EEG, the language of the brain and its neurochemical souffleuse

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Summary

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Neurochemical correlates of EEG activity are discussed concentrating on microdialysis findings and seizure prediction by calculating Lyapunov spectra and related measures of complexity in the EEG. Some other interesting findings in relation to brain stimulation by weak D. C. electromagnetic fields i.e. evocation of epileptiform activity by weak D. C. magnetic fields and *in vivo* polarization (D. C. electrical stimulation) of the hippocampus are reported. In addition a few new findings are presented with regard to histochemical findings of resected epileptogenic brain specimen and proton magnetic resonance spectroscopy (^{1}H-MRS).

Keywords: neurochemical correlation of EEG; microdialysis; seizure prediction; nonlinear EEG analysis; magnetic field stimulation; in vivo polarization of human hippocampus; histochemical findings in resected epileptic hippocampus; ^{1}H-MR spectroscopy; GABA; AMPA

Introduction

In the preface to the fourth edition of "Electroencephalography: Basic Principles, Clinical Applications, and Related Fields" Niedermeyer and Lopes da Silva [1] state that the psychophysiological orientation of the founder of human EEG, Hans Berger [2], has been successfully revived and that the domain of electroencephalography with all its related fields has remained a very important issue – in clinical medicine, psychophysiology, neurophysiology, general electrophysiology and certain areas of basic research. Indeed, EEG has found its way into most clinical and research laboratories, and it has witnessed computerized quantification with all sophisticated modern ramifications. Computational techniques of wave analysis started with the Fourier analysis which has been applied as early as 1932 by the physicist Dietsch [3], a collaborator of Berger, and culminated in the signal analysis using nonlinear methods of so-called chaos theory. These methods are playing a major role in neurocognitive research, albeit in hot competition with functional MRI and PET, as well as MR-spectroscopy.

Although it is tempting to glorify these achievements, in particular at an occasion such as this 50-year jubilee, it is fair to say that the generation of EEG potentials has proved to be extremely complex and difficult to understand. The achievements of non-invasive radiological and radionuclear methods in the field of structural diagnosis on the one hand and the feeling of doing pragmatically useful work with an ill-understood method on the other hand have been depressing for many workers in the field. The history of electroencephalography, masterly compiled by Niedermeyer [4], however, tells us that such challenges can present a stimulus for the electrophysiological field, since the function-oriented aspects of the neurological sciences will always be of paramount significance. With such an attitude we chose the title of this presentation which shall concentrate on our own Zurich work. However, let us first try to answer the question "what do we know about the nature of the EEG?"

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What is the EEG?

Electrical activity of the brain results from ionic currents generated by biochemical processes at the cellular level. The principle EEG generators of the EEG are convoluted dipole layers of pyramidal neurons in the cortical gray matter. The EEG

is due to temporal and spatial summation of postsynaptic potentials (PSPs) from cortical pyramidal cells.

What are epileptiform potentials, such as spike and spike-slow waves?

The epileptiform spike is an excitatory event. In focal epilepsy it represents a summation of synchronous paroxysmal depolarization shifts (PDSs), in generalized epilepsies it represents summated excitatory postsynaptic potentials (EPSPs).

The following slow wave is an inhibitory event related to synchronous after hyperpolarization in focal epilepsy and recurrent inhibition in generalized epilepsy.

Pathological slow waves

are neuronal in origin and generated by dipole layers of cortical pyramidal cells [5]. Some literature suggests that certain types of slow waves may originate in subcortical structures [6]. For many authors such an assumption is difficult to reconcile [7]. However, there exists evidence that for certain slow rhythms the networks responsible may be located in subcortical structures such as the thalamus [8].

Advantages of EEG and evoked potentials (EPs)

The most obvious advantages are (1) the great *temporal resolution,* and (2) the *direct relation* to neuronal-information processing.

Recent advances in understanding the EEG as a "language of the brain"

In the following I shall try to summarize some findings which bear direct evidence for a correlation between the EEG and biochemical brain processes, i.e. (1) microdialysis findings, and (2) seizure prediction by calculating Lyapunov spectra and related measures of complexity in the EEG. I shall also briefly mention some other interesting findings in relation to brain stimulation by weak D. C. electromagnetic fields, i.e. (3) evocation of epileptiform activity by weak D. C. magnetic fields, and (4) *in vivo* polarization (D. C. electrical stimulation) of the hippocampus. Finally a few new findings will be presented with regard to (5) histochemical findings of resected epileptogenic brain specimen, and (6) proton magnetic resonance spectroscopy (^{1}H-MRS).

ad 1) Microdialysis findings

The Yale group has presented interesting data obtained by human *in vivo* microdialysis of hippocampi during spontaneous seizures. Using this technique in epileptic patients who had depth electrodes implanted and were evaluated for epilepsy surgery, a basal glutamate increase of about 10% and a basal gamma-aminobutyric acid (GABA) decrease of about 25% were found in the epileptic hippocampus. Prior to a seizure the glutamate rose in the epileptic hippocampus up to 100 µmol, a level at which neurotoxicity might occur. Furthermore the GABA rose higher contra-lateral to the epileptogenic hippocampus. This findings were interpreted as pointing to a GABA transporter problem [9].

