Robert Fisher, MD, PhD

The Maslah Saul Professor in the Department of Neurology and Professor, by courtesy, of Neurosurgery at the Stanford University Medical Center

Neurology & Neurological Sciences

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Bio

Dr. Fisher is Maslah Saul MD Professor and Director of the Stanford Epilepsy Center. He had research awards from the Klingenstein Foundation, EF, CURE and NIH. He published 160 peer-reviewed articles and 5 books. He was named 1996-2013 in Best Doctors in America. He received the Ambassador Award from the International League Against Epilepsy, the 2005 AES Service Award and the 2006 Annual Clinical Research Award. Dr. Fisher is Past-President of the American Epilepsy Society, and has served on the Board of the ILAE and as Editor-in-Chief of the Journal, Epilepsia. He is past Editor-in-Chief of the website epilepsy.com. His research is on new devices to treat epilepsy.

Clinical Focus

- Epilepsy
- Neurology
- EEG
- Consciousness, Loss of
- Convulsion, Non-Epileptic
- Epilepsy, Complex Partial
- Epilepsy, Generalized
- Epilepsy, Temporal Lobe
- Epilepsy, Tonic-Clonic

Academic Appointments

- Professor - Med Center Line, Neurology & Neurological Sciences
- Professor - Med Center Line (By courtesy), Neurosurgery
- Member, Stanford Neurosciences Institute

Administrative Appointments

- Executive Committee, International League Against Epilepsy (2000 - 2005)
- Editor-In-Chief, Epilepsia (2000 - 2005)
- Director, Neurology Teaching, Stanford (2000 - Present)
- Professor (by courtesy), Neurosurgery (2000 - Present)
- Director, Epilepsy Center, Stanford (2000 - Present)
- Maslah Saul MD Professor of Neurology, Stanford Medical Center (2000 - Present)
- President, American Epilepsy Society (1999 - 2000)
- Chair of Neurology, Barrow Neurological Institute, Phoenix, AZ (1998 - 2000)

- President, Epilepsy Society of Arizona (1997 - 1999)
- Professional Advisory Board, Epilepsy Foundation of America (1990 - 2004)

Honors & Awards

- Best Doctors in America, Woodward and White (1998-2014)
- Pierre Gloor Award, American Clinical Neurophysiology Society (Annual National EEG Award) (2010)
- Annual International Clinical Research Award, American Epilepsy Society (2006)
- Editor-in-Chief, Epilepsia, International League Against Epilepsy (2001-2006)
- President, American Epilepsy Society (2000)
- Ambassador Award, International League Against Epilepsy (2000)
- National Service Award, American Epilepsy Society (2004)
- Hans Berger Award, American EEG Society (1976)
- Frank Ford Award for Teaching, Johns Hopkins Hospital (1984)
- Member, Marquis' Who's Who in America (2000)

Professional Education

- Board Certification: Epilepsy, American Board of Psychiatry and Neurology
- Residency:Stanford University Medical Center (1979) CA
- Board Certification: Clinical Neurophysiology, American Board of Psychiatry and Neurology (1992)
- Board Certification: Neurology, American Board of Psychiatry and Neurology (1983)
- Fellowship:Johns Hopkins University School of Medicine (1982) MD
- Internship:Stanford University Medical Center (1978) CA
- Medical Education:Stanford University School of Medicine (1977) CA
- BS, Caltech, Biology (1971)
- M.D., Stanford, Medicine (1977)
- Ph.D., Stanford, Neuroscience (1976)

Community and International Work

Editor-in-Chief, epilepsy.com, www.epilepsy.com

Topic

The World's most visited epilepsy website

Partnering Organization(s)

Epilepsy Therapy Project

Populations Served

The Epilepsy Community

Location

International

Ongoing Project

Yes

Opportunities for Student Involvement

No

Epilepsy Foundation of N. California Board, Oakland, CA

Topic

Epilepsy advocay and education

Partnering Organization(s)

Epilepsy Foundation of America

Populations Served

N. Calif. Epilepsy Community

Location

International

Ongoing Project

Yes

Opportunities for Student Involvement

No

International League Against Epilepsy Board, Brussels, Belgium

Topic

World Epilepsy

Partnering Organization(s)

international Bureau for Epilepsy

Populations Served

World Epilepsy Community

Location

International

Ongoing Project

No

Opportunities for Student Involvement

No

The Epilepsy Project Advisory Board, New York

Topic

Funds Innovative Approaches to Epilepsy Therapy

Partnering Organization(s)

Epilepsy Foundation, CURE

Populations Served

Epilepsy Community

Location

US

Ongoing Project

Yes

Opportunities for Student Involvement

No

Epilepsy Foundation, Professional Board, Landover, Maryland

Topic

Epilepsy Research, Education and Advocacy

Partnering Organization(s)

EFA

Populations Served

Epilepsy Community

Location

US

Ongoing Project

Yes

Opportunities for Student Involvement

No

President, Epilepsy Society of Arizona, Phoenix, AZ

Topic

Epilepsy Education and Advocacy

Partnering Organization(s)

Epilepsy Foundation of America

Populations Served

People with epilepsy and their families

Ongoing Project

No

Opportunities for Student Involvement

No

Editor-in-Chief

Topic

Epilesia (Journal)

Partnering Organization(s)

International League Against Epilepsy

Populations Served

Neurologists

Location

International

Ongoing Project

Yes

Opportunities for Student Involvement

No

Executive Committee

Topic

International Epilepsy Research and Education

Partnering Organization(s)

International League Against Epilepsy

Populations Served

Epilepsy Professionals

Location

International

Ongoing Project

Yes

Opportunities for Student Involvement

No

Contact

Academic
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Links

Curriculum Vitae PDF
NIH Biosketch PDF
Stanford Epilepsy Center

Research & Scholarship

Current Research and Scholarly Interests

Dr. Fisher is interested in clincal, laboratory and translational aspects of epilepsy research. Prior work has included: electrical deep brain stimulation for epilepsy, studied in laboratory models and clinical trials; drug delivery directly to a seizure focus in the brain; mechanisms of absence (petit mal) epilepsy and how the physiology and chemistry of brain changes in this disorder; hyperthermic (high-temperature) seizures; diagnosis and treatment of non-epileptic seizures, the post-ictal state (the condition in the aftermath of a seizure); driving and epilepsy; new antiepileptic drugs; surgery for epilepsy.

Clinical Trials

- Epilepsy Impact Scale **Recruiting**
  The investigators are developing a questionnaire that can quickly measure the impact that epilepsy has on a person's life. This questionnaire will be useful in following whether the impact of epilepsy increases, decreases or stays the same over time. The results also may point out areas that would benefit from discussion or attention in visits with your doctor.

  View full details

- VNS Therapy Automatic Magnet Mode Outcomes Study in Epilepsy Patients

Exhibiting Ictal Tachycardia (E-37) **Recruiting**
Obtain baseline clinical outcome data (Stage 1) upon which to base a subsequent study (Stage 2) of the Model 106 VNS implantable pulse generator

View full details

- SANTE - Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy
  Not Recruiting
  The purpose of this research is to study the safety and effectiveness of bilateral stimulation of the anterior nucleus of the thalamus as adjunctive therapy for reducing the frequency of seizures in adults diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to antiepileptic medications.

  Stanford is currently not accepting patients for this trial.

  View full details

Teaching

2014-15 Courses

- Independent Studies (7)
  - Directed Reading in Neurology and Neurological Science
    NENS 299 (Aut, Win, Spr, Sum)
  - Directed Reading in Neurosciences
    NEPR 299 (Win, Spr, Sum)
  - Early Clinical Experience in Neurology and Neurological Sciences
    NENS 280 (Aut, Win, Spr, Sum)
  - Graduate Research
    NENS 399 (Aut, Win, Spr, Sum)
  - Graduate Research
    NEPR 399 (Win, Spr, Sum)
  - Medical Scholars Research
    NENS 370 (Aut, Win, Spr, Sum)
  - Undergraduate Research
    NENS 199 (Aut, Win, Spr, Sum)

Publications

All Publications

- Stimulation of the medial septum should benefit patients with temporal lobe

epilepsy *MEDICAL HYPOTHESES* Fisher, R. S. 2015; 84 (6): 543-550

Abstract

Electrical stimulation of the septal nuclei via deep brain stimulating electrodes is proposed as a potentially beneficial therapy for medication-resistant temporal lobe epilepsy. In a multicenter study, stimulation of anterior thalamus was shown to reduce numbers of seizures, but decrease was only in the range of 40%. This might be improved with septal stimulation, which has strong and direct reciprocal connections with the hippocampal formation, the structure most involved in temporal lobe epilepsy. Medial septal neurons drive a 3-12Hz theta rhythm in hippocampus of rodents. Theta rhythm is less obvious in human hippocampus, but it is present and it varies with cognitive tasks. The hippocampal theta rhythm is disrupted by seizures. In animal models, restoration of theta by sensory stimulation, septal electrical stimulation or cholinergic drugs infused into septum ameliorates seizures. Seizure activity in hippocampus is faithfully reflected in septal nuclei, and septum sometimes leads the seizure activity. A subset of patients with temporal lobe epilepsy have structural enlargement of their septal nuclei. At high levels of intensity, septal stimulation is subjectively pleasurable and strongly reinforcing. Rats will repeatedly press a bar to stimulate their septum. Initial experience with human septal stimulation in the 1950s was not favorable, with ineffective therapy for schizophrenia and a high rate of surgical complications. Subsequent experience in 50-100 pain patients employing modern neurosurgical techniques was more favorable and demonstrated septal stimulation to be safe and tolerable. The current state of knowledge is sufficient to consider design of a clinical trial of medial septal stimulation in selected patients with medication-resistant temporal lobe epilepsy.

View details for DOI 10.1016/j.mehy.2015.02.016

View details for Web of Science ID 000355357600004

View details for PubMedID 25771138

- Use of an online epilepsy diary to characterize repetitive seizures *EPILEPSY & BEHAVIOR* Fisher, R. S., Bartfeld, E., Cramer, J. A. 2015; 47: 66-71

Abstract

Little is known about patterns of seizures that occur multiple times a day, sometimes called clusters or serial seizures.The online diary, My Epilepsy Diary (MED), provided self-reported data from community-based patients to describe the characteristics of clusters.We used MED data to define a population of 5098 community outpatients, including 1177 who specified time of multiple seizures in a 24-hour period. Outcomes included cluster prevalence and frequency, distribution of interseizure time intervals, as well as the types of triggers commonly reported.One-fourth of days with any seizures included clusters for these patients. Most days with clusters included 2 seizures, with >5 events occurring in only 10% of days. One-third of seizures occurred within 3h of the initial event and two-thirds within 6h. When more than 2 seizures occurred, the time to the next seizure decreased from an average of over 2h (to the 3rd event) to a quarter-hour (from the

4th to the 5th event).My Epilepsy Diary data have provided the first overview of cluster seizures in a large community-based population. Treatments with less than 3-hour duration of action would be bioavailable at the time of only one-third of subsequent seizures. Although limited by the self-reported and observational nature of the diary data, some general patterns emerge and can help to focus questions for future studies.

View details for DOI 10.1016/j.yebeh.2015.04.022

View details for Web of Science ID 000356366900011

View details for PubMedID 26046724

- Redefining epilepsy *CURRENT OPINION IN NEUROLOGY* Fisher, R. S. 2015; 28 (2): 130-135

Abstract

In 2014, the definition of epilepsy was revised by the International League Against Epilepsy (ILAE).A conceptual definition of epilepsy was proposed by the ILAE in 2005, as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by its psychosocial consequences. Practical application of the epilepsy definition usually is taken to mean at least two unprovoked seizures more than 24□ apart, but a 2014 practical definition refines the description. With this definition, epilepsy is a disease of the brain with either: (1) at least two unprovoked (or reflex) seizures occurring more than 24□ apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals past the applicable age of an age-dependent epilepsy syndrome or those who have remained seizure-free for the past 10 years, with no seizure medicines for the past 5 years.A consensus process has refined the definition of epilepsy.

