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.

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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**).

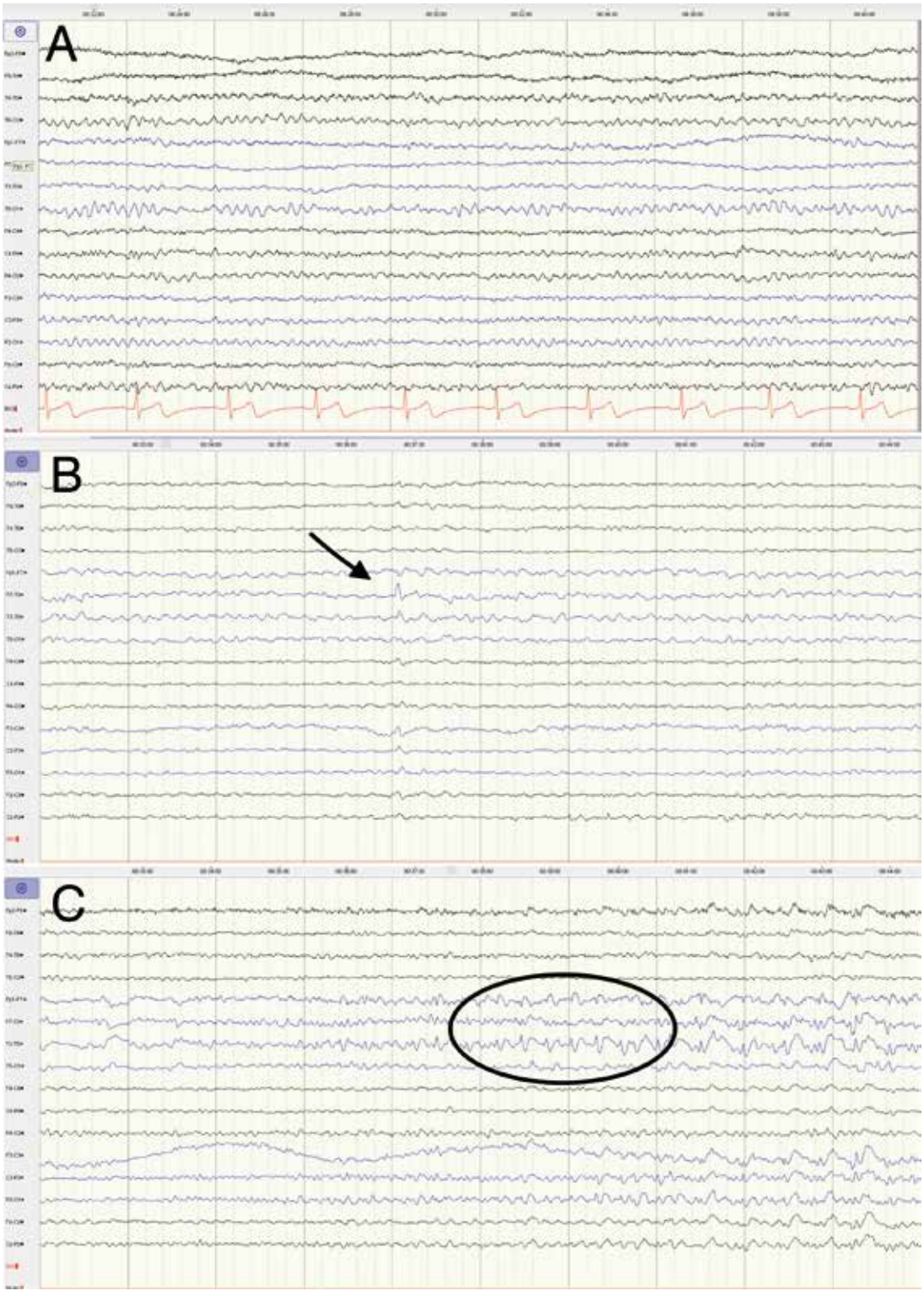

Figure 1: Extracranial EEG during phase 1 pre-surgical evaluation; bipolar longitudinal montage, 10-second epochs.
(A) The interictal EEG in wakefulness was normal with a posterior dominant rhythm at 9-10 Hz, without clear focal slowing or epileptiform signals.
(B) During light sleep (here sleep stage 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.