In Zurich we studied 5 candidates for epilepsy surgery who had intrahippocampal hollow-core depth electrodes [10] implanted for purpose of presurgical evaluation. Into one depth electrode per patient a push-pull cannula was inserted. This way fractionated samples of extracellular fluid were sequentially collected and analyzed with high-pressure liquid chromatography (HPLC). Concentrations of excitatory amino acids, in particular aspartate and glutamate, were positively correlated with the amount and frequency of EEG

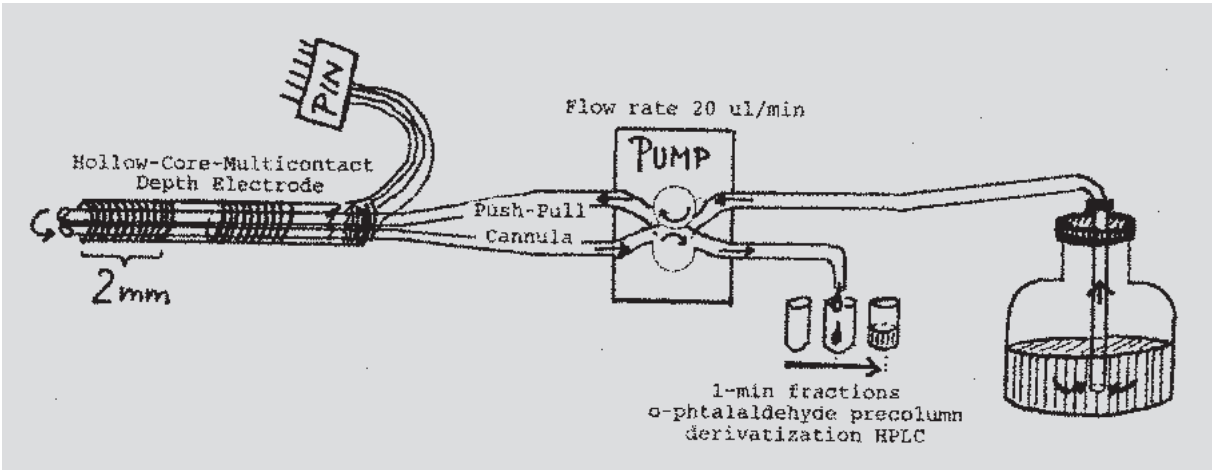


Figure 1
Push-pull device for extracellular fluid analysis.

Figure 2 Aspartic acid concentrations (ASP, bottom) in the perfusate obtained with a push-pull device from the left hippocampus (PP) with concomitant EEG analysis from recording site 2 (left hippocampus, close to PP), recording site 5 (left posterior parahippocampal gyrus) and recording site 1 (left amygdala). Automatic spike detection was performed with two algorithms (Fcomp and Gcomp, i.e. SPECTRAMED® and STELLATE® software) together with visual spike counting. In addition, the spectral power for the frequency range 8–32 Hz was analysed for recording site 2. At the very bottom electrical intracerebral stimulations which led to a local afterdischarge are indicated by an asterisk. The EEG samples (depicted at the top) are indicated as ex:a, ex:b, and ex:AD (corresponding to "AD propagat.to PP-contact"). (From ref. [20] with permission)

