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Clinical Neurophysiology 116 (2005) 493–505

www.elsevier.com/locate/clinph

The First International Collaborative Workshop on Seizure Prediction: summary and data description

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Accepted 7 August 2004
Available online 5 January 2005

Summary

The First International Collaborative Workshop on Seizure Prediction was held at the Department of Epileptology, University of Bonn, in Bonn, Germany on April 24–28, 2002. Organized by the Universities of Pennsylvania and Bonn, and funded by grants from the American Epilepsy Society, the German Section of the International League against Epilepsy, and the German Section of the International Federation of Clinical Neurophysiology, the workshop was attended by 51 researchers from 16 centers in seven countries. There were four major goals for the workshop: (1) to host a one-day didactic session on the science of seizure prediction, with lectures by leaders in the field; (2) to assess the current state of the field by applying current methods used to predict seizures to a shared set of continuous intracranial EEG data and discussing the strengths and weaknesses of each approach; (3) to establish a consensus on minimal data requirements, a common nomenclature, and objective methods for comparing system performance across platforms and laboratories for seizure prediction research; and most importantly (4) to establish a multi-laboratory, international working group dedicated to understanding seizure generation and making on-line, prospective seizure prediction a reality. Following the didactic course, each participating group presented their results, after applying their seizure prediction methods to five common data sets agreed upon in advance and distributed before the meeting. What follows is a description of the shared data set used for analysis, a summary of the major discussion points from the workshop, and points of consensus among the group. The brief discussion serves as a common introduction to the research papers that follow in this issue, and the description of the shared data is referenced in each of these papers. Participants in the workshop are listed at the end of the Conclusions section, in alphabetical order.

1. Introduction

Seizure prediction or anticipation (the terms are used interchangeably), is a topic of great interest in the clinical and basic neuroscience communities, not only for its potential clinical application in warning and therapeutic devices, but because it holds great promise for increasing our understanding of the mechanisms underlying epilepsy. Over the past 15 years, a number of research groups have demonstrated that a measurable pre-seizure period exists, and heralds seizure onset in many patients with temporal and some types of extratemporal epilepsy.

After some early work on the predictability of seizures dating back to the 1970's (Viglione and Walsh, 1975), attempts to extract seizure precursors from the EEG were carried out by different groups using mostly linear approaches such as spectral analysis (Duckrow and Spencer, 1992; Rogowski et al., 1981) or pattern detection by analyzing spike occurrence rates (Gotman and Koffler, 1989; Gotman and Marciani, 1985; Katz et al., 1991; Lange et al., 1983; Wieser, 1989). The earliest attempts to use nonlinear time series analysis were started in the 1990's (Iasemidis et al., 1990, 1994) using the largest Lyapunov exponent to describe changes in brain dynamics. The first studies to describe characteristic changes shortly before an impending seizure in a larger group of patients used the correlation dimension as an estimate for neuronal

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1388-2457/$30.00
doi:10.1016/j.clinph.2004.08.020

complexity (Elger and Lehnertz, 1998; Lehnertz and Elger, 1995, 1998) and the correlation density (Martinerie et al., 1998). These studies were followed by others using measures such as dynamic similarity (Le Van Quyen et al., 1998, 2000, 2001; Navarro et al., 2002), entropy (Van Drongelen et al., 2003), predictability (Drury et al., 2003), or certain signal patterns ('bursts') and changes in signal energy (Litt et al., 2001). Most of these analyses employ univariate measures. More recently bivariate measures, namely the difference of the largest Lyapunov exponents of two channels (Iasemidis et al., 2001), nonlinear interdependence (Arnhold et al., 1999), measures for phase synchronization and cross correlation (Mormann et al., 2000, 2003a,b) as well as a multivariate approach based a fusion of multiple features with neural networks (Litt et al., 2001) and on simulated neuronal cell models (Schindler et al., 2002) have been shown to be capable of defining a pre-seizure period. For an overview, see (Litt and Echauz, 2002; Litt and Lehnertz, 2002; Special Issue on Seizure Prediction, 2001, 2003).

The methods employed in seizure prediction are mathematically complex and not easily accessible to those outside of the world of physicists, mathematicians, and engineers. The work, in its most promising form, requires large amounts of high quality, continuous intracranial EEG data, which are very difficult to acquire in a busy, noisy clinical environment. In addition, despite excellent work in the field, convincing Class I evidence demonstrating unequivocal seizure prediction in blinded, prospective, randomized clinical trials has been elusive. There are a number of reasons for this, in addition to the challenge of developing algorithms to detect the unknown patterns associated with seizure generation. There has been no accepted test data set, and we lack standardized methods and nomenclature for marking continuous EEG data. There are currently no accepted methods for assessing performance of seizure prediction algorithms, although recent attempts aim at bridging this gap (Andrzejak et al., 2003; Aschenbrenner-Scheibe et al., 2003; Kreuz et al., 2004; Winterhalder et al., 2003). Even a clear definition of exactly what constitutes seizure onset and seizure prediction/anticipation are difficult to obtain. For these reasons, beginning with an impromptu meeting at the American Epilepsy Society Meeting in Los Angeles, California in 2000, the International Seizure Prediction Group was formed to provide an informal structure for the major groups working in this area to share data and ideas. A specific goal of this structure is to move the field forward from 'proof of principle' experiments into validated, well-understood methods that can be applied in basic-science and clinical applications.

Specific issues that have recently caused controversy in the field of seizure prediction include: (1) defining the time of seizure onset to which prediction results are compared; (2) defining the prediction horizon, the time window prior to seizure onset in which seizure forecasts are made; (3) predicting seizures by comparing 'baseline' data segments to pre-seizure segments and looking for changes associated with the pre-seizure period; (4) the lack of methods for prospectively forecasting the probability of seizure onset over a given period; and (5) the lack of universally accepted performance measures for seizure prediction algorithms beyond sensitivity, specificity, false negative and false positive rate; specifically the lack of measures demonstrating that algorithm performance is better than random.

The above ideas and other points were discussed in detail at the workshop during the presentation of results by each research group and during a final discussion session at the end of the meeting. Some general conclusions and points of consensus are highlighted in the sections below. The individual papers that accompany this introduction represent each group's research results presented at the meeting, some claiming prediction and some stating that an association with prediction could not be found. The papers, as printed, are not meant to demonstrate implementation of points of consensus from the meeting, but rather the state of the field prior to these points. As the reader will see, they encompass a variety of methods, results and points of controversy. No attempt was made at the workshop to establish the superiority of one method over another, but rather, great effort was made to focus on common ground, agreement between methods, and on the pros and cons of each approach.