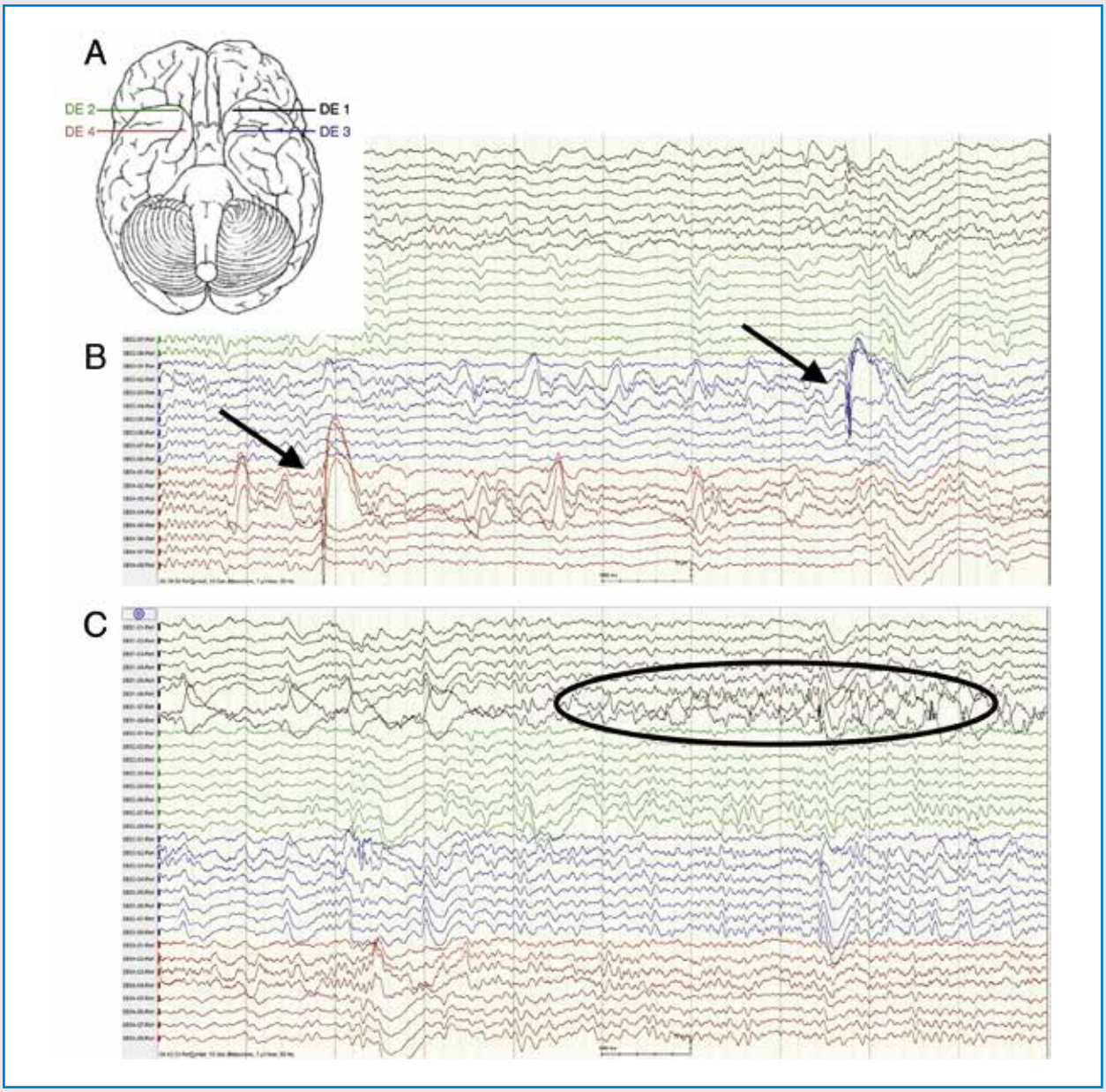

Figure 2: Intracranial EEG during phase 2; monopolar montage, 10-second epochs.
(A) Schematic of electrode placement. Four depth electrodes (DE) were inserted in the temporal lobes: DE1 in the left uncus (anterior temporal lobe), DE2 in the right uncus, DE3 in the left hippocampus, DE4 in the right hippocampus.
(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].