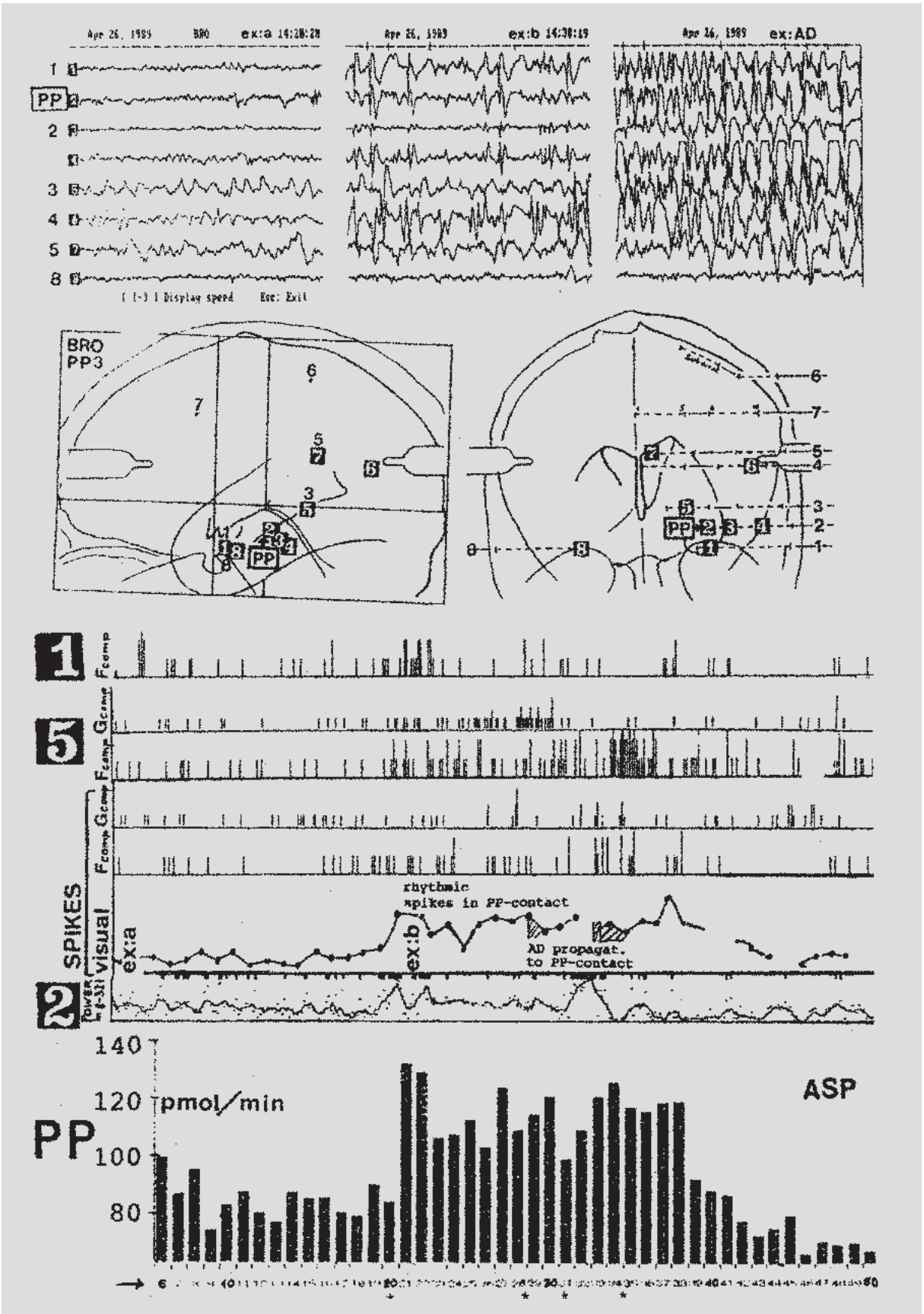
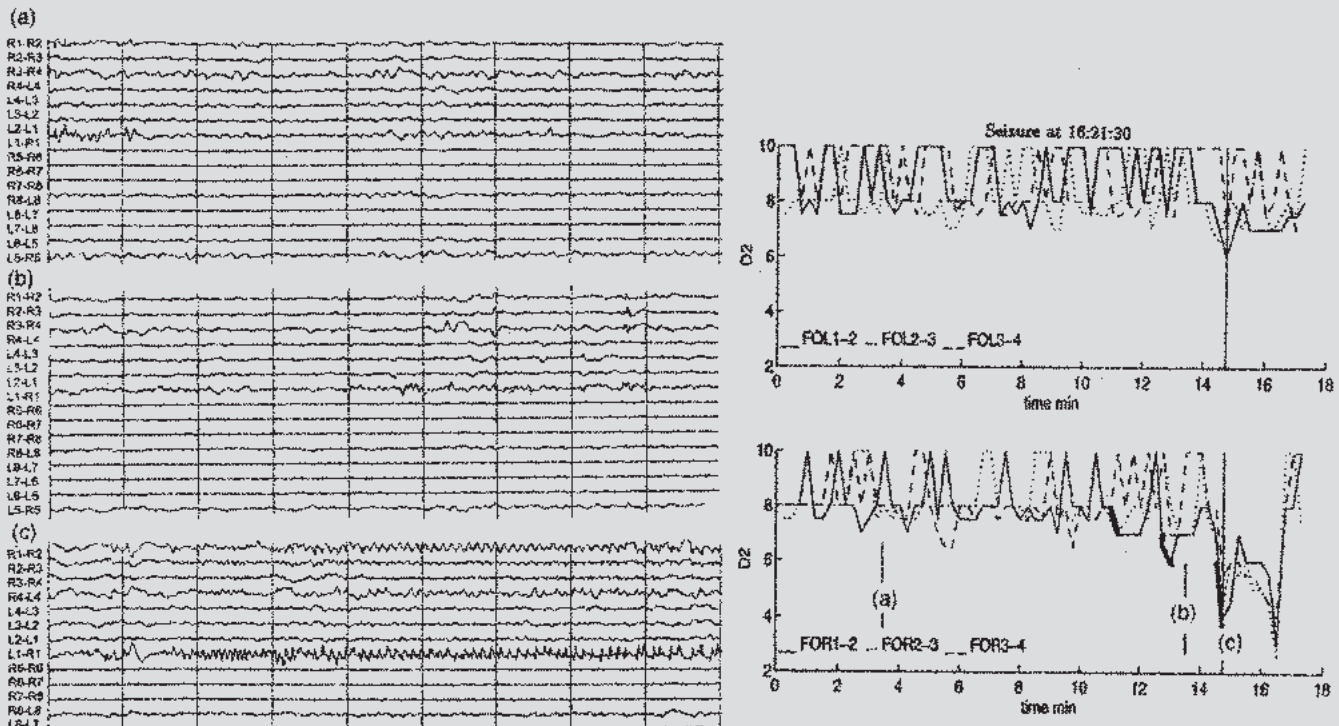


Figure 3 Correlation dimension analysis D2 of foramen ovale (FO)-electrode recordings from the primary epileptogenic hippocampus with a significant decrease of the correlation dimension D2 four minutes before clinical seizure onset. FO electrodes with equally spaced 8 contacts [4 intra-, 4 extracranially]. Note that the extracranially placed FO-electrode contacts (lower 8 channels of the EEG samples) do not pick up the seizure discharge. (a) interictal, (b) preictal, (c) ictal. (From ref. [20] with permission)



spikes in the brain area from which the extracellular fluid was obtained. Figures 1 and 2 show the experimental design [push-pull device] and some results of the extracellular fluid analysis using HPLC with concomitant EEG analysis from epileptogenic hippocampus.