2. Data requirements for the workshop

2.1. Clinical

In an attempt to make data analysis and interpretation as straightforward as possible, participating groups were instructed to supply data from patients with uncomplicated unilateral temporal lobe epilepsy, preferably with mesial temporal onset. Data sets were to be complete hospital stays, without gaps greater than 5 min, if possible, and to include at least 3 seizures over a minimum of 48 h, with at least 4 h between seizures or seizure clusters. Ideally, patients were to be seizure-free after surgery (Engel Class I outcome), and sleep–wake cycle information and daily antiepileptic drug levels were requested, but in general these were not obtainable, as these measurements were not routinely acquired by each participating center. Patients were to be between the ages of 18 and 65. In summary, the clinical requirements for data were specified so that there was a high probability that seizures all came from a single region in one temporal lobe, and that there were electrodes, subdural strips and amygdalo-hippocampal depth electrodes, placed as close as possible to the epileptic focus.

2.2. Technical

Technical requirements for EEG data were specified so that all data were distributed in the same digital format

and easily reconstructed, viewed and processed by participants. Data were to be digitized at a minimum sampling rate of 200 Hz, with minimum resolution of 10 bits, and stored in binary format as 16-bit integers. The reference electrode and amplification factor were identified for each recording, and each participating center provided a map of intracranial electrode placement, and a table listing all recording channels and unequivocal seizure onset times, as defined by each group. Electrode contacts with high impedance or very frequent artifacts were identified and were to be removed from each data set. Data were stored in multiplexed format, and provided either from a 'sample and hold' or corrected sequential sampling analog to digital conversion. The first 10 s of each file and around each seizure were printed out and provided with each data set, to insure appropriate translation of the files for processing. The date and time of the first sample in each file were provided, and the time of clear electrographic onset of each seizure was marked, and listed by sample number. Formats for the header of each data file were provided for each patient.

Data sets were sent by each center to the University of Pennsylvania Engineering and Epilepsy Laboratory, where they were copied, burned onto compact disks, and distributed in a binder, with all accompanying technical and clinical information, to each center participating in the workshop.

3. Description of common data sets

Data sets listed below in alphabetical order were provided from the following departments:

- *Data set A*. The Stichting Epilepsie Instellingen Nederland (SEIN), Dutch Epilepsy Clinics Foundation, Heemstede, The Netherlands; courtesy of D. N. Velis, MD.
- *Data set B*. Department of Epileptology, University of Bonn, Germany; courtesy of C. E. Elger, MD, PhD, FRCP and K. Lehnertz, PhD.
- *Data set C*. Department of Neurology, University of Florida, USA; courtesy of J. C. Sackellares, MD and L. D. Iasemidis, PhD.
- *Data set D*. The Comprehensive Epilepsy Center at Kansas University Medical Center, USA; courtesy of I. Osorio, MD.
- *Data set E*: Department of Neurology, University of Pennsylvania, USA; courtesy of B. Litt, MD and Gordon Baltuch, MD, PhD.

All data sets were recorded intracranially from patients with temporal lobe epilepsy who underwent presurgical evaluation in the respective institutes/departments. Tables 1 and 2, and Fig. 1 below demonstrate characteristics of data sets as they were recorded and submitted for evaluation.

The clinical and technical descriptions below are those provided by each group with their data set. They are purposefully left in the format submitted, so as to highlight the nomenclature and approach of each group to intracranial electrode placement and presurgical evaluation in these patients. Each group submitted data for this project only after obtaining appropriate informed consent from patients and clearance from the institutional research review board (IRB) or equivalent, granting permission for sharing data, in accordance with the requirements of their respective institutions.

Table 1
Technical specifications of test data

Data set	Sampling rate (Hz)	A to D conversion	BandPass (Hz)	# Channels
A	480	16 bits	0.16-70	32
B	200	16 bits	0.30–70	48
C	200	10 bits	0.10–70	32
D	239.75	10 bits	0.10–100	53
E	200	12 bits	0.50–70	81

3.1. Data set A

3.1.1. Patient characteristics

The patient was a 45-year-old-male admitted for resective epilepsy surgery at SEIN, Dutch Epilepsy Clinics Foundation, 'Meer en Bosch' Campus, Heemstede, The Netherlands. The patient suffered from intractable epilepsy and had been treated with sufficient doses of CBZ, VPA, PHT, VGB, TPM and LZP in various combinations without adequate seizure control. He was right handed and had a WAIS total IQ of 94 with a harmonic distribution. Scalp/sphenoidal CCTV/EEG monitoring suggested presence of bilateral independent epileptogenic regions. The most prominent one was located over an extensive area of the right temporal lobe, consistent with an MRI abnormality suggesting presence of mesial temporal sclerosis (MTS). Seizure semiology was stereotyped, suggestive of a temporal lobe origin with early involvement of the frontal lobes. However, there was no definitive lateralizing information. Furthermore, similar seizure semiology was accompanied by a different ictal EEG pattern. The patient successfully underwent an intracranial amobarbital procedure (Wada test) and was cleared for implantation.

Table 2
Patterns of seizure occurrence per test data set: time (mean and standard deviation) between consecutive seizures (ISI), and number of seizures with less than 4 h inter-seizure interval

Data set	#Seizures	ISI (h)	#Seizures (ISI < 4 h)
A	3	13.9 ± 13.7	0
B	10	5.9 ± 4.8	4
C	15	3.9 ± 3.5	10
D	6	8.1 ± 6.0	1
E	17	3.6 ± 3.0	8

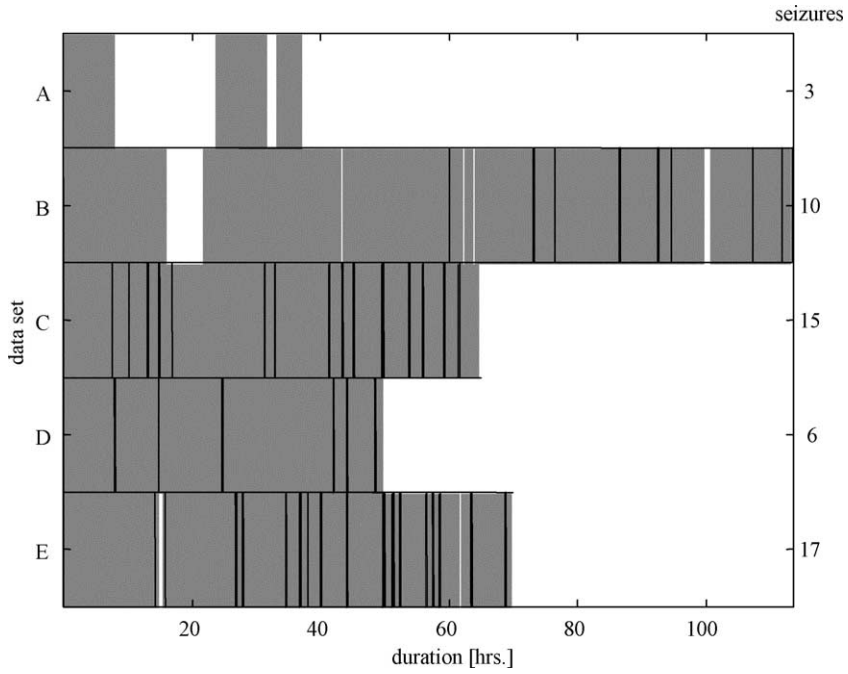

Fig. 1. Length of test data for each group. White blocks or white vertical lines within each bar indicate gaps in data; black vertical lines denote seizures and gray horizontal bars denote length of the recording. Note, that no seizures are marked on the timeline for data set A due to the reasons given in the description of this data set.

