinischen Bild (z.B. faziobrachiale dystone Anfälle bei der Enzephalitis mit LGI1-Antikörpern [4]) oder charakteristischen Befunden der Zusatzuntersuchungen (Hyponatriämie bei Enzephalitis mit LGI1-Antikörpern [4, 5], Delta-Brushes im EEG bei NMDA-Rezeptor-Enzephalitis [5]) in Verbindung gebracht werden.

Gemäss einer britischen Multicenterstudie sind die Autoimmunenzephalitiden mit Antikörpern gegen Zelloberflächenproteine für etwa 7% aller Enzephalitiden (einschliesslich derer mit einer infektiösen Ursache) verantwortlich [6]. Sie sind häufiger als die paraneoplastischen limbischen Enzephalitiden, betreffen alle Altersgruppen und gehen häufig mit einer Prodromalsymptomatik (leichtes Fieber, Kopfschmerzen, Unwohlsein) einher. Epileptische Anfälle treten bei 88% der Patienten mit einer Antikörper-vermittelten Enzephalitis auf (im Vergleich zu 52% bei allen Enzephalitiden und beispielsweise 63% der Patienten mit einer Herpesenzephalitis). Weitere klinische Charakteristika sind Amnesie, Desorientiertheit und psychiatrische Symptome.

Kürzlich wurden klinisch-radiologische Kriterien erarbeitet, anhand derer eine definitive oder wahrscheinliche Autoimmunenzephalitis unabhängig von ihrer Ätiologie diagnostiziert werden kann [7]. Dies ermöglicht einen raschen Therapiebeginn auch ohne Vorliegen der Resultate der Antikörperdiagnostik, was das Outcome verbessern kann und die Tatsache berücksichtigt, dass bislang nicht alle Antikörper bekannt zu sein scheinen (sog. Autoantikörper-negative Autoimmunenzephalitiden).

Die aktuellen Therapieempfehlungen beruhen aufgrund fehlender grösserer klinischer Studien auf Expertenempfehlungen und retrospektiven Fallserien. Autoimmunenzephalitiden sollten unabhängig von einer zugrundeliegenden paraneoplastischen Genese so früh und so intensiv wie möglich mit einer Immuntherapie behandelt werden (z.B. unmittelbarer Beginn einer Kombination von Steroiden mit intravenösen Immunglobulinen oder Plasmapherese und bei fehlendem Erfolg ca. 3-5 Tage nach letzter Immunglobulingabe/ Plasmapherese Beginn mit z.B. Rituximab [8]). Bei einer paraneoplastischen Ätiologie der Enzephalitis, deren Symptomatik in mehr als der Hälfte der Fälle der Diagnose des Malignoms Wochen bis Monate vorausgeht, ist zudem eine Suche und wenn möglich Behandlung des Primärtumors entscheidend. Andere paraneoplastische Manifestationen sollten kontrolliert und ggf. behandelt werden – wie z.B. die im vorgestellten Fall bestehende begleitende Hyponatriämie, welche häufig mit einem kleinzelligen Bronchialkarzinom vergesellschaftet ist.

Epileptische Anfälle, die häufig eines der ersten klinischen Symptome darstellen, sollten ebenfalls aggressiv behandelt werden und bedürfen oft einer Kombination aus einer immunsuppressiven und anfallsunterdrückenden Therapie. Bei Patienten mit hochfrequenten epileptischen Anfällen über mehrere Tage lässt sich häufig – wie auch im vorliegenden Fall – ein Kontinuum zwischen eindeutig epileptischer (**Abb. 3A**) versus rhythmischer, jedoch nicht mehr als sicher epileptisch zu wertender Aktivität (**Abb. 3B/C**) finden. Das EEG und die daraus resultierenden therapeutischen Entscheidungen sollten daher insbesondere bei Situationen mit seriellen Anfällen über einen längeren Zeitraum immer im Gesamtkontext (klinischer Verlauf, bereits installierte Therapie, usw.) interpretiert werden.