ad 2) Seizure prediction by calculating Lyapunov spectra and related measures of complexity in the EEG

Analysis methods of the EEG derived from the theory of nonlinear dynamics are able to give new insights into the dynamics of the EEG. Chaos indicators (Lyapunov exponents, correlation dimensions and related measures of complexity in the EEG) exhibit characteristic changes as a function of certain physiological and pathological brain states. Correlation dimension D2 and largest Lyapunov exponents decrease dramatically at onset and during seizures [11]. Seizure prediction by calculating Lyapunov spectra was possible in several off-line analyzed seizures (Fig. 3 and 4). Discrete alterations of the correlation dimension

Figure 4
Correlation dimension D2 profile of foramen ovale electrode recordings from the primary epileptogenic area. The correlation dimension D2 starts to decrease 3 minutes (at a) before clinical seizure onset (at b). (From ref. [20] with permission)

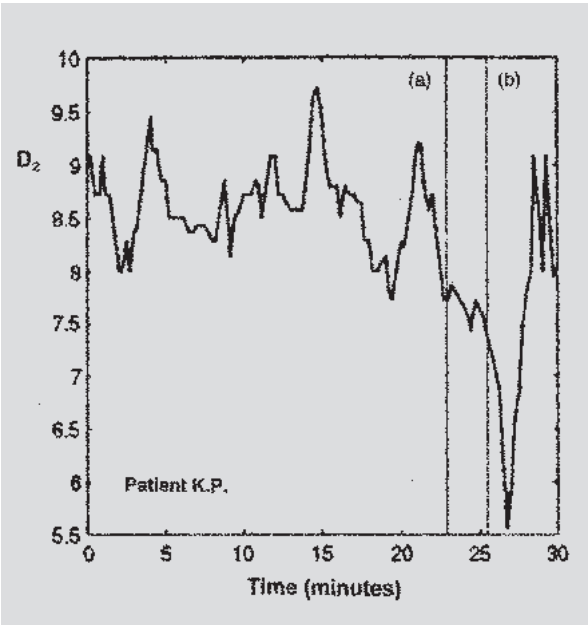


Figure 5
Schematic drawing of the neuromagnetic exposure system. (Courtesy of Dipl. Nat. Sci. ETH Paola Schultheiss-Grassi)

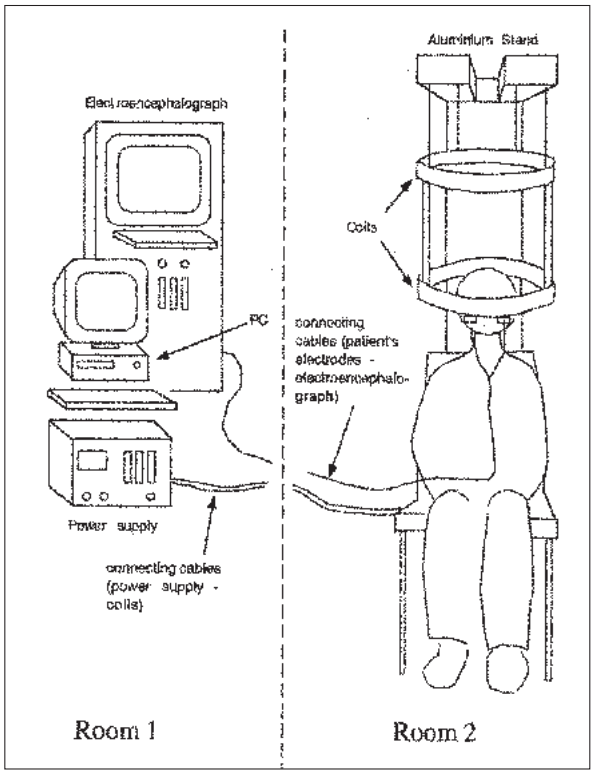
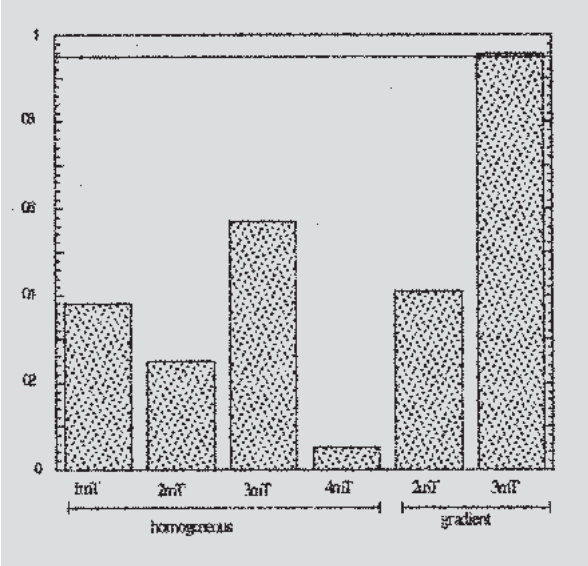


Figure 6
Histogram with the confidence level (1-P) for the power spectral density, calculated using the univariate two-way ANOVA method. A significant result was obtained in the case of stimulating for 30 seconds with the gradient (as opposed to homogeneous) field configuration at a field strength of 3 mT. (Courtesy of Dipl. Nat. Sci. ETH Paola Schultheiss-Grassi)