Subdural and intracerebral electrodes (Brain Electronics, B.V., Houten, The Netherlands) were implanted (see Fig. 2) according to previous findings from clinical history, neuroimaging, neuropsychology, and scalp/sphenoidal video EEG monitoring. Maintenance antiepileptic drugs (PHT 350 mg, TPM 400 mg and LZP 10 mg) were tapered but not stopped.

The patient underwent a tailored right temporal resection in December of 2002 including complete amygdalohippocampectomy and removal of part of the right inferior frontal gyrus. Intraoperative ECoG confirmed the findings of the interictal intracranial EEG study. The pathological anatomy report indicated presence of severe MTS. There was some evidence of neuronal loss in the temporal neocortex and there were focal patches of disturbed neuronal organization in the frontal cortex removed. The patient has remained free of complex partial seizures (Engel outcome class 1B) on medication (PHT, LEV, CLB) with a follow-up period of 17 months.

3.1.2. Data set information

A total of 12 spontaneously occurring complex partial seizures were harvested during a recording spanning nine 24-h-periods of cable telemetry EEG/video seizure monitoring at which time the recording was only interrupted when the patient was bathing in his room. The intracranial EEG records of three clinically manifest and habitual complex partial seizures were selected because they met the criteria agreed upon in the Bonn 2002 Workshop preparatory meeting held in the Spring of 2001, e.g. a first (or 'leader') seizure occurring at least 8 h into the actual recording and two follow-up seizures occurring at least four hours apart and preceded by at least four hours of interictal EEG. The data files consist of 16 bits signed integers, channel multiplexed with 32 channels. EEG was sampled at 480 Hz per channel and band-pass filtered filtered between 0.16 and 70 Hz. The sensitivity is 0.732 μV per unit ($1 <-> 0.732$ μV).

The data files of the two first seizures (i.e. the 'leader seizure' and 'follow-up seizure 1') contain discontinuities approximately 15 min prior to unequivocal electrographic onset (see Fig. 1). These discontinuities are due to external manipulation of the preamplifier (recognized as high amplitude movement artifacts for all channels) and disconnecting the telemetry synch from the preamplifier (recognized as signal loss for all channels) while the patient was assisted by the nursing staff during morning bathing. The third file does not contain any discontinuities. The data files end at electrographic onset of the seizure, i.e. the full-blown ictal record is not included. Seizure onsets occurred at contacts HCR H5 and H6 (right hippocampus). Seizure activity subsequently involved the right anterior and lateral temporal convexity, the right orbitofrontal and inferior frontolateral convexity, the left hippocampus and the left temporal and frontal neocortex in the classical sequential activation pattern. Electrographic seizure onset preceded clinical onset by an average of 30 s, which coincided with the time when seizure activity invaded the right frontal lobe, as seen on the subdural contacts located over the right orbitofrontal and inferior frontal convexity.

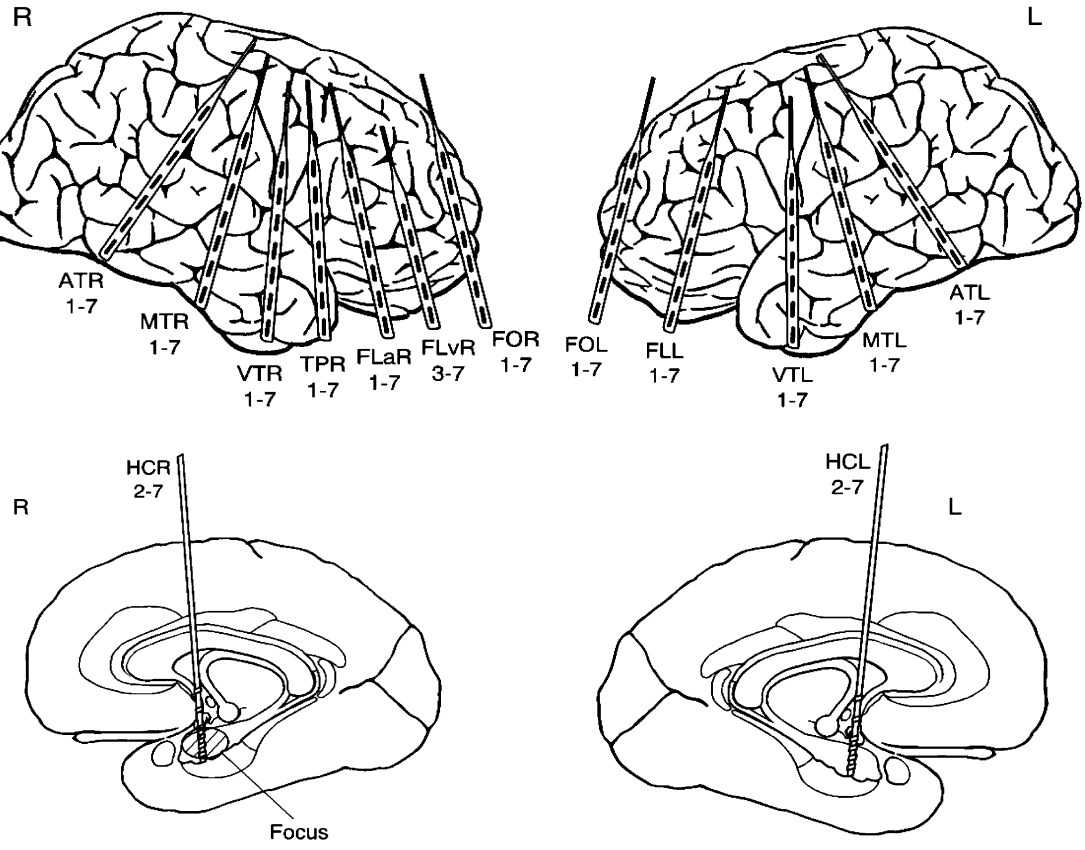

Fig. 2. Electrode implantation scheme for data set A. Subdural electrodes were manufactured as semirigid reeds of MRI compatible metal alloy and consisted of equidistantly placed contacts with a length of 7.5 mm and an inter-contact distance of 7.5 mm. Intracerebral electrodes consisted of MRI compatible metal alloy twisted multistranded microwires having a total of four equidistantly placed contacts each 2.5 mm long. The most distal contact was located at a distance of 2 mm from the tip of each intracerebral electrode or subdural reed. Implantation of bilaterally introduced and symmetrically placed stereo-electrodes aimed at the hippocampus and multi-contact subdural reeds over the frontal, central, temporal and parietal convexities all through two symmetrically placed frontal skull trephine holes of approximately 2.5 cm in diameter was carried out. The position of the hippocampal contacts was verified by postoperative MRI. Channels HCL K5 and HCL K6 record from the left hippocampus; channels HCR H5, HCR H6 and HCR H7 record from the right hippocampus. All other channels record from subdural contacts. The most distal contacts of the subdural electrodes are labeled #1, and #2 for the intracerebral electrodes. The hatched area denotes the region of electrical seizure onset.