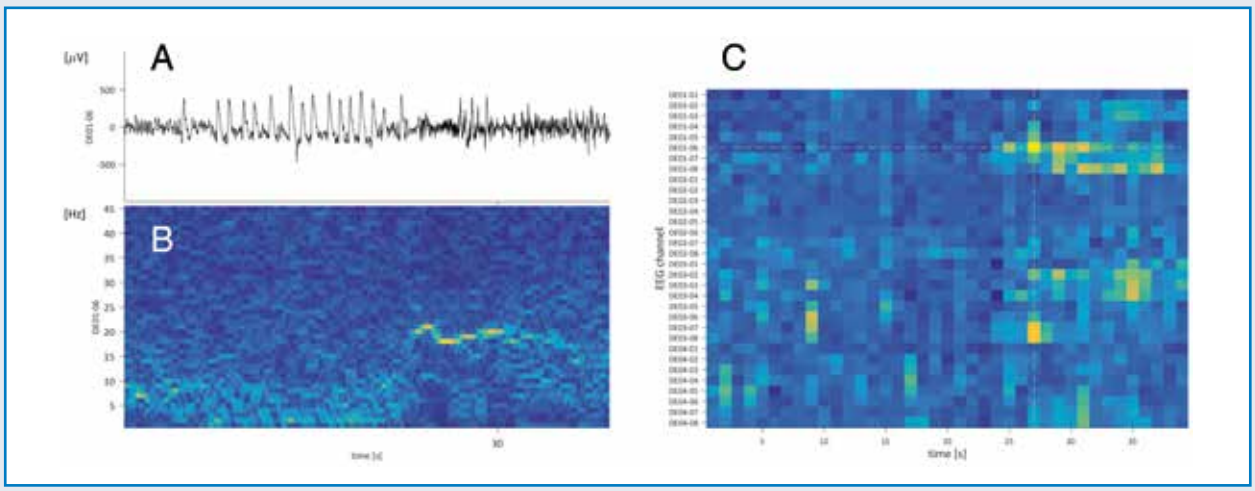

Figure 3: Quantitative analysis of low amplitude fast oscillations (LAFOs).
(A) Intracranial EEG signal recorded at the 6th contact of the left anterior depth electrode (channel DE1-06) at seizure onset (40 seconds); LAFO are visible in the second half of the trace.
(B): JSPECT algorithm applied to this 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.