View details for DOI 10.1097/WCO.0000000000000174

View details for Web of Science ID 000351332600007

View details for PubMedID 25734953

- Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology* Salanova, V., Witt, T., Worth, R., Henry, T. R., Gross, R. E., Nazzaro, J. M., Labar, D., Sperling, M. R., Sharan, A., Sandok, E., Handforth, A., Stern, J. M., Chung, S., Henderson, J. M., French, J., Baltuch, G., Rosenfeld, W. E., Garcia, P., Barbaro, N. M., Fountain, N. B., Elias, W. J., Goodman, R. R., Pollard, J. R., Tröster, A. I., Irwin, C. P., Lambrecht, K., Graves, N., Fisher, R. 2015; 84 (10): 1017-1025

Abstract

To report long-term efficacy and safety results of the SANTE trial investigating deep brain stimulation of the anterior nucleus of the thalamus (ANT) for treatment of localization-related epilepsy.This long-term follow-up is a continuation of a previously reported trial of 5- vs 0-V ANT stimulation. Long-term follow-up began 13 months after device implantation with stimulation parameters adjusted at the investigators' discretion. Seizure

frequency was determined using daily seizure diaries.The median percent seizure reduction from baseline at 1 year was 41%, and 69% at 5 years. The responder rate (⩾50% reduction in seizure frequency) at 1 year was 43%, and 68% at 5 years. In the 5 years of follow-up, 16% of subjects were seizure-free for at least 6 months. There were no reported unanticipated adverse device effects or symptomatic intracranial hemorrhages. The Liverpool Seizure Severity Scale and 31-item Quality of Life in Epilepsy measure showed statistically significant improvement over baseline by 1 year and at 5 years ($p < 0.001$).Long-term follow-up of ANT deep brain stimulation showed sustained efficacy and safety in a treatment-resistant population.This long-term follow-up provides Class IV evidence that for patients with drug-resistant partial epilepsy, anterior thalamic stimulation is associated with a 69% reduction in seizure frequency and a 34% serious device-related adverse event rate at 5 years.

View details for DOI 10.1212/WNL.0000000000001334

View details for PubMedID 25663221

- Electroencephalographic features of moyamoya in adults *CLINICAL NEUROPHYSIOLOGY* Frechette, E. S., Bell-Stephens, T. E., Steinberg, G. K., Fisher, R. S. 2015; 126 (3): 481-485

Abstract

Electroencephalography is useful for evaluating transient neurological events in the setting of moyamoya disease.EEG findings of adults with moyamoya seen at a large moyamoya referral center are summarized. Patients were identified by retrospective chart review.EEGs were ordered after cerebral revascularization for altered mental status, aphasia, limb shaking, or facial twitching. Among the study population of 103 patients having EEGs, 24% of adults with moyamoya had a history of clinical seizures. Ischemic or hemorrhagic strokes were associated with a twofold relative risk of seizures. Overall, 90% of EEGs were abnormal, most commonly focally (78%), or diffusely slow (68%). Epileptiform EEG discharges were seen in 24%. Whereas hemispheres with an ischemic stroke had a 19% risk of epileptiform discharges and an 8% risk of seizures on EEG, hemispheres with hemorrhagic stroke had a 35% risk of epileptiform discharges and 19% risk of seizures on EEG. Focal amplitude attenuation was seen in 19%, breach rhythm in 15%, rhythmic delta in 14%, and electrographic seizures in 12%.Seizures and epileptiform EEG changes are common in patients with moyamoya disease.Transient events in patients with moyamoya can result from seizures as well as ischemia.

View details for DOI 10.1016/j.clinph.2014.06.033

View details for Web of Science ID 000349616700010

View details for PubMedID 25065300

- Optogenetic fMRI reveals distinct, frequency-dependent networks recruited by dorsal and intermediate hippocampus stimulations. *NeuroImage* Weitz, A. J., Fang, Z., Lee, H. J., Fisher, R. S., Smith, W. C., Choy, M., Liu, J., Lin, P., Rosenberg, M., Lee, J. H. 2015; 107: 229-241

Abstract

Although the connectivity of hippocampal circuits has been extensively studied, the way in which these connections give rise to large-scale dynamic network activity remains unknown. Here, we used optogenetic fMRI to visualize the brain network dynamics evoked by different frequencies of stimulation of two distinct neuronal populations within dorsal and intermediate hippocampus. Stimulation of excitatory cells in intermediate hippocampus caused widespread cortical and subcortical recruitment at high frequencies, whereas stimulation in dorsal hippocampus led to activity primarily restricted to hippocampus across all frequencies tested. Sustained hippocampal responses evoked during high-frequency stimulation of either location predicted seizure-like afterdischarges in video-EEG experiments, while the widespread activation evoked by high-frequency stimulation of intermediate hippocampus predicted behavioral seizures. A negative BOLD signal observed in dentate gyrus during dorsal, but not intermediate, hippocampus stimulation is proposed to underlie the mechanism for these differences. Collectively, our results provide insight into the dynamic function of hippocampal networks and their role in seizures.

View details for DOI 10.1016/j.neuroimage.2014.10.039

View details for PubMedID 25462689

- Vagus nerve stimulation magnet activation for seizures: a critical review. *Acta neurologica Scandinavica* Fisher, R. S., Eggleston, K. S., Wright, C. W. 2015; 131 (1): 1-8

Abstract

Some patients receiving VNS Therapy report benefit from manually activating the generator with a handheld magnet at the time of a seizure. A review of 20 studies comprising 859 subjects identified patients who reported on-demand magnet mode stimulation to be beneficial. Benefit was reported in a weighted average of 45% of patients (range 0-89%) using the magnet, with seizure cessation claimed in a weighted average of 28% (range 15-67%). In addition to seizure termination, patients sometimes reported decreased intensity or duration of seizures or the post-ictal period. One study reported an isolated instance of worsening with magnet stimulation (Arch Pediatr Adolesc Med, 157, 2003 and 560). All of the reviewed studies assessed adjunctive magnet use. No studies were designed to provide Level I evidence of efficacy of magnet-induced stimulation. Retrospective analysis of one pivotal randomized trial of VNS therapy showed significantly more seizures terminated or improved in the active stimulation group vs the control group. Prospective, controlled studies would be required to isolate the effect and benefit of magnet mode stimulation and to document that the magnet-induced stimulation is the proximate cause of seizure reduction. Manual application of the magnet to initiate stimulation is not always practical because many patients are immobilized or unaware of their seizures, asleep or not in reach of the magnet. Algorithms based on changes in heart rate at or near the onset of the seizure provide a methodology for automated responsive stimulation. Because literature indicates additional benefits from on-demand magnet mode stimulation, a

potential role exists for automatic activation of stimulation.

View details for DOI 10.1111/ane.12288

View details for PubMedID 25145652

- The Personal Impact of Epilepsy Scale (PIES) *EPILEPSY & BEHAVIOR* Fisher, R. S., Nune, G., Roberts, S. E., Cramer, J. A. 2015; 42: 140-146

Abstract

The impact of epilepsy is manifest by effects related to seizures and side effects of therapy and comorbidities such as depression. This report describes the development of a brief patient-reported outcome (PRO) instrument, the Personal Impact of Epilepsy Scale (PIES), to measure the influence of epilepsy overall and in each of these domains.Instrument development followed standard procedures and an FDA Guidance. People with epilepsy were surveyed with open-ended questions to derive major themes of their concerns, resulting in 4 key areas: seizures, side effects, comorbidities, and overall quality of life (QOL). A preliminary set of 152 questions was based on these themes and completed by 50 patients, age 42.7 (range: 21-71) years, concurrent with comparator instruments, including the NH Seizure Severity Scale (NHSSS), the Liverpool Adverse Events Profile (LAEP), the Quality of Life in Epilepsy (QOLIE-31) scale, the Beck Depression Inventory, and the Epilepsy Foundation Depression: A Checklist. A multiple regression model indicated which PIES measures were associated with scores from the comparator instruments. Questions in each of the domains were selected for correlations and nonduplication. Test-retest consistency at a 3-day interval was completed by 38 subjects and a final set of questions constructed.The final question set comprised 25 items: 9 about characteristics of seizures, 7 about medication side effects, 8 about comorbidities, and 1 about overall quality of life. All items had 5 response choices (0-4), with higher scores reflecting more negative status. A total of 46 subjects completed the 25 questions. Cronbach's alpha was 0.87, indicating good internal consistency. Each of the three domains correlated well with the overall QOL item. The questions pertaining to seizures correlated with the NHSSS, the side effect questions with the LAEP, and the comorbidity questions with the QOLIE-31.The PIES provides a simple, brief PRO measure as a profile of overall impact of seizures, medication side effects, comorbidities, and overall QOL for people with epilepsy. Further study will explore sensitivity to change quantification of the minimal clinically significant change.

View details for DOI 10.1016/j.yebeh.2014.09.060

View details for Web of Science ID 000347048000027

View details for PubMedID 25450530

- Ictal tachycardia: The head-heart connection *SEIZURE-EUROPEAN JOURNAL OF EPILEPSY* Eggleston, K. S., Olin, B. D., Fisher, R. S. 2014; 23 (7): 496-505

Abstract

Epileptic seizures can lead to changes in autonomic function affecting the

sympathetic, parasympathetic, and enteric nervous systems. Changes in cardiac signals are potential biomarkers that may provide an extra-cerebral indicator of ictal onset in some patients. Heart rate can be measured easily when compared to other biomarkers that are commonly associated with seizures (e.g., long-term EEG), and therefore it has become an interesting parameter to explore for detecting seizures. Understanding the prevalence and magnitude of heart rate changes associated with seizures, as well as the timing of such changes relative to seizure onset, is fundamental to the development and use of cardiac based algorithms for seizure detection. We reviewed 34 articles that reported the prevalence of ictal tachycardia in patients with epilepsy. Scientific literature supports the occurrence of significant increases in heart rate associated with ictal events in a large proportion of patients with epilepsy (82%) using concurrent electroencephalogram (EEG) and electrocardiogram (ECG). The average percentage of seizures associated with significant heart rate changes was similar for generalized (64%) and partial onset seizures (71%). Intra-individual variability was noted in several articles, with the majority of studies reporting significant increase in heart rate during seizures originating from the temporal lobe. Accurate detection of seizures is likely to require an adjustable threshold given the variability in the magnitude of heart rate changes associated with seizures within and across patients.

View details for DOI 10.1016/j.seizure.2014.02.012

View details for Web of Science ID 000339603100002

View details for PubMedID 24698385

- Electrical brain stimulation for epilepsy *NATURE REVIEWS NEUROLOGY*
  Fisher, R. S., Velasco, A. L. 2014; 10 (5): 261-270

Abstract

Neurostimulation enables adjustable and reversible modulation of disease symptoms, including those of epilepsy. Two types of brain neuromodulation, comprising anterior thalamic deep brain stimulation and responsive neurostimulation at seizure foci, are supported by Class I evidence of effectiveness, and many other sites in the brain have been targeted in small trials of neurostimulation therapy for seizures. Animal studies have mainly assisted in the identification of potential neurostimulation sites and parameters, but much of the clinical work is only loosely based on fundamental principles derived from the laboratory, and the mechanisms by which brain neurostimulation reduces seizures remain poorly understood. The benefits of stimulation tend to increase over time, with maximal effect seen typically 1-2 years after implantation. Typical reductions of seizure frequency are approximately 40% acutely, and 50-69% after several years. Seizure intensity might also be reduced. Complications from brain neurostimulation are mainly associated with the implantation procedure and hardware, including stimulation-related paraesthesias, stimulation-site infections, electrode mistargeting and, in some patients, triggered seizures or even status epilepticus. Further preclinical and clinical experience with brain stimulation surgery should lead to improved outcomes by increasing our understanding of the optimal surgical candidates, sites and parameters.

View details for DOI 10.1038/nrneurol.2014.59

View details for Web of Science ID 000336264300005

View details for PubMedID 24709892

- ILAE Official Report: A practical clinical definition of epilepsy *EPILEPSIA* Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J., Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshe, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M., Wiebe, S. 2014; 55 (4): 475-482

Abstract

Epilepsy was defined conceptually in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24 h apart. The International League Against Epilepsy (ILAE) accepted recommendations of a task force altering the practical definition for special circumstances that do not meet the two unprovoked seizures criteria. The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off antiseizure medicines for at least the last 5 years. "Resolved" is not necessarily identical to the conventional view of "remission or "cure." Different practical definitions may be formed and used for various specific purposes. This revised definition of epilepsy brings the term in concordance with common use. A PowerPoint slide summarizing this article is available for download in the Supporting Information section here.