3.1.3. Recording techniques

Continuous 32 channel EEG recording was obtained using a Vickers Medelec DG32 Compact system (Oxford Medical, Old Wocking, UK) and a SEIN-manufactured optically isolated PCM encoder and preamplifier system. Data were written on a magneto-optical drive medium. There were no intentional interruptions in the data other than the time gaps between consecutive files (file closing on a magneto-optical drive medium change and resuming with next file opening on next magneto-optical drive medium).

3.2. Data set B

3.2.1. Patient characteristics

The patient is a 19-year-old right-handed male with simple partial (5/month) and complex partial seizures (10/month) referred for presurgical evaluation in February of 2001. Prolonged (duration: 15–30 min.) febrile seizures occurred at age of 5, 5.5, and 6. Family history was negative for epilepsy and other neurological diseases. Seizures manifested at age of 15 and were characterized by an epigastric aura lasting for about 10 s and were sometimes followed by manual and oral automatisms, staring, impaired consciousness and behavioral arrest. Postictal disorientation lasted for 6–8 min, with complex automatisms. The patient had amnesia for the whole period. Earlier medication included valproic acid, carbamazepine, lamotrigene, topiramate and levetiracetam either as monotherapy or in combination. MRI scans showed left mesial temporal sclerosis. PET scan was unremarkable. Right-sided temporal lobe seizure onset was found with surface EEG recordings. Invasive recordings showed left mesial temporal lobe seizure onset. The patient underwent selective amygdalo-hippocampectomy in June of 2001 and has been seizure-free (Engel outcome class 1A) within a follow-up period of 25 months. Postoperative histopathological evaluation showed Ammon's horn sclerosis.

3.2.2. Data set information

The data set consists of a 6-day quasi-continuous recording (see Fig. 1). Twice the patient was briefly (13 and 54 min) disconnected from the EEG acquisition system. A longer discontinuity (340 min) was necessary to carry out an MRI scan to determine the exact location of the implanted electrodes. Prior to the invasive phase of the presurgical evaluation, all antiepileptic drugs other than carbamazepine and levitiracetam were withdrawn. The remaining medications were tapered, reaching zero medication at day 4, and were re-introduced during days 5 and 6. During the first 3 days, three sub-clinical events were recorded either during the night or in the evening. On the third day, the patient was asked to perform a hyperventilation (three blocks of 3 min duration each). During days 4–6, 10 spontaneous typical clinical seizures occurred.

3.2.3. Recording techniques

Electrocorticograms and stereoelectroencephalograms were recorded under video control from bilaterally implanted (see Fig. 3) subdural strip and intrahippocampal depth electrodes (Ad-Tech, Inc.).

EEG signals from a total of 48 channels were passed to an amplifier system (Stellate Systems, Montreal, Canada and Schwarzer, Munich, Germany) with band-pass filter settings of 0.3–70 Hz using an average common reference. After 16 bit A/D conversion the data was written continuously onto a disk of a data acquisition computer system at a sampling rate of 200 Hz.

3.3. Data set C

3.3.1. Patient characteristics

A 41-year-old, right-handed female with seizures since the age of 8 years following measles infection. She was considered medically intractable since the age of 11 years. Before the admission to the hospital for evaluation with invasive EEG electrodes (phase II), she used to have 10–15 simple partial seizures and 15–20 complex partial seizures per month. Simple partial seizures were accompanied by a fearful feeling, while complex partial seizures progressed from a feeling of fear to unresponsiveness with her right hand going to her chest and shaking. During this period she might be unresponsive and in a postictal state for up to 30 min. Over the years, she had been on multiple medications. Upon admission, she was on Dilantin and Neurontin. Invasive EEG recordings showed right mesial temporal lobe seizure onset. The patient has been seizure-free (Engel outcome class I) after selective right amygdalo-hippocampectomy within a follow-up period of 8 years.

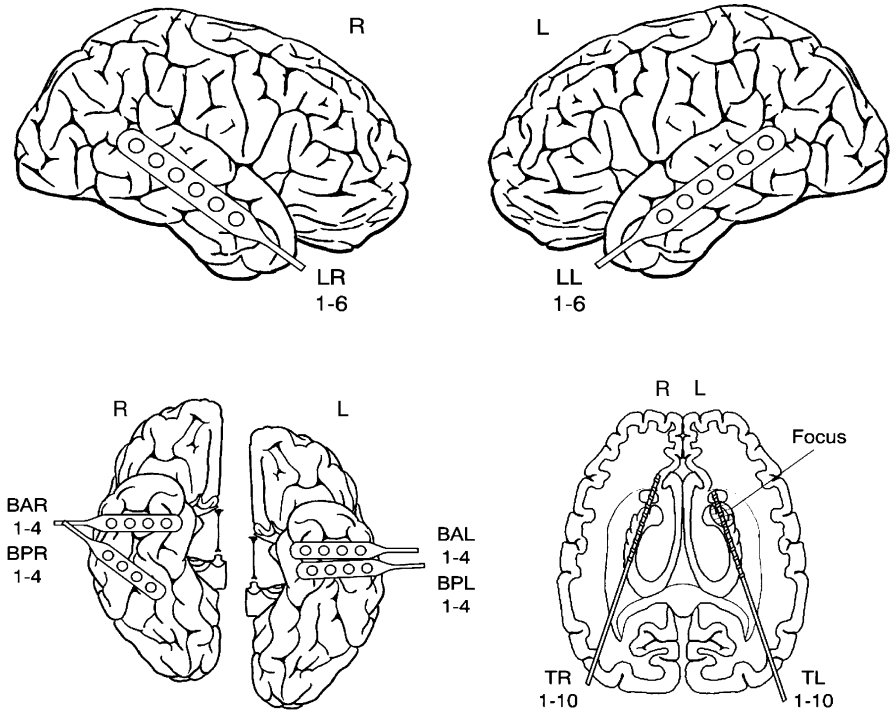

Fig. 3. Electrode implantation scheme for data set B. Intrahippocampal depth electrodes were implanted stereotaxically along the longitudinal axis of the hippocampal formation from an occipital approach with the amygdala as the target for the most anterior electrode. Each catheter-like, 1 mm thick silastic electrode contained 10 cylindrical contacts of a nickel–chromium alloy (2.5 mm) every 4 mm. Subdural strip electrodes consisted of 4–6 stainless steel contacts with a diameter of 2.2 mm, embedded in a silastic strip (intercontact spacing of 10 mm), and were inserted through burr holes. These electrodes were placed over the anterior and posterior inferior temporal cortex and over the medial temporal gyrus. The most distal contact of each electrode is labeled #1. The hatched area denotes the region of electrical seizure onset.