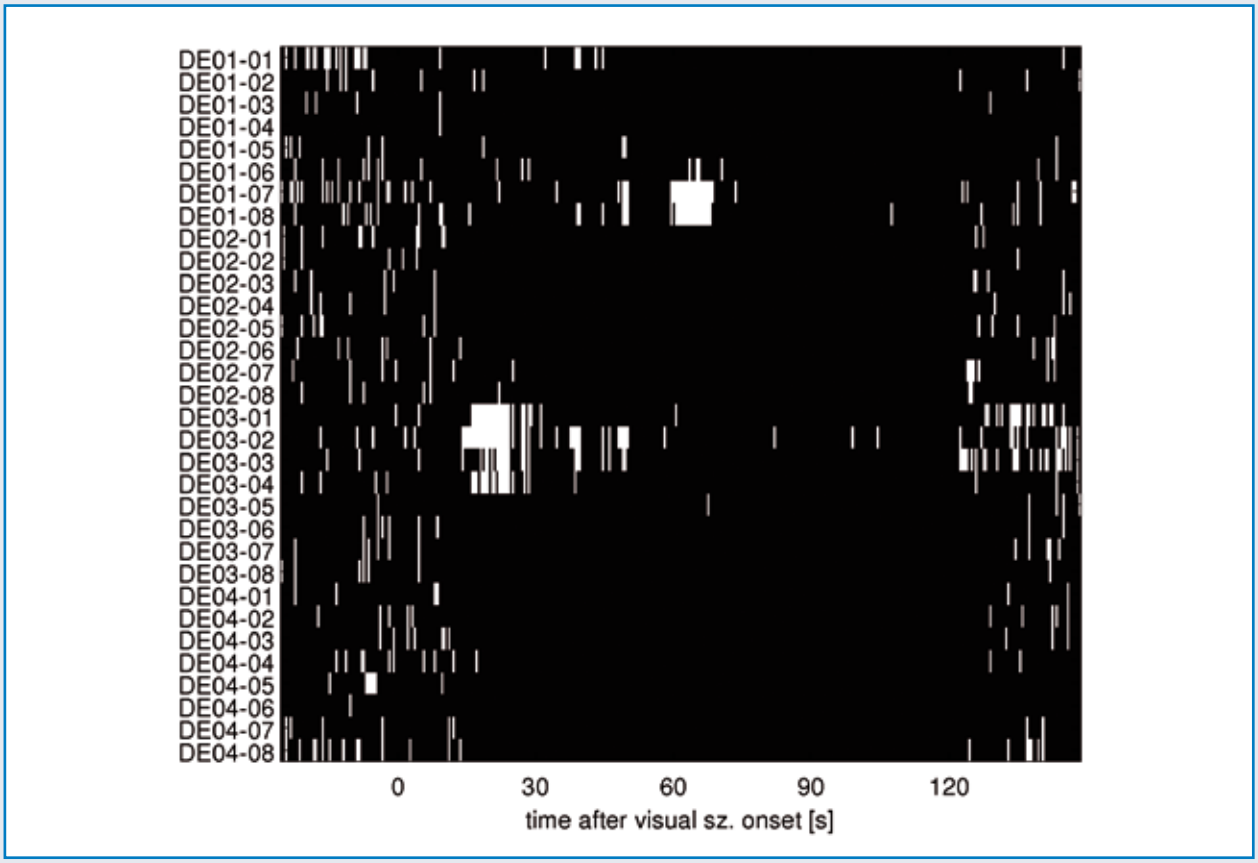

Figure 4: Quantitative analysis of non-linear signal interactions during the first seizure of phase 2. Channels exhibiting extraordinarily high nonlinear interactions are shown in white, those within the normal range in black. Seizure onset is at t = 0 and termination at t = 120s.

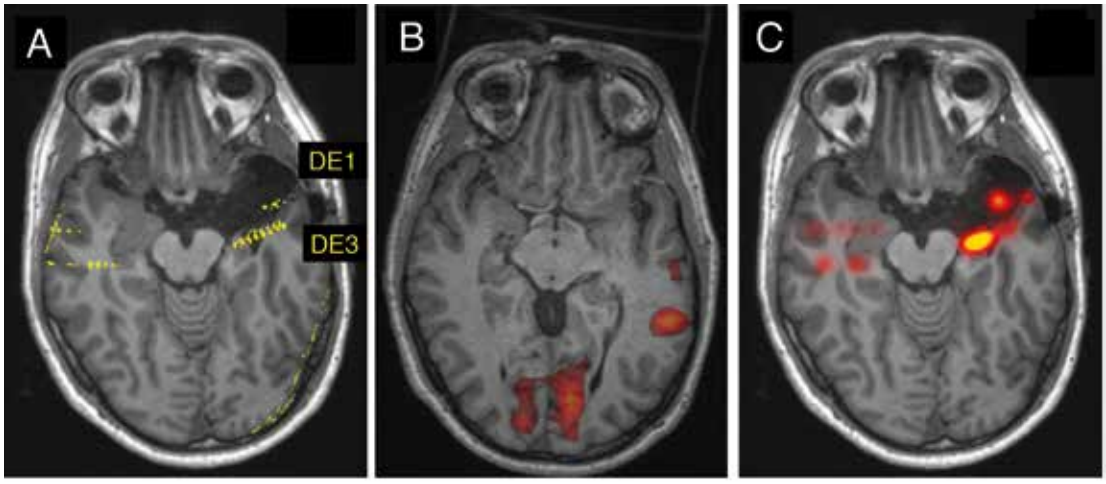

Figure 5: Neuroradiology
(A) Fusion of the computer tomogram during implantation of the electrodes with the postoperative MRI, highlighting the localization of each contact with respect to the resection area. The contacts on DE1 have been removed, the ones on DE3 not completely.
(B) Functional MRI (fMRI) 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].