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Referenzen

1. *Hirsch LJ, LaRoche SM, Gaspard N et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol 2013; 30: 1-27*
2. *Bien CG, Schulze-Bonhage A, Deckert M et al. Limbic encephalitis not associated with neoplasm as a cause of temporal lobe epilepsy. Neurology 2000; 55: 1823-1828*
3. *Vincent A, Buckley C, Schott JM et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 2004; 127: 701-712*
4. *Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol 2011; 69: 892-900*
5. *Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 2012; 79: 1094-1100*
6. *Granerod J, Ambrose HE, Davies NW et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. The Lancet Infectious diseases 2010; 10: 835-844*
7. *Graus F, Titulaer MJ, Balu R et al. A clinical approach to diagnosis of autoimmune encephalitis. The Lancet Neurology 2016; 15: 391-404*
8. *Bartolini L. Practice Current: How do you treat anti-NMDA receptor encephalitis? Neurology Clinical practice 2016; 6: 69-72*

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Epilepsie-Liga-Mitteilungen

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Zum dritten Mal nach 2003 und 2011 hat die Epilepsie-Liga eine repräsentative Stichprobe in der Schweiz nach ihren Einstellungen zu Epilepsie befragen lassen. Die wichtigsten Ergebnisse erfahren Sie in dieser Ausgabe.

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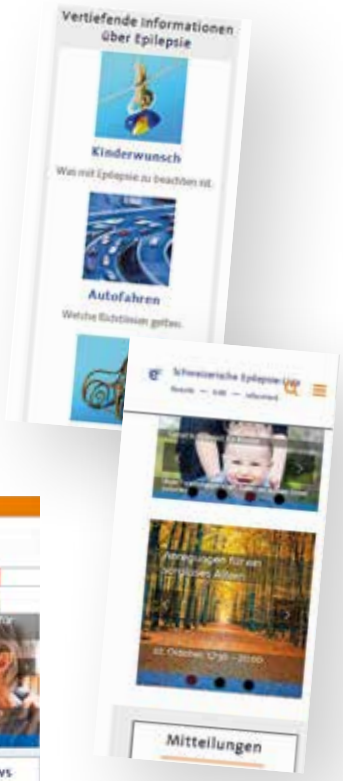

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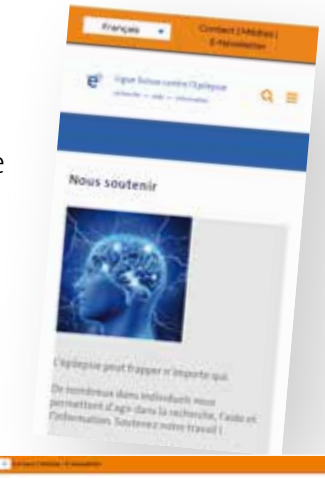

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Le Prix Alfred Hauptmann doit son nom au neurologue et psychiatre allemand éponyme (29.8.1881 – 5.4.1948). Il a découvert l'effet anticonvulsivant du phénobarbital en 1912 et dû quitter l'Allemagne en 1939 en raison de ses origines juives.

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seizuresandstroke.com

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www.ilae.org/congresses/eeg-in-the-first-year-of-life

7.-9.4.2019 I London, UK
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www.statusepilepticus.eu

4.-11.5.2019 I Philadelphia, PA, USA
71st American Academy of Neurology (AAN) Annual Meeting 2019
www.aan.com/conferences/annual-meeting

8.-11.5.2019 I Basel
11. Jahrestagung der Schweizerischen Epilepsie-Liga und der Deutschen und Österreichischen Gesellschaften für Epileptologie („Dreiländertagung")
www.epilepsie-tagung.de

22.-26.6.2019 I Bangkok, Thailand
33. Internationaler Epilepsie-Kongress (IEC)
www.epilepsybangkok2019.org

6.-7.9.2019 I Lausanne
2nd International Congress on Mobile Devices and Seizure Detection in Epilepsy
www.mhsdepilepsy2019.com

23.-25. 10.2019 I Lausanne, EPFL-STCC
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sfcns2019.congress-imk.ch

2020

25.4.-2.5.2020 I Toronto, Ontario, Canada
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4.-8. Juli 2020 I Genève
14th European Congress on Epileptology

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Schweizerische Epilepsie-Liga

Epilepsie und Schlaf

Jeder dritte Epilepsiebetroffene leidet unter Schlafstörungen, nicht nur durch nächtliche Anfälle. Guter Schlaf trägt wesentlich zum Wohlbefinden bei, deshalb gehört das Thema unbedingt zum „Epilepsiemanagement“.

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Der Flyer lässt sich auf Deutsch, Französisch und Italienisch downloaden oder bestellen.

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Epilepsie et sommeil

Une personne atteinte d’épilepsie sur trois souffre de troubles du sommeil, qui ne sont pas toujours dus à des crises nocturnes. Un bon sommeil est essentiel pour le bien-être, c’est pourquoi ce sujet doit impérativement faire partie de la « gestion de l’épilepsie ».

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