D2 in the preictal intracranial EEG appear up to several minutes before clinical seizure onset. Figure 3 shows preictal correlation dimension analysis D2 of foramen ovale (FO)-electrode recordings from the primary epileptogenic hippocampus with a significant decrease of the correlation dimension D2 four minutes before clinical seizure onset and Figure 4 three minutes before clinical seizure onset.

ad 3) Evocation of epileptiform activity by weak D. C. magnetic fields

In order to assess the effects of weak D. C. electromagnetic fields on the EEG, we exposed epileptic patients who had intracranial FO electrodes inserted for presurgical evaluation to weak D. C. magnetic fields[1] (Fig. 5). The EEG recorded from the FO electrodes was analyzed with regard to changes of background activity and frequency of spikes [13]. Besides visual spike counting two "objective" methods were used in order to assess whether weak magnetic field stimulation affects the EEG signal: *Fast Fourier Transform (FFT)* and *filter* analyses. For each method 10-second windows with artifact-free EEG were "extracted" before and after magnetic field stimulation and analyzed. With the first method eventually *the power spectral density* (PSD) was calculated for 7 bands (ranging from 1,5 to 25 Hz) and the *relative* and *absolute power* was calculated. All data sets were then analyzed with a *univariate two-way analysis of variance* (ANOVA) to check for statistical intraindividual differences in the log-transformed PSD. According to Gasser et al. [14], for the analysis of the relative power the log transformation: log (x/(1–x), where x is the relative power in a band, and for the absolute power analysis the log transformation: log (x), where x is the absolute power, were used. In the second method we applied an amplitude filter to all spikes in the background activity. The filter was chosen individually but remained unchanged for the whole experiment.

The results of 10 patients with mesial-temporal lobe epilepsy (MTLE) can be summarized as follows: When crossing the conditions "before" and "after" magnetic field stimulation with the "ipsi-" and "contralateral" (to the focus) side condition, a significant result (p value = 0.04) was obtained in the case of stimulating for 30 seconds with the gradient (as opposed to homogeneous) field configuration at a field strength of 3 mTesla (Fig. 6). The filter analysis revealed the number of spikes that occurred before, during, and after the field stimulation. In order to analyze the statistical significance of pair differences, the Wilcoxon signed rank test was used with the following difference pairs (BB-BA: difference between the 10-second window before and after switching *on* the field. BB-AA: difference between the 10 seconds

[1] Patients had given informed consent and this study protocol was approved by the Ethical Commission.

window before switching *on* the field, and the 10 seconds window after switching it *off*. AB-AA: difference between the 10-second window before and after switching the field *off*. BA-AB: difference between the 10-second window after switching *on* the field, and before switching it *off*). When the data were analyzed without any distinction between homogeneous and gradient fields, in order to increase the number of observations, a weakly significant result was found in condition "BB-AA" (p value = 0.05). Comparing these pooled results with individual data where the spikes were assessed by visual counting, it became obvious that only in 5 out of a total of 10 patients large differences in the spike frequency before and after stimulation were present, i.e. only half of the patients showed a clear-cut "electromagnetic sensitivity". Therefore the results of this study compare well with results reported in earlier studies [15, 16]. Further studies, however, are necessary to confirm the hypothesis that the intraparenchymatously found magnetizable particle (presumably magnetite and maghemite) concentration accounts for these phenomena [17, 18].

ad 4) In vivo polarization (D. C. electrical stimulation) of the hippocampus

The effects of weak direct polarizing currents applied to the primary epileptogenic focus were studied[2] before surgical removal of the amygdala and the hippocampal formation in three patients suffering from drug-resistant MTLE. The primary epileptogenic area responsible for the patients' habitual seizures had been previously localized with stereoelectroencephalography (SEEG). At the end of the SEEG-examination, when the depth electrodes were still *in situ,* weak D. C. currents were applied between poles situated either in the epileptogenic amygdala (El.1) or the hippocampus (El.2) and a large (5 x 5 cm) scalp electrode placed over the ipsilateral fronto-temporal scalp using a 9 V battery-powered constant-current device with additional continuous monitoring of current flow by an amperometer in series (Fig. 7). The influence of the D. C. field on the spontaneously occurring EEG activity with focal epileptic spikes and

[2] Informed consent was given.

Figure 7 Baseline EEG (a) and effects of anodal (b) as well as cathodal (c) polarization of right amygdala. Whereas anodal polarization (b) led to a cessation of spontaneously occurring spikes in the primary epileptogenic zone, cathodal polarization (c) provoked a seizure. (From ref. [20] with permission)