View details for DOI 10.1111/epi.12550

View details for Web of Science ID 000334657000005

- Rehospitalization and Emergency Department Use Rates Before and After Vagus Nerve Stimulation for Epilepsy: Use of State Databases to Provide Longitudinal Data Across Multiple Clinical Settings *NEUROMODULATION* Kalanithi, P. S., Arrigo, R. T., Tran, P., Gephart, M. H., Shuer, L., Fisher, R., Boakye, M. 2014; 17 (1): 60-65
View details for DOI 10.1111/ner.12051

View details for Web of Science ID 000331440000011

- How Can We Identify Ictal and Interictal Abnormal Activity? *ISSUES IN CLINICAL EPILEPTOLOGY: A VIEW FROM THE BENCH* Fisher, R. S., Scharfman, H. E., deCurtis, M. 2014; 813: 3-23

Abstract

The International League Against Epilepsy (ILAE) defined a seizure as "a transient occurrence of signs and/or symptoms due to abnormal excessive

or synchronous neuronal activity in the brain." This definition has been used since the era of Hughlings Jackson, and does not take into account subsequent advances made in epilepsy and neuroscience research. The clinical diagnosis of a seizure is empirical, based upon constellations of certain signs and symptoms, while simultaneously ruling out a list of potential imitators of seizures. Seizures should be delimited in time, but the borders of ictal (during a seizure), interictal (between seizures) and postictal (after a seizure) often are indistinct. EEG recording is potentially very helpful for confirmation, classification and localization. About a half-dozen common EEG patterns are encountered during seizures. Clinicians rely on researchers to answer such questions as why seizures start, spread and stop, whether seizures involve increased synchrony, the extent to which extra-cortical structures are involved, and how to identify the seizure network and at what points interventions are likely to be helpful. Basic scientists have different challenges in use of the word 'seizure,' such as distinguishing seizures from normal behavior, which would seem easy but can be very difficult because some rodents have EEG activity during normal behavior that resembles spike-wave discharge or bursts of rhythmic spiking. It is also important to define when a seizure begins and stops so that seizures can be quantified accurately for pre-clinical studies. When asking what causes seizures, the transition to a seizure and differentiating the pre-ictal, ictal and post-ictal state is also important because what occurs before a seizure could be causal and may warrant further investigation for that reason. These and other issues are discussed by three epilepsy researchers with clinical and basic science expertise.

View details for DOI 10.1007/978-94-017-8914-1_1

View details for Web of Science ID 000346021700003

View details for PubMedID 25012363

- Deep brain stimulation for epilepsy. *Handbook of clinical neurology* Fisher, R. S. 2013; 116: 217-234

Abstract

Deep brain stimulation for seizures has been applied to cerebellum, caudate, locus coeruleus, subthalamic nucleus, mammillary bodies, centromedian thalamus, anterior nucleus of thalamus, hippocampus and amygdala, hippocampal commissure, corpus callosum, neocortex, and occasionally to other sites. Animal and clinical studies have primarily investigated seizure prevention and, to a lessersmaller extent, seizure interruption. No studies have yet shown stimulation able to cure epilepsy. A wide variety of stimulation parameters have been employed in multiple different combinations of frequencies, amplitudes, and durations. Literature review identifies at least 52 clinical studies of brain stimulation for epilepsy in 817 patients. Two studies were large, randomized, and controlled, one in the anterior nucleus of thalamus and another at the cortical or hippocampal seizure focus; both of these studies showed efficacy and tolerability of stimulation. Many questions remain. We do not know the mechanisms, the best stimulation parameters, the best patient population, or how to predict benefit in advance. We do not know why benefit of neurostimulation for

epilepsy seems to increase over time or whether there are long-term deleterious effects. All of these questions may be answerable with a combination of laboratory research and clinical experience.

View details for DOI 10.1016/B978-0-444-53497-2.00017-6

View details for PubMedID 24112896

- Seizure diaries for clinical research and practice: Limitations and future prospects *EPILEPSY & BEHAVIOR* Fisher, R. S., Blum, D. E., Diventura, B., Vannest, J., Hixson, J. D., Moss, R., Herman, S. T., Fureman, B. E., French, J. A. 2012; 24 (3): 304-310

Abstract

An NINDS-sponsored conference in April of 2011 reviewed issues in epilepsy clinical trials. One goal was to clarify new electronic methods for recording seizure information and other data in clinical trials.This selective literature review and compilation of expert opinion considers advantages and limitations of traditional paper-based seizure diaries in comparison to electronic diaries.Seizure diaries are a type of patient-reported outcome. All seizure diaries depend first on accurate recognition and recording of seizures, which is a problem since about half of seizures recorded during video-EEG monitoring are not known to the patient. Reliability of recording is another key issue. Diaries may not be at hand after a seizure, lost or not brought to clinic visits. On-line electronic diaries have several potential advantages over paper diaries. Smartphones are increasingly accessible as data entry gateways. Data are not easily lost and are accessible from clinic. Entries can be time-stamped and provide immediate feedback, validation or reminders. Data can also can be graphed and pasted into an EMR. Disadvantages include need for digital sophistication, higher cost, increased setup time, and requiring attention to potential privacy issues. The Epilepsy Diary by epilepsy.com and Irody, Inc. has over 13,000 registrants and SeizureTracker over 10,000, and both are used for clinical and research purposes. Some studies have documented patient preference and increased compliance for electronic versus paper diaries. Seizure diaries can be challenging in the pediatric population. Children often have multiple seizure types and limited reporting of subjective symptoms. Multiple caregivers during the day require more training to produce reliable and consistent data. Diary-based observational studies have the advantages of low cost, allowing locus-of-control by the patient and testing in a "real-world" environment. Diary-based studies can also be useful as descriptive "snapshots" of a population. However, the type of information available is very different from that obtained by prospective controlled studies. The act of self-recording observations may itself influence the observation, for example, by causing the subject to attend more vigilantly to seizures after changing medication. Pivotal anti-seizure drug or device trials still mostly rely on paper-based seizure diaries. Industry is aware of the potential advantages of electronic diaries, particularly, the promise of real-time transmission of data, time-stamping of entries, reminders to subjects, and potentially automatic interfaces to other devices. However, until diaries are validated as research tools and the regulatory environment becomes clearer, adoption of new types of diaries as markers for a primary study

outcome will be cautious.Recommendations from the conference included: further studies of validity of epilepsy diaries and how they can be used to improve adherence; use and further development of core data sets, such as the one recently developed by NINDS; encouraging links of diaries to electronic sensors; development of diary privacy and legal policies; examination of special pediatric diary issues; development of principles for observational research from diaries; and work with the FDA to make electronic diaries more useful in industry-sponsored clinical trials.

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View details for Web of Science ID 000305208900002

View details for PubMedID 22652423

- Early Surgical Therapy for Drug-Resistant Temporal Lobe Epilepsy A Randomized Trial *JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION* Engel, J., McDermott, M. P., Wiebe, S., Langfitt, J. T., Stern, J. M., Dewar, S., Sperling, M. R., Gardiner, I., Erba, G., Fried, I., Jacobs, M., Vinters, H. V., Mintzer, S., Kieburtz, K. 2012; 307 (9): 922-930

Abstract

Despite reported success, surgery for pharmacoresistant seizures is often seen as a last resort. Patients are typically referred for surgery after 20 years of seizures, often too late to avoid significant disability and premature death.We sought to determine whether surgery soon after failure of 2 antiepileptic drug (AED) trials is superior to continued medical management in controlling seizures and improving quality of life (QOL).The Early Randomized Surgical Epilepsy Trial (ERSET) is a multicenter, controlled, parallel-group clinical trial performed at 16 US epilepsy surgery centers. The 38 participants (18 men and 20 women; aged ⩾12 years) had mesial temporal lobe epilepsy (MTLE) and disabling seizues for no more than 2 consecutive years following adequate trials of 2 brand-name AEDs. Eligibility for anteromesial temporal resection (AMTR) was based on a standardized presurgical evaluation protocol. Participants were randomized to continued AED treatment or AMTR 2003-2007, and observed for 2 years. Planned enrollment was 200, but the trial was halted prematurely due to slow accrual.Receipt of continued AED treatment (n = 23) or a standardized AMTR plus AED treatment (n = 15). In the medical group, 7 participants underwent AMTR prior to the end of follow-up and 1 participant in the surgical group never received surgery.The primary outcome variable was freedom from disabling seizures during year 2 of follow-up. Secondary outcome variables were health-related QOL (measured primarily by the 2-year change in the Quality of Life in Epilepsy 89 [QOLIE-89] overall T-score), cognitive function, and social adaptation.Zero of 23 participants in the medical group and 11 of 15 in the surgical group were seizure free during year 2 of follow-up (odds ratio = ∞; 95% CI, 11.8 to ∞; P < .001). In an intention-to-treat analysis, the mean improvement in QOLIE-89 overall T-score was higher in the surgical group than in the medical group but this difference was not statistically significant (12.6 vs 4.0 points; treatment effect = 8.5; 95% CI, -1.0 to 18.1; P = .08). When data obtained after surgery from participants in the medical group were excluded, the effect of surgery on QOL was significant (12.8 vs 2.8 points; treatment effect = 9.9;

95% CI, 2.2 to 17.7; P = .01). Memory decline (assessed using the Rey Auditory Verbal Learning Test) occurred in 4 participants (36%) after surgery, consistent with rates seen in the literature; but the sample was too small to permit definitive conclusions about treatment group differences in cognitive outcomes. Adverse events included a transient neurologic deficit attributed to a magnetic resonance imaging-identified postoperative stroke in a participant who had surgery and 3 cases of status epilepticus in the medical group.Among patients with newly intractable disabling MTLE, resective surgery plus AED treatment resulted in a lower probability of seizures during year 2 of follow-up than continued AED treatment alone. Given the premature termination of the trial, the results should be interpreted with appropriate caution.clinicaltrials.gov Identifier: NCT00040326.

View details for DOI 10.1001/jama.2012.220

View details for Web of Science ID 000301172100020

View details for PubMedID 22396514

- Therapeutic devices for epilepsy *ANNALS OF NEUROLOGY* Fisher, R. S. 2012; 71 (2): 157-168

Abstract

Therapeutic devices provide new options for treating drug-resistant epilepsy. These devices act by a variety of mechanisms to modulate neuronal activity. Only vagus nerve stimulation (VNS), which continues to develop new technology, is approved for use in the United States. Deep brain stimulation of anterior thalamus for partial epilepsy recently was approved in Europe and several other countries. Responsive neurostimulation, which delivers stimuli to 1 or 2 seizure foci in response to a detected seizure, recently completed a successful multicenter trial. Several other trials of brain stimulation are in planning or underway. Transcutaneous magnetic stimulation (TMS) may provide a noninvasive method to stimulate cortex. Controlled studies of TMS are split on efficacy, which may depend on whether a seizure focus is near a possible region for stimulation. Seizure detection devices in the form of shake detectors via portable accelerometers can provide notification of an ongoing tonic-clonic seizure, or peace of mind in the absence of notification. Prediction of seizures from various aspects of electroencephalography (EEG) is in early stages. Prediction appears to be possible in a subpopulation of people with refractory seizures, and a clinical trial of an implantable prediction device is underway. Cooling of neocortex or hippocampus reversibly can attenuate epileptiform EEG activity and seizures, but engineering problems remain in its implementation. Optogenetics is a new technique that can control excitability of specific populations of neurons with light. Inhibition of epileptiform activity has been demonstrated in hippocampal slices, but use in humans will require more work. In general, devices provide useful palliation for otherwise uncontrollable seizures, but with a different risk profile than with most drugs. Optimizing the place of devices in therapy for epilepsy will require further development and clinical experience.

View details for DOI 10.1002/ana.22621

View details for Web of Science ID 000300715300004

View details for PubMedID 22367987

- An online diary for tracking epilepsy *EPILEPSY & BEHAVIOR* Le, S., Shafer, P. O., Bartfeld, E., Fisher, R. S. 2011; 22 (4): 705-709

Abstract

My Epilepsy Diary is a free Web-based application on the public website epilepsy.com, available for patients to track epilepsy and to aid clinicians with data-based, individualized management. The first aim of this descriptive study was to outline electronic diary functions. Second, the study retrospectively profiled a large cohort of 2010 calendar year diary users including demographics, seizure types, temporal distribution of seizures, triggers, and use and side effects of antiepileptic drugs (AEDs). A total of 1944 users provided demographic information and 1877 recorded seizure data. Most (64%) users were women. Average age was 29.9$\pm$16.0 years. A total of 70,990 seizure entries and 15,630 AED entries were logged. Events were apportioned as 79% seizures and 21% seizure clusters. Specific AEDs were detailed in 7331 entries: monotherapy was used in 18% and polytherapy in 82%. Mood-related side effects were most commonly reported in 19% of 1027 users.

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View details for Web of Science ID 000298067600012

View details for PubMedID 21975298

- Benefits of trigeminal nerve stimulation *EPILEPSY & BEHAVIOR* Fisher, R. S. 2011; 22 (4): 615-616
View details for DOI 10.1016/j.yebeh.2011.09.024

View details for Web of Science ID 000298067600001

View details for PubMedID 22019017

- Neurostimulation for Epilepsy: Do We Know the Best Stimulation Parameters? *EPILEPSY CURRENTS* Fisher, R. S. 2011; 11 (6): 203-204
View details for Web of Science ID 000300152600012

View details for PubMedID 22130194

- Direct brain stimulation is an effective therapy for epilepsy *NEUROLOGY* Fisher, R. S. 2011; 77 (13): 1220-1221
View details for DOI 10.1212/WNL.0b013e3182312000

View details for Web of Science ID 000295253800007

View details for PubMedID 21917779

- Detection of seizure-like movements using a wrist accelerometer *EPILEPSY & BEHAVIOR* Lockman, J., Fisher, R. S., Olson, D. M. 2011; 20 (4): 638-641

Abstract

Caregivers of people with epilepsy are commonly concerned about unwitnessed seizures causing injury and even death. The goal of this study

was to determine if a wrist-worn motion detector could detect tonic-clonic seizures. Individuals admitted for continuous video/EEG monitoring wore a wristwatch-size device that was programmed to detect rhythmic movements such as those that occur during tonic-clonic seizures. When such movement was detected, the device sent a Bluetooth signal to a computer that registered the time and duration of the movements. Recorded detections were compared with the routinely recorded video/EEG data. Six of 40 patients had a total of eight tonic-clonic seizures. Seven of the eight seizures were detected. Nonseizure movements were detected 204 times, with opportunity for canceling transmission by the patient. Only one false detection occurred during sleep. In principle, this device should allow caregivers of people with tonic-clonic seizures to be alerted when a seizure occurs.