3.3.2. Data set information

The data set consists of about 2.5 days of continuous, without any gaps, EEG recordings and includes 15 spontaneous typical clinical seizures (see Fig. 1). These data were recorded after a period of about 5 days following patient's admission to the hospital and progressive tapering of the antiepileptic medication. During that period, no clinical or subclinical seizures were recorded. All recorded seizures, except seizure 6, originated from the right hippocampus and were secondarily generalized partial complex seizures. Seizure 6 appeared to originate from left mesial temporal structures. Antiepileptic medication started to be reintroduced after seizure 5. The patient was asleep at the onset of seizures 1–5 and 12–14, awake at 6–11, awake/asleep at the onset of seizure 15. Interictally, as well as in the baseline period, frequent spikes and spike trains appear in the right temporal lobe and right hippocampus occasionally accompanied with a slowing in the left orbito-frontal lobe.

3.3.3. Recording techniques

Video/EEG monitoring using implanted depth and subdural strip electrodes (see Fig. 4) was performed with a Nicolet BMSI 4000 EEG machine.

EEG signals from a total of 32 channels were recorded with band-pass filter settings of 0.1–70 Hz using an average common reference. The data were A/D sampled at 200 Hz with a 10-bit quantization and recorded on VHS tapes continuously over days via three time-interleaved VCRs. Decoding of the data from the tapes and transfer to computer media (hard disks, CD-ROMs) was subsequently performed offline.

3.4. Data set D

3.4.1. Patient characteristics

The patient is a 41-year-old woman with complex partial seizures since age 13, occurring with a frequency of 5–10/month, with a tendency to cluster pre-menstrually. At the time of evaluation this subject was on carbamazepine 400 mg tid and had received all first-line antiseizure drugs and also gabapentin without improvement. Additionally, a trial with progesterone was of no benefit. Neurological examination was non-focal. MRI showed decreased volume in the left hippocampal formation with slightly increased signal intensity in the area of the dentate gyrus. Neuropsychologic evaluation showed significant compromise of complex attention, speed of functioning, confrontational naming and lexical verbal fluency.

3.4.2. Data set information

Continuous CCTV-Electrocorticogram (ECoG) was recorded from bilateral mesial temporal, and frontal lobes. Six typical seizures originating from the left amygdalo-hippocampal region, with rapid spread to ipsilateral orbitofrontal and contralateral mesial temporal structures were recorded during the hospitalization. Carotid sodium amytal injections revealed left hemispheric dominance for

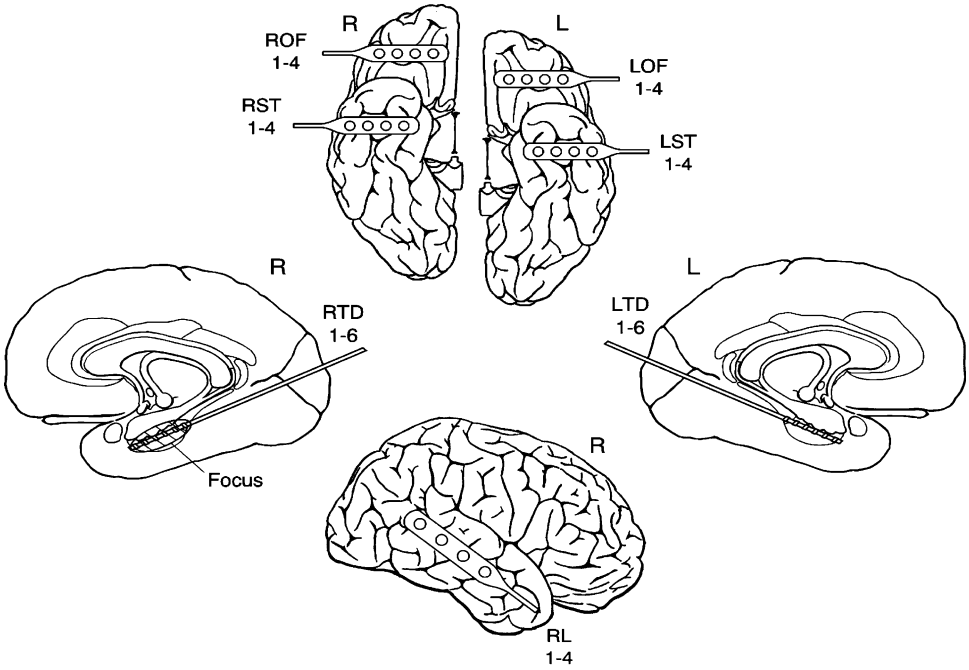

Fig. 4. Electrode implantation scheme for data set C. Bilateral depth electrodes were implanted stereotaxically along the longitudinal axis of the hippocampal formation from an occipital approach. The most anterior electrode contact was located adjacent to the amygdala. Two subdural strip electrodes were placed bilaterally over the orbitofrontal and over the temporal lobes. In addition, a right lateral subtemporal strip was placed over the right middle temporal gyrus. The most distal contact of each electrode is labeled #1. The hatched area denotes the region of electrical seizure onset.

language and highly asymmetrical memory performance (left mesial structures did not support memory). A modified left temporal lobectomy was performed in 1997. The subject had no new post-operative deficits and has remained free of seizures on a reduced dose of carbamazepine (200 mg bid).

3.4.3. Recording techniques

Since scalp recording was not clearly lateralizing, each temporal lobe was implanted with three depth electrodes, along the lateral plane. In addition, two frontal electrodes were aimed at the orbital frontal regions (see Fig. 5).

Two-channel EKG was also simultaneously recorded and included in the data set. All data (Video/ECoG) were recorded to VHS tape with front-end amplifier filters of 0.5–70 Hz, a sampling rate of 239.75 Hz, using a common reference (a quiet contact—the outermost contact on the left posterior temporal electrode), and digitized with 10 bits of precision and a dynamic range of $+/-0.3$ mV (0.59 μV/bit). The data were recorded continuously during the entire patient stay. The contributed data set consists of 180043.7 s ($\sim$50 h) of continuously-recorded data containing the 6 clinical seizures (see Fig. 1).

3.5. Data set E

3.5.1. Patient characteristics

The patient is a 25-year-old, right-handed woman referred for presurgical evaluation in August of 2001. She had her first febrile seizure at age 2, with no other early risk factors for epilepsy. She had onset of epilepsy at age 17, when she began to experience events, initially in the evening and at night, characterized by a 'gas-like smell,' followed by a sensation of déjà vu and then staring. Episodes were followed by a headache and fatigue. She was amnestic of all of her seizures. Events initially occurred approximately two times per week. Prior to evaluation, the patient had only two secondarily generalized, convulsive events, both in her early twenties. Medication trials included phenytoin and carbamazepine, both of which caused allergic reactions (primarily rash), and then valproic acid, topiramate, and lamotrigene, all pushed to toxicity as monotherapy and in combination. Family history was remarkable for a maternal uncle with seizures. Physical and neurological examinations were normal. MRI of the brain was unremarkable. PET scan