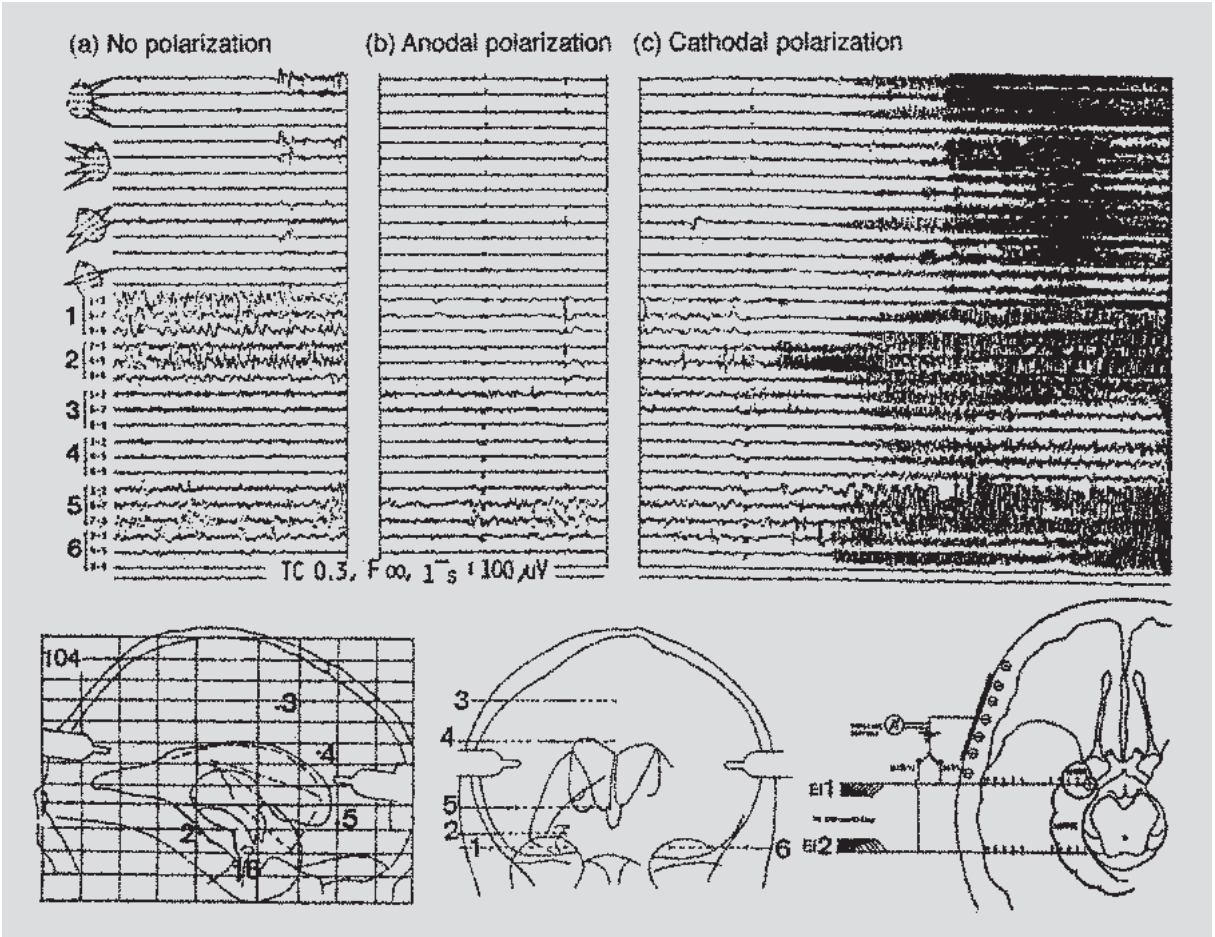
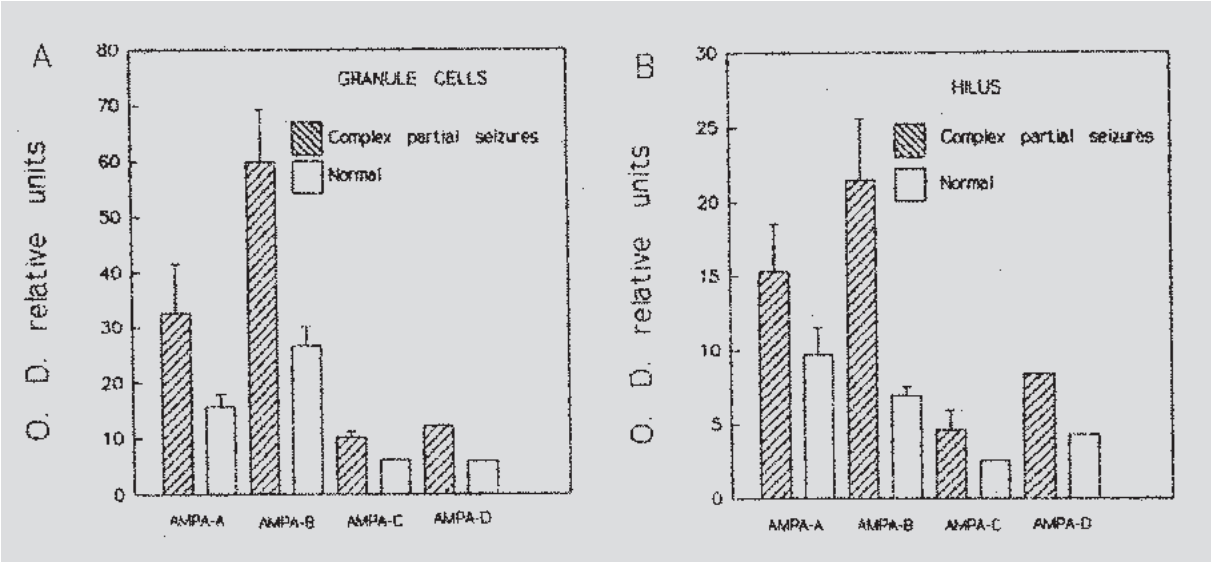


Figure 8 Relative content of mRNA coding for the four AMPA receptor subunits in the hippocampus: (A) dentate gyrus and (B) hilus. Filled bars, epileptic patients suffering from mesial-temporal lobe epilepsy (n 3); open bar, normal human hippocampus (n 2). The levels of AMPA-A and AMPA-B correspond to the mean of relative optical density units from three epileptic cases and two controls, whereas the levels of AMPA-C correspond to the three epileptic brains and one control, and AMPA-D correspond to one control and one epileptic patient. Semiquantitative analysis of calibrated autoradiograms were done using an image analyzer system (MCID). (From Garcia-Ladona et al., 1994 [22]; with permission)



the changes of evoked EEG responses recorded within the hippocampus and evoked by electrical 1/s pulse stimulation of the ipsilateral amygdala were studied. At each session we started low initial current flow of 1 μA for 10 seconds and carefully observed the EEG and the behaviour of the patient.