View details for DOI 10.1016/j.yebeh.2011.01.019

View details for Web of Science ID 000290056200008

View details for PubMedID 21450533

- Definition of the postictal state: When does it start and end? *EPILEPSY & BEHAVIOR* Fisher, R. S., Engel, J. J. 2010; 19 (2): 100-104

Abstract

The postictal state is the abnormal condition occurring between the end of an epileptic seizure and return to baseline condition. Applying this definition operationally can be difficult, especially for complex partial seizures, where cognitive and sensorimotor impairments merge imperceptibly into the postictal state. Many patients are unaware of even having had a seizure. Electroencephalography sometimes helps to distinguish ictal from postictal periods, but may demonstrate focal slowing both during and after a seizure. Epileptiform electroencephalographic changes do not always correspond precisely to behavioral changes, especially with scalp recordings. The postictal state ends at the interictal state, but this too can be ambiguous. Interictal spikes and spike-waves can be associated with cognitive and behavioral impairments, suggesting that they may represent fragments of ictal episodes. Except where boundaries are clear, it is better to describe a sequence of behaviors and electroencephalographic changes, without labeling arbitrary stages as being ictal or postictal.

View details for DOI 10.1016/j.yebeh.2010.06.038

View details for Web of Science ID 000283204300003

View details for PubMedID 20692877

- Prospective, Double-Blind, Randomized, Placebo-Controlled Comparison of Acetazolamide Versus Ibuprofen for Prophylaxis Against High Altitude Headache: The Headache Evaluation at Altitude Trial (HEAT) *WILDERNESS & ENVIRONMENTAL MEDICINE* Gertsch, J. H., Lipman, G. S., Holck, P. S., Merritt, A., Mulcahy, A., Fisher, R. S., Basnyat, B., Allison, E., Hanzelka, K., Hazan, A., Meyers, Z., Odegaard, J., Pook, B., Thompson, M., Slomovic, B., Wahlberg, H., Wilshaw, V., Weiss, E. A., Zafren, K. 2010; 21 (3): 236-243

Abstract

High altitude headache (HAH) is the most common neurological complaint at altitude and the defining component of acute mountain sickness (AMS). However, there is a paucity of literature concerning its prevention. Toward this end, we initiated a prospective, double-blind, randomized, placebo-controlled trial in the Nepal Himalaya designed to compare the effectiveness of ibuprofen and acetazolamide for the prevention of HAH.Three hundred forty-three healthy western trekkers were recruited at altitudes of 4280 m and 4358 m and assigned to receive ibuprofen 600 mg, acetazolamide 85 mg, or placebo 3 times daily before continued ascent to 4928 m. Outcome measures included headache incidence and severity, AMS incidence and severity on the Lake Louise AMS Questionnaire (LLQ), and visual analog scale (VAS).Two hundred sixty-five of 343 subjects completed the trial. HAH incidence was similar when treated with acetazolamide (27.1%) or ibuprofen (27.5%; P = .95), and both agents were significantly more effective than placebo (45.3%; P = .01). AMS incidence was similar when treated with acetazolamide (18.8%) or ibuprofen (13.7%; P = .34), and both agents were significantly more effective than placebo (28.6%; P = .03). In fully compliant participants, moderate or severe headache incidence was similar when treated with acetazolamide (3.8%) or ibuprofen (4.7%; P = .79), and both agents were significantly more effective than placebo (13.5%; P = .03).Ibuprofen and acetazolamide were similarly effective in preventing HAH. Ibuprofen was similar to acetazolamide in preventing symptoms of AMS, an interesting finding that implies a potentially new approach to prevention of cerebral forms of acute altitude illness.

View details for Web of Science ID 000282163300007

View details for PubMedID 20832701

- Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy *EPILEPSIA* Fisher, R., Salanova, V., Witt, T., Worth, R., Henry, T., Gross, R., Oommen, K., Osorio, I., Nazzaro, J., Labar, D., Kaplitt, M., Sperling, M., Sandok, E., Neal, J., Handforth, A., Stern, J., DeSalles, A., Chung, S., Shetter, A., Bergen, D., Bakay, R., Henderson, J., French, J., Baltuch, G., Rosenfeld, W., Youkilis, A., Marks, W., Garcia, P., Barbaro, N., Fountain, N., Bazil, C., Goodman, R., McKhann, G., Krishnamurthy, K. B., Papavassiliou, S., Epstein, C., Pollard, J., Tonder, L., Grebin, J., Coffey, R., Graves, N. 2010; 51 (5): 899-908

Abstract

We report a multicenter, double-blind, randomized trial of bilateral stimulation of the anterior nuclei of the thalamus for localization-related epilepsy.Participants were adults with medically refractory partial seizures, including secondarily generalized seizures. Half received stimulation and half no stimulation during a 3-month blinded phase; then all received unblinded stimulation.One hundred ten participants were randomized. Baseline monthly median seizure frequency was 19.5. In the last month of the blinded phase the stimulated group had a 29% greater reduction in seizures compared with the control group, as estimated by a generalized estimating equations (GEE) model (p = 0.002). Unadjusted median declines at the end of the blinded phase were 14.5% in the control group and 40.4% in the stimulated group. Complex partial and "most severe" seizures were

significantly reduced by stimulation. By 2 years, there was a 56% median percent reduction in seizure frequency; 54% of patients had a seizure reduction of at least 50%, and 14 patients were seizure-free for at least 6 months. Five deaths occurred and none were from implantation or stimulation. No participant had symptomatic hemorrhage or brain infection. Two participants had acute, transient stimulation-associated seizures. Cognition and mood showed no group differences, but participants in the stimulated group were more likely to report depression or memory problems as adverse events.Bilateral stimulation of the anterior nuclei of the thalamus reduces seizures. Benefit persisted for 2 years of study. Complication rates were modest. Deep brain stimulation of the anterior thalamus is useful for some people with medically refractory partial and secondarily generalized seizures.

View details for DOI 10.1111/j.1528-1167.2010.02536.x

View details for Web of Science ID 000277000900024

View details for PubMedID 20331461

- What is a classification essay? *EPILEPSIA* Fisher, R. S. 2010; 51 (4): 714-715
  View details for Web of Science ID 000276245600029

  View details for PubMedID 20394643

- Tracking epilepsy with an electronic diary *ACTA PAEDIATRICA* Fisher, R. S. 2010; 99 (4): 516-518
  View details for DOI 10.1111/j.1651-2227.2010.01694.x

  View details for Web of Science ID 000274951200014

  View details for PubMedID 20105139

- Recurrent Seizures Related to Motor Cortex Stimulator Programming *NEUROMODULATION* Henderson, J. M., Heit, G., Fisher, R. S. 2010; 13 (1): 37-42

Abstract

Objective.?Motor cortex stimulation (MCS) is increasingly being utilized for the treatment of intractable pain. While the risks of MCS are relatively low, focal or generalized seizures may be produced during programming of MCS systems. Occasionally, patients may experience seizures hours after programming. In order to understand this phenomenon better, we undertook a retrospective analysis of five patients in whom seizures limited the efficacy of MCS. Methods.?A retrospective chart review was performed in five patients who underwent MCS between 2002 and 2006 and who had persistent seizures that limited programming. Results.?The initial seizure during programming in these patients occurred at amplitudes of between 4.8 and 6.6?V. Four patients experienced generalized tonic-clonic seizures and one patient experienced focal seizures. Subsequent seizures occurred at amplitudes of between 4.4 and 5.5?V, with a tendency for seizure thresholds to progressively decrease. All five patients experienced at least one seizure occurring many minutes to hours after programming, with no side-effects initially observed once the final settings had been programmed. Four out of

five patients were programmed with frequencies documented at between 70 and 90?Hz; documentation on frequency was unavailable for the remaining patient. One patient never achieved adequate pain relief and had the MCS system explanted. Conclusions.?Despite the overall safety of MCS for the treatment of chronic pain, seizures during and after programming are a serious risk that should be anticipated. In this group of patients, seizures were associated only with stimulus rates between 70 and 90?Hz. No patient developed chronic epilepsy from the stimulation.

View details for DOI 10.1111/j.1525-1403.2009.00256.x

View details for Web of Science ID 000273318200016

View details for PubMedID 21992763

- Therapeutic Brain Stimulation for Epilepsy *NEUROLOGIC CLINICS* Lockman, J., Fisher, R. S. 2009; 27 (4): 1031-?

Abstract

DBS has been a possible therapy for epilepsy for more than 30 years, and now it is moving to the point of clinical utility. Animal models have shown efficacy of DBS at several brain regions, although not all animal studies have shown efficacy. Clinically, an array of sites have been explored, including the cerebellum, anterior nucleus of the thalamus, CM nucleus, hippocampus, subthalamic nucleus, brainstem, and corpus callosum; direct stimulation of the cortex has also been explored. Interest in evaluating these sites for treatment of epilepsy has been enhanced by the success of vagus nerve stimulation for epilepsy and DBS for movement disorders. Literature consists of mostly small and uncontrolled studies that are subject to limitations in interpretation. A pivotal large, double-blind controlled trial of anterior nucleus of the thalamus has recently been completed, and it showed efficacy for partial seizures with or without secondary generalization.28 A controlled trial for RNS is underway.57 In addition, pilot studies of hippocampal stimulation 41,43 are expected to lead to more definitive trials of this site.Brain stimulation for epilepsy holds several challenges for the future. Mechanisms of DBS are poorly understood, although investigations are actively being pursued. Little is known about optimal stimulation parameters. DBS has been little examined in cases of intractable generalized epilepsy. Because DBS carries some risk, mainly of hemorrhage and infection, clinicians will need to develop an effective method of identifying the best candidates. DBS is palliative rather than curative, but experience suggests that this relatively new therapy may be of benefit to some people with otherwise untreatable epilepsy.

View details for DOI 10.1016/j.ncl.2009.06.005

View details for Web of Science ID 000271872600012

View details for PubMedID 19853222

- What clinicians want to know from epilepsy researchers *EPILEPSIA* Fisher, R. S. 2009; 50 (3): 364-367
View details for DOI 10.1111/j.1528-1167.2009.02026.x

View details for Web of Science ID 000266198000009

View details for PubMedID 19317884

- Group therapy for patients with psychogenic nonepileptic seizures: A pilot study *EPILEPSY & BEHAVIOR* Barry, J. J., Wittenberg, D., Bullock, K. D., Michaels, J. B., Classen, C. C., Fisher, R. S. 2008; 13 (4): 624-629

Abstract

Great advances have been made in the diagnosis of people with psychogenic nonepileptic seizures (PNES) since the advent of video/EEG monitoring. However, treatment options for this population have lagged significantly. This pilot study was undertaken to evaluate whether group therapy done with a psychodynamic focus would offer a useful intervention. Twelve patients entered the study and seven completed at least 75% of the 32 weekly sessions. The Beck Depression Inventory and the Global Severity Index of the Symptom Checklist-90 showed improvement as well as an overall decrease in PNES frequency. The data suggest that group therapy focusing on interpersonal issues may benefit patients with PNES.

View details for DOI 10.1016/j.yebeh.2008.06.013

View details for Web of Science ID 000260701500008

View details for PubMedID 18621147

- Debate: When does a seizure imply epilepsy? *EPILEPSIA* Fisher, R. S., Leppik, I. 2008; 49: 7-12

Abstract

Epilepsy recently has been defined conceptually as a condition of at least one seizure, with an enduring predisposition to have seizures. It is not yet clear how to make this definition operational and practical. A diagnosis of epilepsy has potentially serious consequences for health, psychosocial well-being, and economics, and, therefore, it should be made with a high level of certainty. A definite diagnosis of epilepsy can be made with two unprovoked seizures at least 24 h apart. This method has the benefit of simplicity and consistency with past epidemiologic studies. Nevertheless, certain circumstances suggest a high likelihood of having a second seizure, as evidenced by common clinical practice of considering treatment after a first unprovoked seizure in conjunction with additional risk factors (surrogate markers). One unifying approach is an operational definition of "definite epilepsy" after two unprovoked seizures at least 24 h apart. An operational definition of "probable epilepsy" can be established with one unprovoked seizure and clinical, electroencephalography (EEG), neuroimaging, genetic, or other information to suggest greater than a 50% chance of having another seizure. "Possible epilepsy" operationally would exist with a single unprovoked seizure and insufficient evidence to predict a high likelihood of recurrence. Future clinical and epidemiologic evidence would allow refinements of the operational definitions.