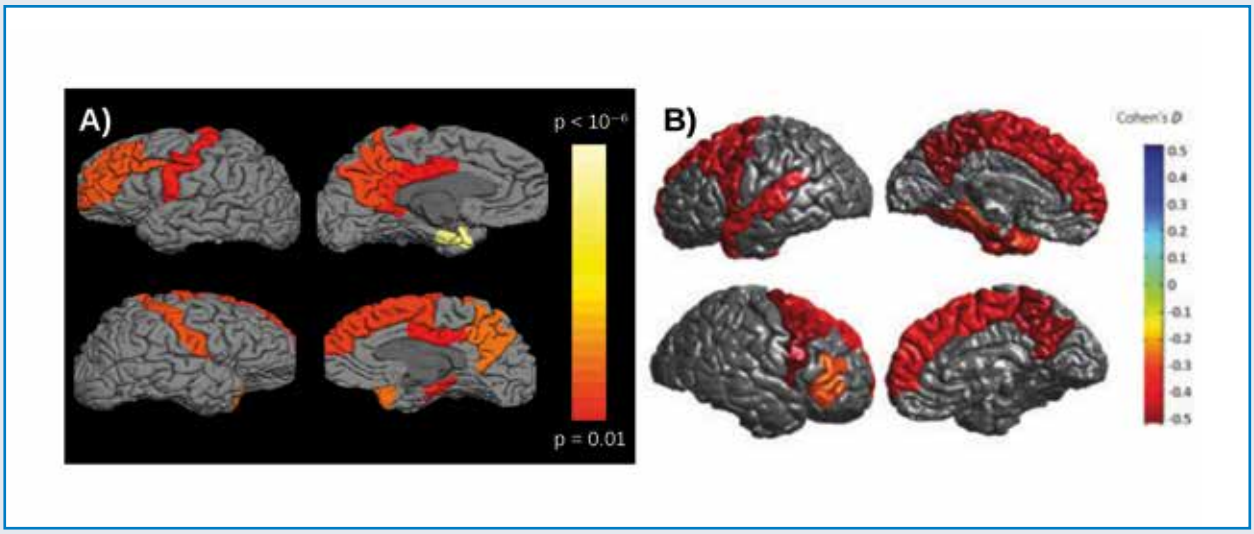

Figure 6: Morphometry
(A) Summary classifier of cortical anomalies in our patient.
(B) Group finding of cortical thickness reduction in temporal lobe epilepsy with left mesio-temporal sclerosis according to the ENIGMA epilepsy study (reproduced with permission from [10]). Note the similarities of the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

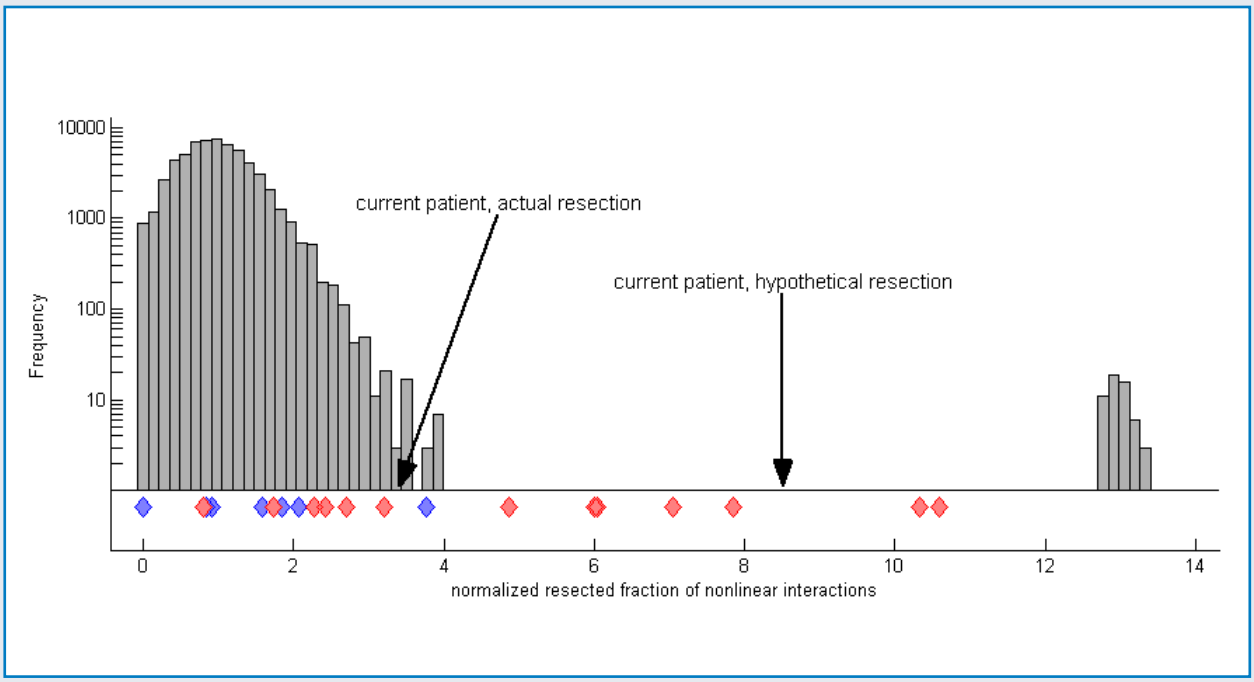

Figure 7: Normalized nonlinearity fraction of random (histogram) and actual resections in 13 patients with Engel class I (red diamonds) and 7 patients with Engel class IV (blue diamonds) [12]. A value of one indicates that the fraction is as large as the average fraction removed under random resections. 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.

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