Results of these experiments (published in abstract form [19]) can be summarized as follows: some of the observed effects were clearly polarity-dependent. Anodal (positive pole) polarization decreased the epileptic spike incidence, while cathodal (negative pole) polarization had an opposite effect (Fig. 7). Evoked potentials recorded from the hippocampus and elicited by electrical pulse stimulation of the ipsilateral amygdala were altered in shape by a weak polarizing current and these effects were related to current intensity. Whereas in two patients there were no clinical accompaniments, i.e., patients were unchanged and unable to tell whether they were under the influence of D. C. currents, in one patient a marked temporary behavioural alteration in the sense of an acute psychotic state was observed following the polarization experiment [20].

ad 5) Histochemical findings in resected epileptogenic brain specimen

In an attempt to better understand the pathophysiology of epilepsies we have undertaken several specific histochemical studies with the tissue resected during epilepsy surgery, in particular during selective amygdalohippocampectomy [21]. Excitatory amino acid (EAA), in particular α-amino-isoxazolproionic acid (AMPA) receptor mRNA localization was studied in several regions of normal and neurological disease-affected human brain using an *in situ* hybridization histochemistry technique [22]. Whereas *in situ* hybridization in the hippocampus of patients affected by Alzheimer's disease revealed a decrease of the content of the mRNAs coding for these AMPA receptors, an increase was detected in epileptic human hippocampi. This increase was most evident for AMPA-A and AMPA-B subunits in the granule cell layer of dentate gyrus (Fig. 8). We interpreted these findings as a consequence of dramatic modifications of hilar circuitry involving excitatory interneurons (mossy neurons) that are targets of mossy fiber collaterals from dentate gyrus granule cells.

Recently Loup et al. [23] have designed a protocol to improve the immunohistochemical analysis of human brain structures. In particular a highly sensitive immunofluorescence procedure for analyzing the subcellular distribution of $GABA_A$ receptor subunits by using antibodies against major $GABA_A$ receptor subunits such as α_1, α_2, α_3, and γ_2 in surgical specimens of amygdalohippocampectomy patients was developed. Using this procedure, a distinct neuron-specific expression pattern of the α-subunit variants was observed in the hippocampal formation, along with widespread expression of the γ_2-subunit. Of particular interest was the prominent α_2- and α_3-subunit staining on

the initial axon segment of pyramidal neurons. Since a dysfunction in the GABA-ergic transmitter system is believed to contribute to the pathophysiology of certain types of epilepsy, further insights into the epilepsies and in particular into the syndrome of MTLE might be achieved using these techniques.

ad 6) ^{1}H-magnetic resonance spectroscopy measured brain GABA levels before and after GABA-ergic AED treatment: prediction of responders

^{1}H-magnetic resonance spectroscopy (^{1}H-MRS), and particularly the recently developed GABA editing ^{1}H-MRS, is a very interesting tool in epileptology. GABA is the main inhibitory neurotransmitter of mammalian brain. At least in some epilepsy syndromes it is assumed that the GABA-ergic inhibition is deficient. Vigabatrin (VGB) is a new antiepileptic drug, which increases the brain GABA level by irreversible inhibition of GABA transaminase. Clinical studies have shown that VGB has antiepileptic efficacy. However, while some patients benefit from VGB treatment, others do not, or develop so-called "tolerance", i.e. a loss of efficacy after initial good response. In order to find criteria for the identification of responders to VGB treatment we have performed several studies using ^{1}H-MRS with the editing sequence for selective enhancements of GABA signals, developed at our site.

Methods: GABA concentrations were measured in the the temporal lobes and occipital lobes in epileptic patients with MTLE, and occipital lobe epilepsy. In a subpopulation of epileptic patients we measured GABA, N-acetylaspartate (NAA), creatine plus creatine phosphate (Cre), choline containing compounds (Cho), glutamate/glutamine (Glu/Gln) and Myo-inositol. For the measurement of these metabolites, the point-resolved spectroscopy (PRESS) localization sequence and short (TE = 30 ms) and long (TE = 136) echo times were used. Resonance spectra were measured in the volume of interest (VOI) in the normal tissue near the presumed epileptic focus and on the contralateral side.

Patients in the VGB study were measured before the treatment, after a titration period of one month (1 g/d VGB during the 1st week, 1.5 g/d week during the 2nd, and 2 g/d during the last two weeks), and after a maintenance period of 3 months during which the dose could be increased to 3 g/d if necessary. At the end of the maintenance period all patients had a steady dose for at least one month. In the occipital lobe the VOI was 8 ccm, in the lateral TL region it was 7.8 ccm.

Main *findings* of hitherto performed studies in partial epilepsies are [24–26].

The decrease in NAA, which serves as a neuronal marker in the adult brain, measured in the hippocampus *in vivo* in patients with MTLE before selective amygdalohippocampectomy correlated well with the degree of hippocampal sclerosis assessed by histopathological analysis of resected tissue samples.