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View details for Web of Science ID 000262282900003

View details for PubMedID 19087112

- Gender and age differences in expression of GABA(A) receptor subunits in rat somatosensory thalamus and cortex in an absence epilepsy model *NEUROBIOLOGY OF DISEASE* Li, H., Huguenard, J. R., Fisher, R. S. 2007; 25 (3): 623-630

Abstract

Absence epilepsy is more prevalent in females, but reasons for this gender asymmetry are unknown. We reported previously that perinatal treatment of Long-Evans Hooded rats with the cholesterol synthesis inhibitor (CSI) AY9944 causes a life-long increase in EEG spike-wave discharges (SWDs), correlated with decreased expression of GABA(A) receptor subunit gamma2 protein levels in thalamic reticular and ventrobasal nuclei (SS thalamus) [Li, H., Kraus, A., Wu, J., Huguenard, J.R., Fisher, R.S., 2006. Selective changes in thalamic and cortical GABA(A) receptor subunits in a model of acquired absence epilepsy in the rat. Neuropharmacology 51, 121-128]. In this study, we explored time course and gender different effects of perinatal AY9944 treatment on expression of GABA(A) receptor alpha1 and gamma2 subunits in SS thalamus and SS cortex. Perinatal AY9944 treatment-induced decreases in GABA(A) gamma2 receptor subunits in rat SS thalamus and increases in SS cortex are gender and age specific. The findings suggest a mechanism for the higher prevalence of absence epilepsy in female patients.

View details for DOI 10.1016/j.nbd.2006.11.004

View details for Web of Science ID 000244872200018

View details for PubMedID 17208003

- Intraventricular administration of gabapentin in the rat increases flurothyl seizure threshold. *Neurosci Lett* Oommen J, Kraus AC, Fisher RS. 2007; 417 (3): 308-11
- New routes for delivery of anti-epileptic medications. *Acta neurologica Taiwanica* Fisher, R. S., Chen, D. K. 2006; 15 (4): 225-231

Abstract

Use of novel drug delivery methods might enhance efficacy and reduce toxicity, in comparison with currently existing oral anti-epileptic drugs (AEDs). Novel methods aim to deliver optimal drug concentration more specifically to the seizure focus or foci. In this review, we first consider unconventional routes of drug delivery to the peripheral system, then potential new methods of targeted CNS drug delivery. Intrathecal or intraventricular AEDs might circumvent systemic toxicity. Drug-eluting wafers could be surgically positioned over an epileptogenic region of brain. Drug can be delivered to a seizure focus by an implanted catheter and subcutaneous pump. Inactive prodrugs, given systemically, can be made active only at the seizure focus, by interaction with locally-released substances. Liposomes and polysomes are engineered slow-release storage vehicles for drugs. Targeting components can hold liposomes near a region of interest, provided that they can penetrate the blood brain barrier. Lastly, we discuss future prospects for the use of transplanted cells and genes as potential vehicles for local delivery of renewable anti-epileptic regimen.

View details for PubMedID 17214084

- Selective changes in thalamic and cortical GABA(A) receptor subunits in a model of acquired absence epilepsy in the rat *NEUROPHARMACOLOGY* Li, H., Kraus, A., Wu, J., Huguenard, J. R., Fisher, R. S. 2006; 51 (1): 121-128

Abstract

Neonatal treatment of Long-Evans Hooded rats with the cholesterol synthesis inhibitor (CSI) AY9944 has been shown to increase occurrence of spike-waves in EEG recordings and decrease benzodiazepines sensitivity of GABA(A) receptor-mediated responses in neurons from the thalamic reticular nuclei (nRt, Wu et al., 2004). The present experiments were designed to investigate the changes in the gamma2 and alpha1 subunits of the GABA(A) receptor in CSI model rats as possible mechanisms of these changes. Western blot, immunohistochemistry and real-time PCR techniques were performed to measure the levels of GABA(A) receptor gamma2 and alpha1 subunit transcripts and protein in the nRt and ventrobasal (VB) relay nuclei of thalamus and in somatosensory cortex. In CSI model animals, Western blot results showed that gamma2 subunit expression significantly decreased in thalamus (control, n=6: 0.17+/-0.02 relative to actin vs. CSI model, n=6: 0.11+/-0.01, P<0.05) but neither in cortex nor in hippocampal tissues. Conversely, alpha1 subunit expression decreased in CSI model somatosensory cortex, but not in nRt and VB. The present results demonstrate that neonatal block of cholesterol synthesis produces region- and subunit-specific decreases in GABA(A) receptor subunits in thalamus and cortex. Selective reductions in GABA(A) receptor subunits in thalamus may play a role in pathophysiology of absence epilepsy.

View details for DOI 10.1016/j.neuropharm.2006.03.003

View details for Web of Science ID 000239100600014

View details for PubMedID 16678865

- Measuring effects of antiepileptic medication on balance in older people *Epilepsy Research* Fife TD, Fisher RS, Blum DE 2006; 70: 103-109
- Nonepileptic seizures: Clinical case conference: Conversion disorder *American Journal of Psychiatry* Stonnington CM, Barry JJ, Fisher RS 2006; 163: 1510-1517
- Use of serum prolactin in diagnosing epileptic seizures - Report of the therapeutics and technology assessment subcommittee of the American academy of neurology *NEUROLOGY* Chen, D. K., So, Y. T., Fisher, R. S. 2005; 65 (5): 668-675

Abstract

The purpose of this article is to review the use of serum prolactin assay in epileptic seizure diagnosis.The authors identified relevant studies in multiple databases and reference lists. Studies that met inclusion criteria were summarized and rated for quality of evidence, and the results were analyzed and pooled where appropriate.Most studies used a serum prolactin of at least twice baseline value as abnormal. For the differentiation of epileptic seizures from psychogenic nonepileptic seizures, one Class I and seven

Class II studies showed that elevated serum prolactin was highly predictive of either generalized tonic-clonic or complex partial seizures. Pooled sensitivity was higher for generalized tonic-clonic seizures (60.0%) than for complex partial seizures (46.1%), while the pooled specificity was similar for both (approximately 96%). Data were insufficient to establish validity for simple partial seizures. Two Class II studies were consistent in showing prolactin elevation after tilt-test-induced syncope. Inconclusive data exist regarding the value of serum prolactin following status epilepticus, repetitive seizures, and neonatal seizures.Elevated serum prolactin assay, when measured in the appropriate clinical setting at 10 to 20 minutes after a suspected event, is a useful adjunct for the differentiation of generalized tonic-clonic or complex partial seizure from psychogenic nonepileptic seizure among adults and older children (Level B). Serum prolactin assay does not distinguish epileptic seizures from syncope (Level B). The use of serum PRL assay has not been established in the evaluation of status epilepticus, repetitive seizures, and neonatal seizures (Level U).

View details for Web of Science ID 000231821300004

View details for PubMedID 16157897

- Epileptic seizures and epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) *AKTUELLE NEUROLOGIE* Fisher, R. S., Boas, W. V., Blume, W., Elger, C., Genton, P., Lee, P., Engel, J. 2005; 32 (5): 249-252
View details for DOI 10.1055/s-2005-866879

View details for Web of Science ID 000230221900002

- Epileptic seizures and epilepsy: Definitions proposed by the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) *EPILEPSIA* Fisher, R. S., BOAS, W. V., Blume, W., Elger, C., Genton, P., Lee, P., Engel, J. 2005; 46 (4): 470-472

Abstract

The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) have come to consensus definitions for the terms epileptic seizure and epilepsy. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

View details for Web of Science ID 000227837200001

View details for PubMedID 15816939

- A blinded pilot study of artwork in a comprehensive epilepsy center population *EPILEPSY & BEHAVIOR* Anschel, D. J., Dolce, S., Schwartzman, A., Fisher, R. S. 2005; 6 (2): 196-202

Abstract

The production of artwork is a complex neurological task. A controlled study

of artwork produced by people with epilepsy has not previously been performed. The present report details the results of a three-part study involving 60 subjects from a comprehensive epilepsy center population. Subjects were grouped by the following diagnoses: seizures, partial seizures, complex partial seizures with temporal focus, and nonepileptic events. Data were collected in a blinded fashion. The Formal Elements Art Therapy Scale task showed significant effects in patients with epileptic seizures. The Free Drawing was most sensitive to complex partial seizures with temporal focus, while the Outline was most predictive of nonepileptic events. In addition to giving some insight into the neurological functioning of these subjects, this pilot study provides a basis for the future development of diagnostic tests to be used within this patient group.

View details for DOI 10.1016/j.yebeh.2004.12.004

View details for Web of Science ID 000227219000011

View details for PubMedID 15710304

- Experimental Electrical Stimulation Therapy for Epilepsy. *Current treatment options in neurology* Oommen, J., Morrell, M., Fisher, R. S. 2005; 7 (4): 261-271

Abstract

Electrical stimulation of the nervous system is an attractive possible therapy for intractable epilepsy, but only stimulation of the vagus nerve has been subjected to large, controlled, and completed clinical trials. Controlled trials are in progress for intermittent cycling stimulation of the anterior nuclei of the thalamus, and for cortical stimulation at a seizure focus, responsive to detection of seizure onset. Anecdotal experience has been gathered with stimulation of cerebellum, centromedian thalamus, subthalamus, caudate, hippocampus, and brainstem. All stimulation of the central nervous system for epilepsy must be considered experimental.

View details for PubMedID 15967089

- Neurostimulation for epilepsy, including a pilot study of anterior nucleus stimulation *Clinical Neurosurgery* Graves NM, Fisher RS 2005; 52: 1-8
- Photic- and pattern-induced seizures: expert consensus of the Epilepsy Foundation of America Working Group *Epilepsia* Harding G, Wilkins AJ, Erba G, Barkley GL, Fisher RS 2005; 46: 1423-5
- Photic- and pattern-induced seizures: a report by the Epilepsy Foundation of America Working Group *Epilepsia* Fisher RS, Harding G, Wilkins AJ, Erba G, Barkley G 2005; 46: 1426-1441
- Neurostimulation for epilepsy, including a pilot study of anterior nucleus stimulation *Clinical Neurosurgery* Graves NM, Fisher RS 2005; 52: 1-8
- Focally injected adenosine prevents seizures in the rat *EXPERIMENTAL NEUROLOGY* Anschel, D. J., Ortega, E. L., Kraus, A. C., Fisher, R. S. 2004; 190 (2): 544-547

Abstract

Prophylactic drug injection directly onto a seizure focus has the potential to improve seizure control with fewer side effects than is produced by systemic

therapy. Using a dose-response model, we evaluated the effectiveness of adenosine application for focal seizure prophylaxis in 12 rats. Total spikes and electroencephalographic ictal events were reduced significantly by treatment with adenosine compared to control ($P < 0.0001$). This study demonstrates effectiveness and feasibility in a model system using intracranial injection of adenosine to prevent epileptiform events.

View details for DOI 10.1016/j.expneurol.2004.07.017

View details for Web of Science ID 000225261200026

View details for PubMedID 15530893

- Peer-reviewed publication: A view from inside *EPILEPSIA* Fisher, R. S., Powers, L. E. 2004; 45 (8): 889-894
View details for Web of Science ID 000223212100001

View details for PubMedID 15270753

- Abnormal benzodiazepine and zinc modulation of GABA(A) receptors in an acquired absence epilepsy model *BRAIN RESEARCH* Wu, J., Ellsworth, K., Ellsworth, M., Schroeder, K. M., Smith, K., Fisher, R. S. 2004; 1013 (2): 230-240

Abstract

Brain cholesterol synthesis inhibition (CSI) at a young age in rats has been shown to be a faithful model of acquired absence epilepsy, a devastating condition for which few therapies or models exist. We employed the CSI model to study cellular mechanisms of acquired absence epilepsy in Long-Evans Hooded rats. Patch-clamp, whole-cell recordings were compared from neurons acutely dissociated from the nucleus reticularis of thalamus (nRt) treated and untreated with a cholesterol synthesis inhibitor, U18666A. In U18666A-treated animals, 91% of rats developed EEG spike-waves (SWs). Patchclamp results revealed that although there was no remarkable change in GABAA receptor affinity, both a loss of ability of benzodiazepines to enhance GABAA-receptor responses and an increase of Zn2+ inhibition of GABAA-receptor responses of nRt neurons occurred in Long-Evans Hooded rats previously administered U18666A. This change was specific, since no significant changes were found in neurons exposed to the GABA allosteric modulator, pentobarbital. Taken collectively, these findings provide evidence for abnormalities in benzodiazepine and Zn2+ modulation of GABAA receptors in the CSI model, and suggest that decreased gamma2 subunit expression may underlie important aspects of generation of thalamocortical SWs in atypical absence seizures. The present results are also consistent with recent findings that mutation of the gamma2 subunit of the GABAA receptor changes benzodiazepine modulation in families with generalized epilepsy syndromes.