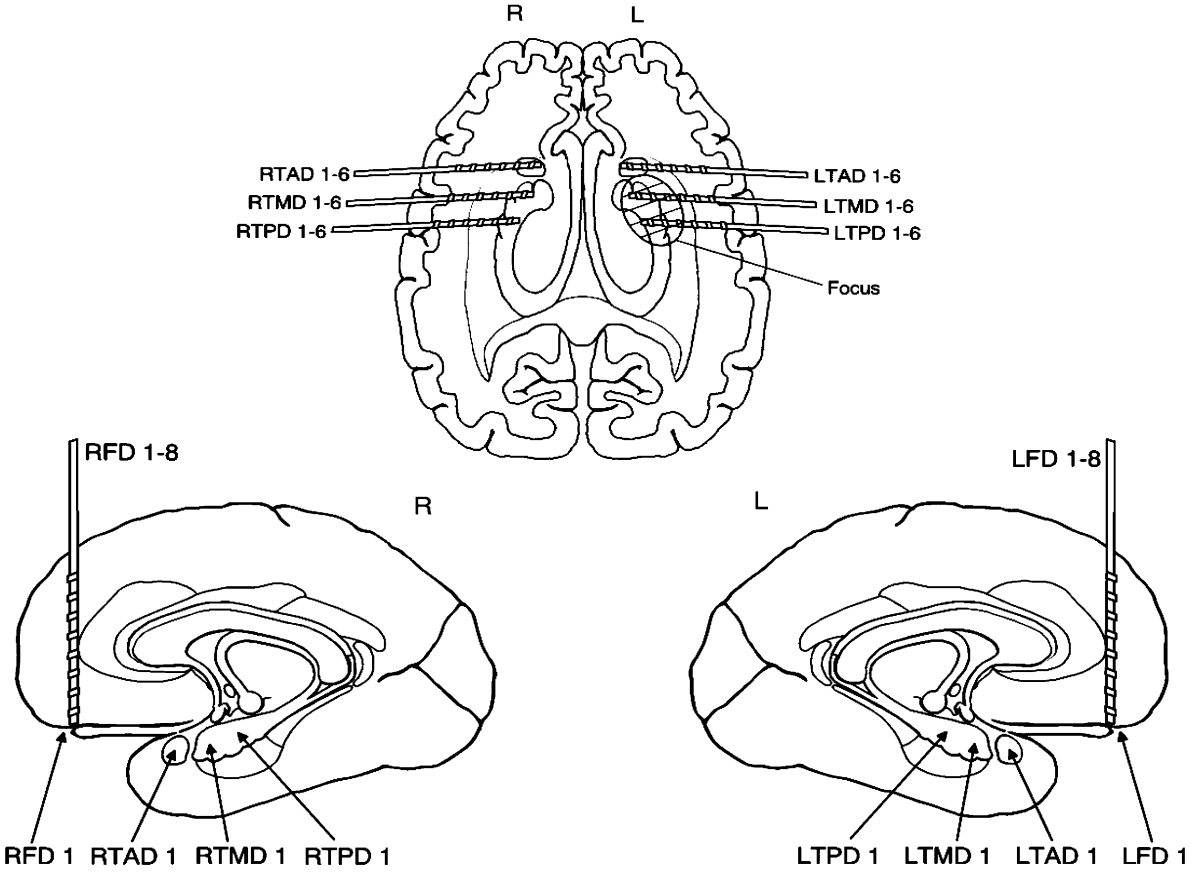

Fig. 5. Electrode implantation scheme for data set D. The depth electrode contacts are platinum, 1.1 mm diameter cylindrical each 2.3 mm in length with 7.7 mm inter-contact spacing. The anterior temporal electrodes were implanted stereotaxically into the amygdala, the middle ones into the anterior hippocampus (close to the pes), and the posterior ones about 13.5 mm behind the middle electrode. The frontal electrodes have identical material, contact size and spacing as the temporal electrodes, but have eight contacts each. They were aimed at the orbital frontal regions, through a superior (dorsal convexity) approach. The most distal contact of each electrode is labeled #1. The hatched area denotes the region of electrical seizure onset.

demonstrated bitemporal hypometabolism, neuropsychological testing showed full scale IQ of 73, verbal IQ of 71 and performance IQ of 79. Scalp video-EEG monitoring demonstrated interictal epileptiform activity arising from the right anterior temporal region, with rare contralateral discharges, and a single spontaneous seizure with right anterior temporal onset over a 1-week medication taper. Because of non-localizing brain imaging, PET and neuropsychological evaluations, the patient was admitted for phase II video-EEG monitoring with bilateral depth and subdural strip electrodes (Ad-Tech, Inc.). The patient has been seizure-free (Engel outcome class 1A) after right standard anterior temporal lobectomy with amygdalo-hippocampectomy in March of 2002.

3.5.2. Data set information

The patient was monitored continuously for a period of 69 h over 4 days. During the monitoring period the patient had 17 partial seizures, all arising from the right hippocampus and inferior temporal neocortex. Ten seizures arose from sleep. Nine of the 17 recorded events were clinically accompanied by either a brief arousal from sleep or no clinical signs. The first seizure, which occurred 13.5 h into the recording, secondarily generalized. The remaining seven seizures were typical complex partial events. There were minimal gaps in the recording (see Fig. 1).

3.5.3. Recording techniques

EEG and video were recorded on a Nicolet-5000 epilepsy monitoring system (Nicolet Biomedical, Madison Wisconsin). EEG was digitized at 400 Hz through a hard-wired bandpass of 0.1–200 Hz, and then automatically down-sampled by the manufacturer's equipment to 200 Hz when down-loaded to computer hard-drive and then archived to compact disks. Analog to digital conversion was performed with 12-bit resolution at a gain of 1.08 μV/bit. Eighty-one electrode contacts were placed, including three depth electrodes on each side placed via the transverse (Montreal) approach in the amygdala, anterior hippocampus and posterior hippocampus, respectively, bilateral subdural strips over the dorsal lateral frontal neocortex, posterior temporal neocortex, and inferior temporal neocortex (see Fig. 6).

High impedance electrodes were removed from the distributed recordings. One technical problem arose during data analysis, as the last seizure was recorded after the patient pulled the right depth electrodes out approximately one half centimeter during a period of confusion, changing the channel of earliest and maximal onset for this seizure.