In MTLE patients ^{1}H-MRS was not only able to lateralize the epileptogenic focus in agreement with invasive or semi-invasive EEG recordings, but also revealed metabolic impairment in over 50% of patients in the contralateral hippocampus.

Within a small subgroup of young MTLE patients with early onset age of seizures evidence was found for an association between the duration of the epileptic disorder and the decrease of NAA ipsi- as well as contralateral to the primary focus.

With a specific spectral-editing sequence for resolution enhancement of GABA resonance signals, a dose-dependent increase of GABA in the brain of healthy volunteers taking VGB was demonstrated.

GABA-edited ^{1}H-MRS measurements were able to identify responders to VGB treatment. Full-responders (defined as patients with a ≥50% seizure reduction at the end of the maintenance period) and "partial responders" (defined as patients with a ≥50% seizure reduction after the titration period but <50% at the end of the maintenance period) had a significant lower brain GABA level ipsilateral and contralateral to the epileptogenic focus. However, in full- and partial-responders GABA levels were significantly lower ipsilateral to the focus compared to the contralateral homotopic region. A steep increase during

Figure 9 ^{1}H-MRS measured brain GABA levels (circled) before [2] and after [3] GABA-ergic treatment with Vigabatrin. (Courtesy of Dr. med. S. Müller)

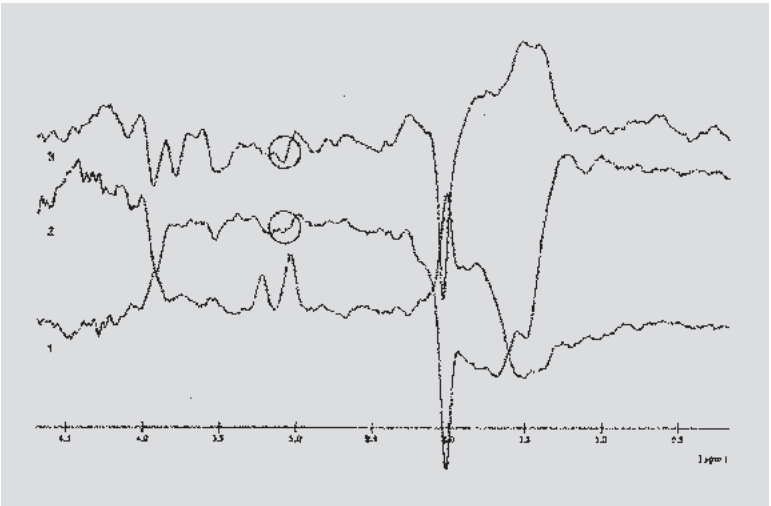
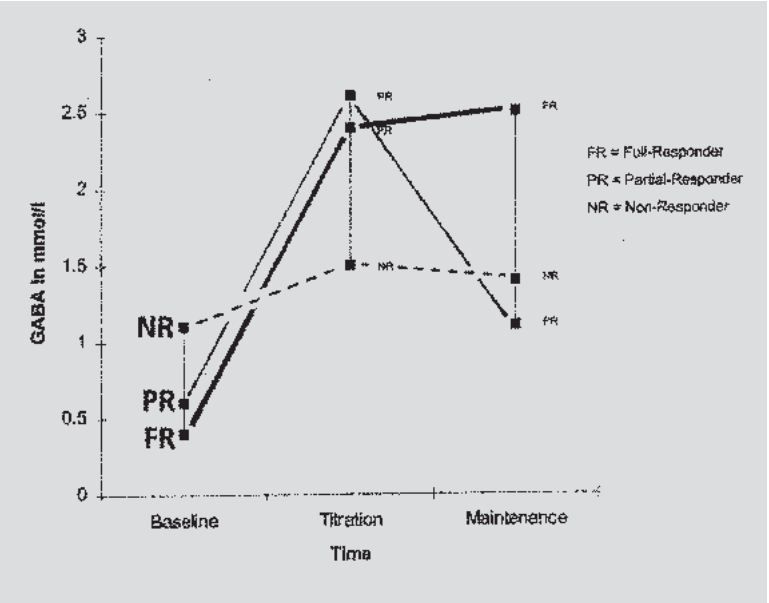


Figure 10 ^{1}H-MRS measured brain GABA levels before (baseline) and after (titration period, maintenance periods) Vigabatrin treatment allow for prediction of responders to GABA-ergic treatment with Vigabatrin. Full-responders (FR) and partial-responders (PR, defined as patients with a ≥50% seizure reduction after the titration period but <50% at the end of the maintenance period) had a significant lower brain baseline GABA level and a steep increase during the titration period. This increase of VGB-induced brain GABA was significantly higher in full- and partial-responders compared to "non-responders". (Courtesy of Dr. med. S. Müller)



the titration period characterized full- and partial responders. This increase of VGB-induced brain GABA was significantly higher in full- and partial responders compared to "non-responders" (defined as patients with a <50% seizure reduction during both the titration and the maintenance period).

Whereas in full-responders the GABA levels remained high, in partial-responders GABA-levels decreased in parallel with the development of "tolerance" to VGB.

Most interesting the VGB-levels were similar when measured near the epileptogenic focus as compared to measurements distant to the focus, indicating that the underlying biochemical abnormality reflects a more wide-spread phenomenon (see Figures 9 and 10).

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