View details for DOI 10.1016/j.brainres.2004.03.075

View details for Web of Science ID 000222257600012

View details for PubMedID 15193533

- Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy *EPILEPSIA* Kerrigan, J. F., Litt, B., Fisher,

R. S., Cranstoun, S., French, J. A., Blum, D. E., Dichter, M., Shetter, A., Baltuch, G., Jaggi, J., Krone, S., Brodie, M., Rise, M., Graves, N. 2004; 45 (4): 346-354

Abstract

Animal studies and sporadic case reports in human subjects have suggested that intermittent electrical stimulation of the anterior nucleus of the thalamus reduces seizure activity. We embarked on an open-label pilot study to determine initial safety and tolerability of bilateral stimulation of the anterior nucleus of the thalamus (ANT), to determine a range of appropriate stimulation parameters, and to begin to gather pilot efficacy data.We report an open-label pilot study of intermittent electrical stimulation of the anterior nucleus of the thalamus in five patients (three men, two women; age range, 24-47 years), with follow-up between 6 and 36 months. All patients had intractable partial epilepsy. Four of the five patients also had secondarily generalized seizures. Stimulation was delivered by bilateral implantable, programmable devices by using an intermittent, relatively high-frequency protocol. Stimulation parameters were 100 cycles per second with charge-balanced alternating current; pulse width, 90 ms; and voltages ranging between 1.0 and 10.0 V. Seizure counts were monitored and compared with preimplantation baseline.Four of the five patients showed clinically and statistically significant improvement with respect to the severity of their seizures, specifically with respect to the frequency of secondarily generalized tonic-clonic seizures and complex partial seizures associated with falls. One patient showed a statistically significant reduction in total seizure frequency. No adverse events could clearly be attributed to stimulation. None of the patients could determine whether the stimulator was on or off at these parameters.Electrical stimulation of the ANT appears to be well tolerated. Preliminary evidence suggests clinical improvement in seizure control in this small group of intractable patients. Further controlled study of deep brain stimulation of the anterior nucleus is warranted.

View details for Web of Science ID 000220796800007

View details for PubMedID 15030497

- Diazepam prophylaxis for bicuculline-induced seizures: a rat dose-response model *NEUROSCIENCE LETTERS* Anschel, D. J., Ortega, E., Fisher, R. S. 2004; 356 (1): 66-68

Abstract

We developed a screening methodology to test the ability of putative antiepileptic drugs delivered directly to a seizure focus to prevent epileptiform activity. The left hippocampi of 15 rats were implanted with an injection cannula and bipolar recording electrodes. Bone screws were used to record neocortical EEG activity. Diazepam (DZP) at one of four possible concentrations or control solution was injected into the hippocampus, followed 5 min later by bicuculline methiodide. DZP suppressed spikes and ictal events in a dose-dependent manner ($P<0.0001$). At 100 mM, DZP reduced spikes from 678+/-128 to 87+/-35 for a 15 min segment. Numbers of ictal events (seizure) and latency to the first event were reduced by prophylactic DZP. The study establishes a protocol for testing of

intracranially-injected drugs to prevent focal seizures.

View details for DOI 10.1016/j.neulet.2003.10.082

View details for Web of Science ID 000188598100017

View details for PubMedID 14746903

- Brain stimulation for epilepsy *LANCET NEUROLOGY* Theodore, W. H., Fisher, R. S. 2004; 3 (2): 111-118

Abstract

Neural stimulation is a promising new technology for the treatment of medically-intractable seizures. Vagus-nerve stimulation (VNS) is licensed in several countries as an adjunctive therapy. VNS is as effective as antiepileptic drug therapy, and serious complications are rare. Transcranial magnetic stimulation is simple, non-invasive, and widely used in neurophysiology. Therapeutic results in a few studies are equivocal at best. Deep brain stimulation, although experimental, has been applied to the cerebellum, caudate nucleus, centromedian thalamus, anterior thalamus, subthalamus, hippocampus, and neocortical seizure foci. Preliminary results are encouraging, but not conclusive. Electrode implantation in the brain for indications other than seizures has been associated with a 5% risk for intracranial haemorrhage and 5% for infection. A controlled study of anterior thalamic stimulation in patients with intractable partial and secondarily generalised seizures has been started. Future investigations are likely to study extrathalamic sites of stimulation, and effects of stimulation contingent upon detection of or prediction of EEG patterns of epileptiform activity.

View details for Web of Science ID 000188818500021

View details for PubMedID 14747003

- Intracellular energy failure does not underlie hyperthermic spreading depressions in immature rat hippocampal slice *BRAIN RESEARCH* Wu, H., Takeo, T., Wakui, M., Ellsworth, K., Fisher, R. S. 2003; 987 (2): 240-243

Abstract

Hyperthermic spreading depression (HSD) in immature rat hippocampal slices is mediated by Na+/K(+)-ATPase failure. Here, we test whether depleting intracellular ATP serves as a possible mechanism for HSD genesis. Results indicate that (1) pre-incubation with 3 mM creatine for 3 h failed to prevent hyperthermic spreading depression occurrence; and (2) intracellular ATP concentration doubled during experimental hyperthermia. This study suggests that HSD is not be mediated by depletion of intracellular ATP during hyperthermia.

View details for DOI 10.1016/S0006-8993(03)03355-9

View details for Web of Science ID 000185945900013

View details for PubMedID 14499969

- Seizure-related motor vehicle crashes in Arizona before and after reducing the driving restriction from 12 to 3 months *MAYO CLINIC PROCEEDINGS* Drazkowski, J. F., Fisher, R. S., Sirven, J. I., Demaerschalk, B. M., Uber-Zak,

L., Hentz, J. G., Labiner, D. 2003; 78 (7): 819-825

Abstract

To evaluate whether changing the seizure-free interval in Arizona from 12 months to 3 months affected the number of seizure-related motor vehicle crashes.We performed a time trend study with analysis of motor vehicle crash reports in the state of Arizona 3 years before (1991-1993) and 3 years after (1994-1996) the seizure-free interval was decreased from 12 to 3 months. The number of motor vehicle crashes related to seizures, other medical conditions, and other nonmedical crashes was compared before and after the law changed. Other population trends, including population growth, registered vehicles, and registered drivers, are also reported.Seizure-related crashes increased from 125 to 136 for the 3 years before and 3 years after the law changed, respectively. The total rate of seizure-related crashes did not increase on the basis of an incidence rate difference of -0.03/10(9) miles (95% confidence interval [CI], -0.30 to 0.24) and a relative risk of 0.98 (95% CI, 0.77 to 1.24). Over the same time interval, crashes related to other medical conditions increased from 288 to 310, respectively, for an incidence rate difference of -0.09/10(9) miles (95% CI, -0.51 to 033) and a relative risk of 0.97 (95% CI, 0.82 to 1.13). Fatalities due to seizure-related crashes decreased during the same period, whereas the number of multiple vehicle crashes increased.The rate of seizure-related crashes did not significantly increase in the state of Arizona after the seizure-free interval was reduced from 12 to 3 months.

View details for Web of Science ID 000183848100003

View details for PubMedID 12839076

- Psychological factors in the genesis and management of nonepileptic seizures: clinical observations *EPILEPSY & BEHAVIOR* Prigatano, G. P., Stonnington, C. M., Fisher, R. S. 2002; 3 (4): 343-349
  View details for Web of Science ID 000178784900008

- Cooling abolishes neuronal network synchronization in rat hippocampal slices *EPILEPSIA* Javedan, S. P., Fisher, R. S., Eder, H. G., Smith, K., Wu, J. 2002; 43 (6): 574-580

Abstract

We sought to determine whether cooling brain tissue from 34 to 21 degrees C could abolish tetany-induced neuronal network synchronization (gamma oscillations) without blocking normal synaptic transmission.Intracellular and extracellular electrodes recorded activity in transverse hippocampal slices (450-500 microm) from Sprague-Dawley male rats, maintained in an air-fluid interface chamber. Gamma oscillations were evoked by afferent stimulation at 100 Hz for 200 ms. Baseline temperature in the recording chamber was 34 degrees C, reduced to 21 degrees C within 20 min.Suprathreshold tetanic stimuli evoked membrane potential oscillations in the 40-Hz frequency range (n = 21). Gamma oscillations induced by tetanic stimulation were blocked by bicuculline, a gamma-aminobutyric acid (GABA)A-receptor antagonist. Cooling from 34 to 21 degrees C reversibly abolished gamma oscillations in all slices tested. Short, low-frequency discharges persisted after cooling in six of 14 slices. Single-pulse-evoked potentials, however,

were preserved after cooling in all cases. Latency between stimulus and onset of gamma oscillation was increased with cooling. Frequency of oscillation was correlated with chamber cooling temperature (r = 0.77). Tetanic stimulation at high intensity elicited not only gamma oscillation, but also epileptiform bursts. Cooling dramatically attenuated gamma oscillation and abolished epileptiform bursts in a reversible manner.Tetany-induced neuronal network synchronization by GABAA-sensitive gamma oscillations is abolished reversibly by cooling to temperatures that do not block excitatory synaptic transmission. Cooling also suppresses transition from gamma oscillation to ictal bursting at higher stimulus intensities. These findings suggest that cooling may disrupt network synchrony necessary for epileptiform activity.

View details for Web of Science ID 000176828400002

View details for PubMedID 12060015

- Employment for People with Epilepsy. To the Editor. *Epilepsy & behavior : E&B* Fisher, R. S., Callanan, M. 2002; 3 (2): 203
  View details for PubMedID 12609432

- Psychological factors in the genesis and management of nonepileptic seizures: clinical observations. *Epilepsy & behavior : E&B* Prigatano, G. P., Stonnington, C. M., Fisher, R. S. 2002; 3 (4): 343-349

Abstract

Nonepileptic seizures (NES) are frequently thought to have a "psychogenic" basis. Two 6-month group psychotherapy programs were provided for patients diagnosed as having NES [eight patients were treated during the first program, seven during the second (N=15)] to explore the potential role of psychological factors in the genesis of NES and to determine if psychotherapeutic interventions reduced the frequency of NES. Of the 15 patients, 9 (60%) completed at least 58% of the treatment sessions. Of those 9 patients, 6 (66%) reported a decline in "seizure frequency." One reported an increase (11%). Self-reported frequency highly correlated with paranoid ideation. Dissociative phenomena were common as was a history of sexual abuse. Each patient reported being in an adult situation that they found unacceptable or intolerable. None perceived a solution to their situation. Reports by health care providers that their seizures were not "real" (i.e., true epilepsy) restimulated feelings associated with their not being believed when they reported being sexually abused as children. The psychological genesis of NES in this sample of patients appears rooted in the recurrent experience of being in abusive or exploited relationships for which they perceived no solution.

View details for PubMedID 12609332

- Potential new methods for antiepileptic drug delivery *CNS DRUGS* Fisher, R. S., Ho, J. 2002; 16 (9): 579-593

Abstract

Use of novel drug delivery methods could enhance the efficacy and reduce the toxicity of antiepileptic drugs (AEDs). Slow-release oral forms of

medication or depot drugs such as skin patches might improve compliance and therefore seizure control. In emergency situations, administration via rectal, nasal or buccal mucosa can deliver the drug more quickly than can oral administration. Slow-release oral forms and rectal forms of AEDs are already approved for use, nasal and buccal administration is currently off-label and skin patches for AEDs are an attractive but currently hypothetical option. Therapies under development may result in the delivery of AEDs directly to the regions of the brain involved in seizures. Experimental protocols are underway to allow continuous infusion of potent excitatory amino acid antagonists into the CSF. In experiments with animal models of epilepsy, AEDs have been delivered successfully to seizure foci in the brain by programmed infusion pumps, acting in response to computerised EEG seizure detection. Inactive prodrugs can be given systemically and activated at the site of the seizure focus by locally released compounds. One such drug under development is DP-VPA (or DP16), which is cleaved to valproic acid (sodium valproate) by phospholipases at the seizure focus. Liposomes and nanoparticles are engineered micro-reservoirs of a drug, with attached antibodies or receptor-specific binding agents designed to target the particles to a specific region of the body. Liposomes in theory could deliver a high concentration of an AED to a seizure focus. Penetration of the blood-brain barrier can be accomplished by linking large particles to iron transferrin or biological toxins that can cross the barrier. In the near future, it is likely that cell transplants that generate neurotransmitters and neuromodulators will accomplish renewable endogenous drug delivery. However, the survival and viability of transplanted cells have yet to be demonstrated in the clinical setting. Gene therapy also may play a role in local drug delivery with the use of adenovirus, adeno-associated virus, herpesvirus or other delivery vectors to induce brain cells to produce local modulatory substances. New delivery systems should significantly improve the therapeutic/toxic ratio of AEDs.