3.6. Comments on the data

As seen in Tables 1 and 2, and in Fig. 1, several centers were able to find data sets that satisfied entry criteria for

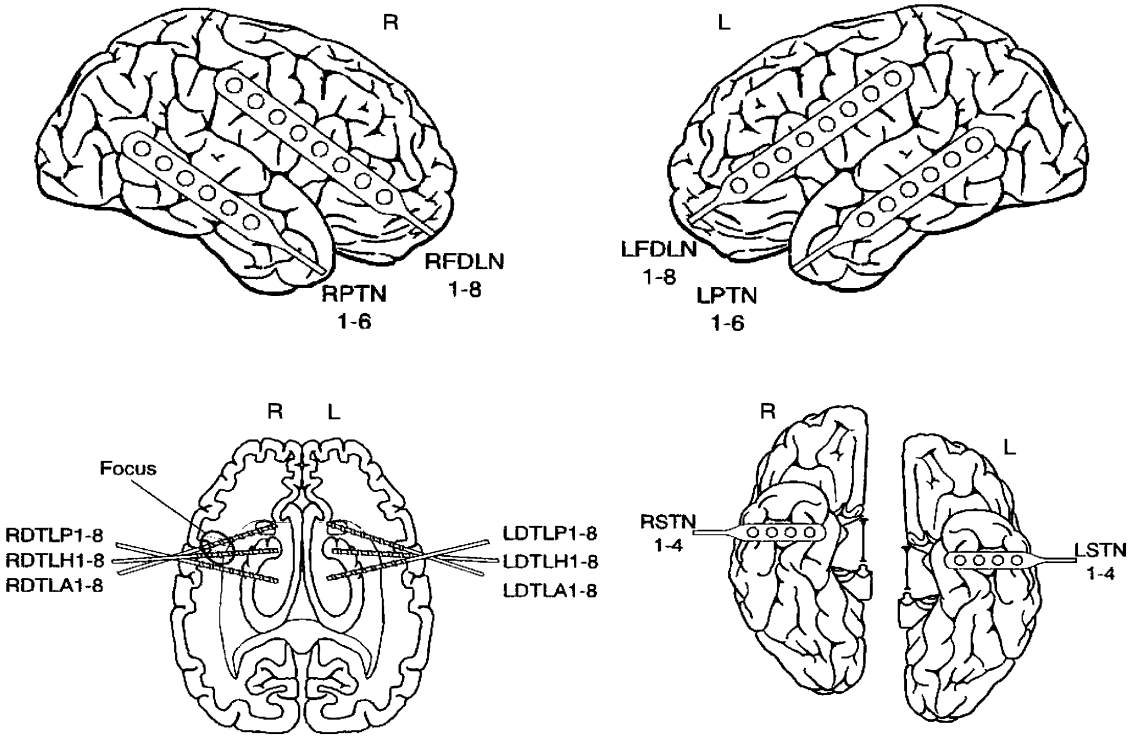

Fig. 6. Electrode implantation scheme for data set E. Depth electrodes contained eight cylindrical contacts 2.3 mm long, 1.0 cm apart on center, which were placed stereotaxically using an introducing stylette. Subdural strip electrodes (Ad-Tech, Inc.) were 1.0 cm apart on center, 4.0 mm in diameter, with 2.3 mm exposure through a silastic membrane. Electrode placement was verified by post-operative MRI. The most distal contact of each electrode is labeled #1. The hatched area denotes the region of electrical seizure onset.

the workshop, with minimal gaps during recording. During the data collection process, it became clear that clinical protocols, such as follow-up imaging, machine and reference electrode failures are great challenges in assembling continuous, high quality data sets for recording.

Narrow bandwidth, limited to 70 Hz in most data sets, eliminated high frequency data, which might be of interest, but it is not clear from the methods used in this workshop that this affected results. Movement of electrodes, as mentioned above, appeared to change the epileptic focus in the last seizure in data set E. Fortunately, this type of problem is relatively rare, but still needs to be taken into consideration in prediction analysis.

Of interest, the three longest data sets included very frequent seizures, though no requirements other than >3 seizures in the data were posted for data submission to the workshop. It is assumed that the contributing centers chose these patients in the hope of providing more opportunity for obtaining reproducible results. Each of these sets had clusters of seizures, defined by some groups as seizures spaced closer than 4 h apart (see Table 2). It is not clear what impact seizure clusters had on prediction results, however, at least one group's methods demonstrate that seizure generation may be different in clustered than 'leading' seizures. Also of note, only one group was able to provide sleep–wake data for analysis, which has been demonstrated to be required for some of the methods presented in the papers that follow. For this reason, sleep–wake data were not provided or used in any prediction analysis, potentially compromising these methods.

3.7. Points of discussion and consensus

The 4 days of the workshop were comprised as much of periods of spirited discussion as they were of scientific presentations. Prior to the workshop, the organizers (BL and KL) gave Jean Gotman, a participant, a list of questions to address at the workshop, so that Dr Gotman could stimulate discussion on these topics. Some of these questions, and the discussion that followed, are touched on briefly below. They summarize much of what was discussed at the workshop and some main points of consensus.

3.7.1. What are appropriate data requirements for seizure prediction studies and statistical validation? How can we make seizure prediction results believable?

The group's consensus was that in order to demonstrate believable seizure prediction, results had to be demonstrated on a large data set, collected by different individuals in a variety of conditions and in patients demonstrating a variety of epilepsy syndromes. The group agreed that validating algorithms on data gathered by other centers was the best overall test of algorithm performance. The group emphasized the importance of performing prospective studies, relating results to raw EEG data, and to investigating data of all kinds without pre-selection.

The group also agreed that the current workshop was an important first step toward achieving this goal. Some concern was raised regarding the relationship between the time horizon for seizure prediction (e.g. how far in advance seizures are predicted) and the density of seizures in a record. The group responded that no data selection criteria should be imposed to space seizures a certain distance apart, however, there was agreement that prediction validation should be statistically sound, that outputs of prediction algorithms be shown, in addition to numerical results, and that it should be statistically demonstrated that 'real' prediction results be distinguished from those that could be achieved by chance. The group agreed that the data selection criteria should be explicitly stated, and that great care should be taken to demonstrate that the method was not developed and tailored to the experimental data collected. It was agreed that experimental data should represent all conditions and states of consciousness. There was considerable discussion on the use of 'baseline' data segments on analysis. While baseline segments were felt to be useful for prediction algorithms, especially as a method for reducing computational burden, it was also the groups opinion that choice of baseline segments, even if done randomly, could exert great influence over experimental results. In general, the group felt that it would be best to avoid the use of baseline segments because of statistical and practical considerations associated with interpreting such experimental designs.

Participants also voiced concern that a decline in invasive monitoring due to better patient selection and improved functional imaging would eventually make a diverse archive of intracranial EEG more difficult to acquire in the future. There was consensus that finding or establishing a formal funding mechanism for assembling an internationally accessible archive of intracranial EEG data from the full spectrum of refractory partial epilepsy was a priority for seizure prediction research.

3.7.2. What is a seizure? Is it a clinical event, an EEG event, or both?

Participants at the workshop suggested that this was one of the main issues obscuring seizure prediction, particularly the question of whether seizure generation was part of a continuum of activity whose beginning might be minutes or even hours prior to clinical onset, and that predicting seizure onset might only be measuring seizure generation in its early stages. Exactly defining what constitutes a seizure, all agreed, is not possible, without further knowledge of the basic mechanisms underlying seizure generation. A more practical definition of seizure, as was used at the workshop, is a function of the methods used to observe it. Participants suggested that other methods, such as functional imaging (e.g. fMRI) and biochemical markers might be relevant to defining seizure onset and to seizure prediction research in the future, but these tools are not practical at present. For example, it might be possible to monitor the generation of spontaneous seizures in humans or animal models of

epilepsy with functional imaging protocols, looking for activation of broad regions in the epileptic network over the periods of time identified to be important to seizure generation, such as thalamus and nigral pathways. In this way functional imaging might compensate for the very narrow spatial sampling necessitated by invasive electrophysiologic monitoring. These techniques might be tuned to imaging on particular biomarkers for neuronal activity, such as compounds related to glutamate or GABA synthesis or metabolism. More rapid imaging sequences, currently being tested, might provide better temporal resolution than current methods tuned primarily to blood flow. Similarly, monitoring biomarkers associated with gene transcription and protein synthesis, in well defined models, may give more insight into mechanisms underlying seizure generation.