View details for Web of Science ID 000177670500001

View details for PubMedID 12153331

- Gamma oscillation underlies hyperthermia-induced epileptiform-like spikes in immature rat hippocampal slices *BMC NEUROSCIENCE* Wu, J., Javedan, S. P., Ellsworth, K., Smith, K., Fisher, R. S. 2001; 2

Abstract

Recently a hyperthermic rat hippocampal slice model system has been used to investigate febrile seizure pathophysiology. Our previous data indicates that heating immature rat hippocampal slices from 34 to 41 degrees C in an interface chamber induced epileptiform-like population spikes accompanied by a spreading depression (SD). This may serve as an in vitro model of febrile seizures.In this study, we further investigate cellular mechanisms of hyperthermia-induced initial population spike activity. We hypothesized that GABA(A) receptor-mediated 30-100 Hz gamma oscillations underlie some aspects of the hyperthermic population spike activity. In 24 rat hippocampal slices, the hyperthermic population spike activity occurred at an average frequency of 45.9 +/- 14.9 Hz (Mean +/- SE, range = 21-79 Hz, n = 24), which does not differ significantly from the frequency of post-tetanic gamma

oscillations (47.1 +/- 14.9 Hz, n = 34) in the same system. High intensity tetanic stimulation induces hippocampal neuronal discharges followed by a slow SD that has the magnitude and time course of the SD, which resembles hyperthermic responses. Both post-tetanic gamma oscillations and hyperthermic population spike activity can be blocked completely by a specific GABA(A) receptor blocker, bicuculline (5-20 microM). Bath-apply kynurenic acid (7 mM) blocks synaptic transmission, but fails to prevent hyperthermic population spikes, while intracellular diffusion of QX-314 (30 mM) abolishes spikes and produces a smooth depolarization in intracellular recording.These results suggest that the GABA(A) receptor-governed gamma oscillations underlie the hyperthermic population spike activity in immature hippocampal slices.

View details for Web of Science ID 000207529000001

View details for PubMedID 11747470

- A Pilot Study of Donepezil for Memory Problems in Epilepsy *EPILEPSY & BEHAVIOR* Fisher, R. S., Bortz, J. J., Blum, D. E., Duncan, B., Burke, H. 2001; 2 (4): 330-334

Abstract

We performed a pilot 3-month, open-label study of 5-10 mg donepezil, an anticholinesterase inhibitor, as treatment for memory problems in people with epilepsy. The Buschke Selective Reminding Test was administered at baseline and after 3 months of donepezil. In 18 completing patients, the total number of words recalled across learning trials was greater on donepezil (P = 0.4). No change was noted in attention, visual sequencing, mental flexibility, psychomotor speed, or reported quality-of-life scores. Mean 3-month seizure frequency at baseline was 2.70 $\pm$ 4.60, and during treatment, 3.06 $\pm$ 4.52 (P = 0.19, not significant). Two patients experienced increased tonic-clonic seizures. Side effects included diarrhea, stomach cramps, insomnia, depression, and blurred vision. Cholinergic medication is worthy of investigation as treatment for memory problems in people with epilepsy, but attention must be paid to possible exacerbation of seizures.

View details for DOI 10.1006/ebeh.2001.0221

View details for Web of Science ID 000208208600008

- Rapid initiation of gabapentin - A randomized, controlled trial *NEUROLOGY* Fisher, R. S., Sachdeo, R. C., Pellock, J., Penovich, P. E., Magnus, L., Bernstein, P. 2001; 56 (6): 743-748

Abstract

To compare the tolerability of two different dose-initiation regimens of gabapentin for the adjunctive treatment of partial seizures.Patient compliance is a key feature of successful outpatient pharmacologic therapy for epilepsy, and one aspect of compliance is simplicity of initiation. By using a rapid titration rate, leading to a rapid therapeutic gabapentin dose, perhaps there could be an improvement with compliance.Male or female patients, at least 12 years old, with a recent history of partial seizures with or without secondary generalization, were randomized to receive gabapentin (following a blinded placebo period of an undisclosed number of days) as

either a Slow initiation (300 mg day 1, 600 mg day 2, then 900 mg/day) or a Rapid initiation (900 mg/day immediately following the placebo lead-in).Starting gabapentin therapy at an initial therapeutic dosage of 900 mg/day is well tolerated by patients with epilepsy and is as safe as initiating with a titration schedule over 3 days. Of the four most common adverse events (somnolence, dizziness, ataxia, fatigue), only one, dizziness, occurred more often in the nontitrated (Rapid initiation) group than in the titrated (Slow initiation) group.Initiation of gabapentin at 900 mg/day is as well tolerated as is a 3-day titration, except for a higher incidence of dizziness.

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- The etiology and mechanisms of symptomatic acute seizures. *Neurologia* Fisher RS 2001; 16 (Suppl 2)
- Hyperthermic spreading depressions in the immature rat hippocampal slice *JOURNAL OF NEUROPHYSIOLOGY* Wu, J., Fisher, R. S. 2000; 84 (3): 1355-1360

Abstract

Febrile seizures are the most common seizure type in children (6 mo to 5 yr). The pathophysiology of febrile seizures is unknown. Current genetic studies show that some febrile seizures result from channelopathies. We have performed electrophysiological experiments in in vitro hippocampal slices to test a novel hypothesis that a disordered regulation of ionic homeostasis underlies the genesis of febrile seizures. In transverse hippocampal CA1 slices from 104 rats, temperature increase from 34 degrees to 40 degrees C produced a series of spreading depressions (SDs), called hyperthermic SDs. The hyperthermic SDs were age-dependent, occurring in only 1/17 8-16 day-old animals, 44/49 17-60 day-old animals, and 11/20 rats older than than 60 days. The hyperthermic SDs usually occurred on the rising phase of the temperature. The mean temperature to trigger a first hyperthermic SD was 38.8 +/- 1.3 degrees C (mean +/- SD, n = 44). The hyperthermic SDs induced a reversible loss of evoked synaptic potentials and a dramatic decrease of input resistance. Neuronal and field epileptiform bursting occurred in the early phases of the hyperthermic SD. During hyperthermic SDs, pyramidal cell membrane potential depolarized by 38.3 +/- 4.9 mV (n = 20), extracellular field shifted negative 18.5 +/- 3.9 mV (n = 44), and extracellular K(+) rose reversibly to 43.8 +/- 10.9 mM (n = 6). Similar SDs could be evoked by ouabain or transient hypoxia with normal temperature. Tetrodotoxin could block initial epileptiform bursting, without blocking SDs. Hyperthermia-induced SDs should be investigated as possible contributing factors to febrile seizures.

View details for Web of Science ID 000089185200021

View details for PubMedID 10980008

- The impact of epilepsy from the patient's perspective II: views about therapy and health care *EPILEPSY RESEARCH* Fisher, R. S., Vickrey, B. G., Gibson, P., Hermann, B., Penovich, P., Scherer, A., Walker, S. 2000; 41 (1):

53-61

Abstract

A national survey of 1023 people with epilepsy in the US assessed their attitudes about their therapies. Subjects were drawn from responders to a previous national survey of US households or from those who phoned the Epilepsy Foundation. Overall response rate was 49%. Approximately 90% of the respondents were taking medications for their epilepsy. Only 56% were on monotherapy, while 26% were taking two, 6% three, and 2% four medications. Only 68% of respondents were very satisfied with their current seizure medications. When asked to rank five areas of importance regarding their seizure medication, the rank order (highest to lowest) was seizure control, fewer side effects, convenient dosing regimens and cost. Adverse medication events were listed in descending rank order as problems with cognition, energy level, school performance, childbearing, coordination, and sexual function. Inter-individual differences in side effects of concern were listed, suggesting medication choices should be individualized according to potential side effects. Twenty percent of 920 respondents adjusted their medications on their own, by adjusting amount (62%), dosing schedule (31%), or both (3%). Eighty percent of respondents were satisfied with their medical care systems. In this group, 82% had health insurance that covered epilepsy. The large majority (94%) of respondents had seen a neurologist. Subjects expressed dissatisfaction about time limits and lack of accessible information about epilepsy. People with epilepsy are generally satisfied with efforts to treat their disorder, but adverse events are of concern. Many patients requested more information about epilepsy.

View details for Web of Science ID 000088290800006

View details for PubMedID 10924868

- The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions *EPILEPSY RESEARCH* Fisher, R. S., Vickrey, B. G., Gibson, P., Hermann, B., Penovich, P., Scherer, A., Walker, S. 2000; 41 (1): 39-51

Abstract

This study surveyed the perceptions about and subjective experience of 1023 people with epilepsy in two community-based samples: one from a national postal survey; the other callers to the Epilepsy Foundation. Response to a mail survey was 49%. In comparison with US Census Bureau norms, respondents had received less education, were less likely to be employed or married, and came from lower income households. Complex partial seizures were the most prevalent seizure type, but a convulsion had occurred in 61%. Fifty percent of respondents reported incomplete control of their seizure disorder, although 25% of these had a seizure in the prior year. Thirteen percent had a longest inter-seizure interval of a year or greater, 37% of 3 months, 22% of 1 month, 10% of 1 week and 4% of 1 day. Respondents listed uncertainty and fear of having a seizure as the worst thing about having epilepsy. Lifestyle, school, driving, and employment limits were also listed as major problems. When asked to rank a list of potential problems, cognitive impairment was ranked highest. These data indicate

that ongoing medical and psychosocial problems continue for those with epilepsy in the view of those questioned and their families, even in a sample where the majority report good control of their epilepsy.

View details for Web of Science ID 000088290800005

View details for PubMedID 10924867

- The Postictal State: A Neglected Entity in the Management of Epilepsy *EPILEPSY & BEHAVIOR* Fisher, R. S., Schachter, S. C. 2000; 1 (1): 52-59

Abstract

Some of the disability deriving from epilepsy derives from the postictal state (PS). The PS may be complicated by impaired cognition, headache, injuries, or secondary medical conditions. Postictal depression is common, postictal psychosis relatively rare, but both add to the morbidity of seizures. The mechanisms of the PS are poorly understood. Alteration of cerebral blood flow both results from and contributes to the PS. Many neurotransmitters or neuromodulators are involved in the physiology of the PS. Response to glutamate may partially desensitize after a seizure. Endogenous opiates and adenosine serve as natural antiepileptic medications in some circumstances. Nitric oxide has numerous effects on brain excitability, and may be particularly important in regulating postictal cerebral blood flow. Just as the pathophysiology of seizures is complicated, so is that of the PS multifactorial. As a practical issue, it would be very useful to have medications that reduce the morbidity of the PS.

View details for DOI 10.1006/ebeh.2000.0023

View details for Web of Science ID 000208203300013

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- Epilepsy from the patient?s perspective: Review of results of a community-based survey *Epilepsy and Behavior* Fisher RS 2000; 1: S9-S14
- The postictal state: a neglected entity in the management of epilepsy *Epilepsy and Behavior* Fisher RS, Schachter SC 2000; 1: 52-59
- Epilepsy from the Patient's Perspective: Review of Results of a Community-Based Survey. *Epilepsy & behavior : E&B* Fisher, R. S. 2000; 1 (4): S9-S14

Abstract

A total of 1023 individuals with epilepsy responded to a community-based questionnaire survey. Relative to U.S. population norms, respondents had lower household incomes and lesser levels of educational and vocational attainment. Although 89% of respondents reported that their seizures were, in their estimation, at least somewhat controlled, 57% reported having suffered at least one seizure in the preceding year. Of the many concerns that accompanied life with epilepsy, fear (of a seizure, of embarrassment, even of death) was the issue most frequently reported. Eighty-eight percent of respondents reported having health insurance, and this insurance covered epilepsy treatment in 93% of cases. The majority of respondents said that they were satisfied with the medical care they were receiving but wished for more information about epilepsy. Despite advances in epilepsy therapy, freedom from seizures and optimal quality of life eludes many.