There was a general consensus that for the time being, the type of seizure prediction research that was the focus of the workshop should concentrate on EEG events, rather than requiring clinical symptoms, since intracranial EEG provides the most straightforward way to define seizures at this time. Some participants raised concern that overtly clinical and subclinical (or less overtly clinical) seizures may be different enough to warrant separate analysis, particularly if algorithms are to be implemented in a therapeutic device in which delivering treatment has some 'cost,' such as side effects, decreased battery life etc. For this workshop, participants visually identified the time of seizure onset on the intracranial EEG in two ways: (1) the time of earliest clear change from the patient's baseline or normal background EEG that eventually led to an electrographic seizure, and (2) the time at which a clear, unequivocal ictal pattern on the EEG was easily identified. The group recognized the importance of clinical symptoms accompanying ictal EEG changes, but given imperfect methods for determining exact clinical as well as EEG onset times for seizures, it was proposed that reference to EEG onset of seizures was preferred, as opposed to clinical seizure onset.

3.7.3. What results should be presented in seizure prediction studies?

There was no general consensus on what results should be presented in seizure prediction studies. Suggested measures included:

1. Receiver-operator characteristic (ROC) curves, including measures of sensitivity/specificity or false positives/negatives
2. Prediction horizon (within what time frame are seizures 'predictable?')
3. Percentage of patients in whom seizures are 'predictable,' by a given method
4. Raw products (outputs) of prediction methods plotted over time
5. Correlation of 'predictors' with the raw EEG (or other EEG parameters, such as power spectra, etc.)
6. Computational requirements

3.7.4. Can all seizures be predicted?

This question generated considerable controversy. Given the heterogeneity of epilepsy, some participants postulated that some types of seizures might not be predictable, and that determining which types of seizures could be predicted was a priority. There was some discussion that primary generalized epilepsies differ greatly from partial disorders, and might, therefore, be less predictable. Other forms of reflex epilepsy, in which seizures are abruptly precipitated by sensory stimulation (e.g. somatosensory reflex epilepsy provoked by sound, touch etc., photoconvulsive epilepsy—precipitated by photic stimulation, 'calculating epilepsy,' by manipulating series of numbers etc.) might also not be predictable, given that they are precipitated acutely by a sensory stimulus. Other participants remarked that a specific seizure disorder, for example mesial temporal lobe epilepsy, might be precipitated in different ways at different times, some of which might be predictable and others may not. For example, spontaneous complex partial seizures might be predictable over hours, but clinically indistinguishable seizures in the same individual precipitated by a toxic exposure (e.g. alcohol) or a drug (e.g. ephedra), might not be predictable. By the end of the workshop there was consensus that this point of controversy quickly leads to a discussion of basic neurophysiological mechanisms underlying seizure generation, and would be best addressed at the next collaborative workshop, which would be focused more on mechanisms underlying seizure generation in humans and animal models of epilepsy. It was agreed that a discussion of which types of seizures might be predictable was perhaps less relevant to the narrow focus of this first workshop on temporal lobe epilepsy, in which significant evidence supporting seizure prediction, both quantitatively and clinically, has gained more acceptance. It was the group's consensus in setting up this workshop that it was best to start with the simplest and best understood substrate for predicting seizures before moving on to more challenging seizure types and disorders.

4. Conclusions

At the end of the First International Collaborative Workshop on Seizure Prediction there appeared to be a consensus that this initial meeting was a success, and an important step in moving research into seizure generation forward. The papers that follow in this issue embody many of the controversial points discussed at the workshop. Several papers present methods that did not demonstrate that seizures were predictable in the test data, generating considerable debate. Other studies were able to identify periods of increased probability of seizure onset, but generated controversy either due to statistical considerations, comparing baseline to pre-seizure segments, or for other technical reasons. Finally, some work presented at

the workshop focused on seizure spread, and seemed to be only peripherally related to prediction, though these methods may provide useful tools to follow the spread of seizure precursors during seizure generation. One important controversy, which was not resolved at the conference, was the need to use several complementary quantitative methods to capture the diverse group of changes leading to seizure onset, which may vary greatly from patient to patient. At least two groups presented data supporting this conclusion, though other groups felt equally strongly that single parameters could accomplish equal or better 'predictivity.'

Most importantly, the efforts represented in the papers produced by the workshop are seen as a very important initial step in creating an international collaborative group that shares data and discusses results and controversies in a collegial, constructive environment. In this goal there was universal agreement that the workshop was successful. At the end of the meeting the attendees agreed to publish our work together, and set the following goals:

1. To establish an international database of complete, high quality intracranial EEG recordings representing the full spectrum of partial epilepsies for use in validation studies of methods for seizure prediction/anticipation
2. To plan other consecutive meetings to further advance this work, our collaboration and to expand the group's interest into mechanisms underlying seizure generation
3. To attempt to be more inclusive of others with similar interests in further workshops, as funding allows.

It should be stressed that as a result of this meeting, a task force of the International League Against Epilepsy has been appointed to look at standardization of data to facilitate this type of collaborative research projects, as well as to facilitate sharing of clinical data to achieve better patient care.

Whether more scientific goals with regard to advancing the field of seizure prediction were met at the workshop is left to the reader's judgement. We can clearly state that the workshop was enjoyed by everyone who attended it. A number of new scientific approaches, collaborations and friendships have sprung up as a result of the group's first gathering, and the field continues to move forward with accelerating speed. We are anxiously looking forward to our next meeting.

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Acknowledgements

Dr. Litt's research has been funded by the The Whitaker Foundation, The Esther and Joseph Klingenstein Foundation, The Dana Foundation, The American Epilepsy Society, The CURE Foundation, the Partnership for Pediatric Epilepsy and through a grant from the National Institutes of Health, Grant # RO1NS041811-01. We are grateful to the generous financial support provided in the form of grants from the American Epilepsy Society, the German Section of the International League against Epilepsy, and from the German Section of the International Federation of Clinical Neurophysiology, which made this meeting possible. We also wish to express our gratitude to Christian Elger and the Department of Epileptology of the University of Bonn, for hosting the meeting and arranging lodging and meals for all participants. Special thanks to Judith Hoffmann, M.D., for supervising all workshop functions, group meals, academic and social functions for the visiting faculty and graduate students; to Steve Cranstoun for organizing, copying and distributing the shared data sets; to Landi Parish for her work in data distribution and handling travel arrangements, registration and reimbursements on site; and to Gregor Gast for his work in the preparation of the standardized brain schematics.

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