View details for PubMedID 12609456

- The potential for vigabatrin-induced intramyelinic edema in humans: a review *Epilepsia* Cohen JA, Fisher RS, Brigell MG, Peyster RG, Sze G 2000; 41: 148-157
- Raising the Bar on Seizure Control. *Epilepsy & behavior : E&B* Fisher, R. S. 2000; 1 (4): 212-214
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- An automated drug delivery system for the treatment of intractable focal epilepsy. *Epilepsy Research* Stein A, Eder HG, Jones D, Drachev A, Blum DE, Fisher RS 2000; 39: 103-114
- Reassessment: Vagus nerve stimulation for epilepsy - A report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology *NEUROLOGY* Fisher, R. S., Handforth, A. 1999; 53 (4): 666-669
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- Epilepsy surgery where there is dual pathology *LANCET* Fisher, R. S., Blum, D. 1999; 354 (9175): 267-268
  View details for Web of Science ID 000081646000003

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- Can patients perform volitional motor acts at the start of a seizure? *JOURNAL OF CLINICAL NEUROPHYSIOLOGY* Block, A., Fisher, R. S. 1999; 16 (2): 141-145

Abstract

A seizure warning device might allow some individuals with partial seizures to protect themselves against consequences of seizures, but a prerequisite is the ability to take volitional action in response to a warning. The authors reviewed consecutive seizures in their epilepsy monitoring unit to determine whether patients could squeeze an event bulb, as instructed, at the start of their seizure. Only complex partial seizures with EEG changes and with the patient on camera were analyzed. Data were obtained from 77 patients, 42 with scalp monitoring and 35 with depth electrodes. Forty-seven percent had a left-hemisphere focus, 42% a right-hemisphere focus, and 11% multifocal seizures. The seizure focus was temporal in 68%. A magnetic resonance imaging consistent with mesial temporal sclerosis was seen in 29% of patients. Overall, 44% of the patients made at least one attempt to reach for the event bulb at the start of their seizures. Among the 72% of patients who gave a history of auras, 53% were able to press the event bulb compared to 20% with no history of auras (P = 0.016). EEG changes occurred a mean of 2.9+/-30.5 seconds after reaching for the bulb for scalp-recorded seizures (n = 20), and 16.2+/-13.7 seconds before behavior for depth-recorded seizures (n = 14, difference significant at P = 0.02). Neither seizure focus nor seizure laterality influenced the ability to press the event bulb. The authors conclude that nearly half of individuals with complex partial seizures can take volitional motor action at the start of their seizure. A method to enhance the intensity and timeliness of a seizure warning would not be

wasted.

View details for Web of Science ID 000080527800006

View details for PubMedID 10359499

- Oxcarbazepine: double-blind, randomized, placebo-control, monotherapy trial for partial seizures *Neurology* Schachter SC, Vazquez B, Fisher RS, Laxer KD, Montouris GD, Combs-Cantrell DT, Faught E, Willmore LJ, Morris GL, Ojemann L, Bennett D, Mesenbrink P, DSouza J, Kramer L 1999; 52: 732-7
- New antiepileptic drugs: Comparison of key clinical trials *Epilepsia* Cramer JA, Fisher R, Ben Menachem E, French J, Mattson RH 1999; 40: 590-600
- Neurology *Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology* Fisher RS, Handforth A 1999; 53: 666-9
- Bilateral temporal hypometabolism in epilepsy *EPILEPSIA* Blum, D. E., Ehsan, T., Dungan, D., Karis, J. P., Fisher, R. S. 1998; 39 (6): 651-659

Abstract

Positron emission tomography (PET) has proven useful in epilepsy surgery for its ability to identify unilateral temporal hypometabolism (UTH), which is predictive of good surgical outcome. The significance of bilateral temporal hypometabolism (BTH) is not known.We identified all patients who had marked bilateral reduction in temporal lobe metabolism relative to the cerebellar hemispheres and compared their clinical features and treatment outcomes with those of control patients with UTH.BTH was evident in 10% of PET scans for epilepsy at our institution. We compared these patients with age-matched controls with UTH. The BTH patients had a higher percentage of generalized seizures; were more likely to have bilateral, diffuse or extratemporal seizure onsets; and had bilateral or diffuse magnetic resonance imaging (MRI) findings. UTH patients were more likely to have unilateral mesial temporal atrophy on MRI. Even when electrical seizure onsets were well localized, surgical outcomes were markedly worse in these patients than in controls. Medical treatment was also less successful. Social and cognitive functioning was worse in the BTH group. The only death occurred in the group with BTH.Patients with BTH have features distinct from those with UTH and have a worse prognosis for seizure remission after surgery.

View details for Web of Science ID 000073983500012

View details for PubMedID 9637608

- Open label pilot study of oxcarbazepine for inpatients under evaluation for epilepsy surgery *Drug Development research* Fisher RS, Eskola J, Blum D, Kerrigan JF III, Drazkowski J, M.D., Duncan B 1998; 38: 43-49
- Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat *EPILEPSY RESEARCH* Mirski, M. A., Rossell, L. A., Terry, J. B., Fisher, R. S. 1997; 28 (2): 89-100

Abstract

Evidence suggests that a specific subcortical pathway synaptically linking the anterior thalamic nuclear complex (AN) to the hypothalamus and

midbrain is important in the expression of pentylenetetrazol (PTZ) seizures. Perturbation of neuronal activity along this path via focal disruption or chemical inhibition significantly raises seizure threshold. Recent data has demonstrated that focal electrical stimulation within the hypothalamic component of this pathway inhibited seizure expression in a current and frequency dependent fashion. Similar experiments were conducted in the AN to investigate the hypothesis that stimulation of this thalamic nuclear region can prevent the propagation of PTZ seizures between cortical and subcortical regions. Our results indicate that high frequency (100 Hz) stimulation of AN did not alter the expression of low dose PTZ induced cortical bursting but did raise the clonic seizure threshold compared to naive animals or those stimulated at sites near, but not in AN ($P < 0.01$). Low frequency stimulation (8 Hz) was in contrast, proconvulsant and could induce behavioral arrest responses accompanied by rhythmic high voltage EEG even without PTZ challenge. This data further highlights the role of AN in mediating the expression of seizures and provides experimental support for the concept that this thalamic region may be a promising target for focal stimulation to treat intractable seizures in humans.

View details for Web of Science ID A1997XQ95600001

View details for PubMedID 9267773

- Assessment of vagus nerve stimulation for epilepsy: Report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology *NEUROLOGY* Fisher, R. S., Krauss, G. L., Ramsay, E., Laxer, K., Gates, J. 1997; 49 (1): 293-297
View details for Web of Science ID A1997XK35300050

View details for PubMedID 9222210

- Local perfusion of diazepam attenuates interictal and ictal events in the bicuculline model of epilepsy in rats *EPILEPSIA* Eder, H. G., Jones, D. B., Fisher, R. S. 1997; 38 (5): 516-521

Abstract

We evaluated the efficacy of local perfusion of diazepam (DZP) in suppression of EEG spikes and behavioral seizures produced by bicuculline methiodide (BMI) applied to rat sensory motor cortex and hippocampus.Data were obtained from 37 rats implanted with EEG head plugs and perfusion cannulas. BMI 4 mM, 5 microliters was infused on neocortex through the epidural space in 23 rats. BMI 0.1 mM, 2 microliters was infused into the left hippocampus in 14 rats.DZP 0.75-1.0 mg markedly reduced the spiking to a level of 9.9 +/- 15.8% of baseline for DZP as compared with 90.2 +/- 57.9% of baseline for vehicle-treated rats. DZP reduced spiking in a hippocampal BMI focus to 1.9 +/- 2.4% of baseline spiking, as compared with 98.0 +/- 95.6% of that in vehicle-treated animals. The amount of spread of solution was estimated with methylene blue (MB) injections. Ictal events also were attenuated. In most of the animals, systemic levels of DZP were unmeasurable and injection on the contralateral side did not reduce spiking.These findings suggest that focal application of antiepileptic drugs (AEDs) in brain may be a useful new avenue for therapy of intractable partial seizures.

View details for Web of Science ID A1997WX71900002

View details for PubMedID 9184595

- Epilepsy for the neuroradiologist *AMERICAN JOURNAL OF NEURORADIOLOGY* Fisher, R. S., Stein, A., Karis, J. 1997; 18 (5): 851-863
View details for Web of Science ID A1997WZ04600007

View details for PubMedID 9159362

- Interictal and ictal activity in the rat cobalt/pilocarpine model of epilepsy decreased by local perfusion of diazepam *Epilepsy Research* Eder HG, Stein A, Fisher RS 1997; 29: 17-24
- The selective GABA(B) antagonist CGP-35348 blocks spike-wave bursts in the cholesterol synthesis rat absence epilepsy model *BRAIN RESEARCH* Smith, K. A., Fisher, R. S. 1996; 729 (2): 147-150

Abstract

Slow IPSPs, which are believed to be involved in generation of the wave of spike-wave epileptiform discharges, are mediated by the GABAB receptor. We therefore examined the effect of the GABAB antagonist, Ciba Geigy Product, CGP-35348, in the cholesterol synthesis inhibitor model of absence epilepsy in rat. Rats received Ayerst-9944 (AY-9944), from 6-45 mg i.p. in the first few weeks of life. By 2 months after AY-9944 administration these rats exhibited recurrent spike-waves and behavioral arrests. In 10 such animals CGP-35348 was administered intraperitoneally in doses of 0 (vehicle), 10, 25 or 100 mg/kg. EEG recordings were obtained via previously implanted bone screws. Technologists blinded to treatment group counted spike-waves over a 4 h period post-injection. The average number of spike-wave burst seconds per 4 h of recording for all dosages and times was 52.4 +/- 81.4 (mean +/- S.D.) s. Mean burst times (seconds) were vehicle = 93.5 +/- 106.5; 10 mg/kg = 69.9 +/- 79.7; 25 mg/kg = 30.8 +/- 46.9; 100 mg/kg = 15.2 +/- 54, a mean 84% reduction at 100 mg/kg (ANOVA regression significant at 0.0001). Spike-waves were suppressed for at least 4 h after injection of CGP-35348. These findings supplement similar findings in other absence models, and support a potential role for GABAB antagonists in treatment of absence seizures.

View details for Web of Science ID A1996VE64400001

View details for PubMedID 8876982

- Newer antiepileptic drugs as monotherapy: Data on vigabatrin *NEUROLOGY* Fisher, R., Kalviainen, R., Tanganelli, P., Regesta, G. 1996; 47 (1): S2-S5

Abstract

Studies examining the use of vigabatrin as monotherapy for the treatment of epilepsy are relatively scarce, and of the few that have been reported, only two were of sufficient size to provide definitive data. In both trials, vigabatrin was compared with carbamazepine for efficacy and safety. In one of these studies, carbamasepine was found to be more effective than vigabatrin in reducing seizure frequency, and the two were found to be comparably efficacious in the other study. What differed significantly, however, was vigabatrin's favorable safety profile. Vigabatrin appears to be a reasonable

choice for single-drug therapy in the treatment of certain types of seizures. In other patients, it remains useful as an adjunct to other antiepileptic drugs.

View details for Web of Science ID A1996UX77000002

View details for PubMedID 8677032

- Patient awareness of seizures *NEUROLOGY* Blum, D. E., ESKOLA, J., Bortz, J. J., Fisher, R. S. 1996; 47 (1): 260-264

Abstract

In 31 consecutive patients who were admitted to an epilepsy monitoring unit, we prospectively determined whether the patients were aware of having seizures. On admission, all patients stated that they knew of at least some of their seizures. Eight of 23 with classifiable epileptic seizures recognized that they were occasionally unaware of their seizures. During telemetry, following full recovery of consciousness after each seizure, we asked the patients whether they had recently had a seizure. For control purposes, we asked the patients the same question at random times. Among patients with seizures, there were no false-positive answers. Only 6 of 23 (26%) of the patients with epilepsy were always aware of their seizures, including complex partial and secondarily generalized events, and 7 of 23 (30%) were never aware of any seizures. Self-reporting of seizures was unreliable: Patients reporting the lowest baseline frequency of seizures had the highest fraction of unrecognized seizures. Seizure awareness was lowest for patients with temporal lobe foci, especially on the left side. Patients with primarily generalized epilepsy were more likely to be aware of tonic-clonic seizures than were patients with secondarily generalized partial seizures. All four patients with nonepileptic attacks believed that they always knew of their seizures, but only three of the four patients actually did always know. Unrecognized seizures are frequent and should be considered in patient management and in studies.

View details for Web of Science ID A1996UX18800047

View details for PubMedID 8710091

- Titanium aneurysm clips .2. Seizure and electroencephalographic studies in implanted rabbits *NEUROSURGERY* Fisher, R. S., Ehsan, T., Smith, K., Lawton, M. T., Bichard, W. D., Spetzler, R. F. 1996; 38 (6): 1165-1169

Abstract

Because titanium is widely used in neurosurgical procedures, we compared spontaneous and induced epileptiform activity in 12 rabbits with titanium clips implanted in the subarachnoid space with 12 rabbits with cobalt alloy clips and 6 rabbits that were not operated on that served as controls. Beginning 1 week after surgery, 30-minute electroencephalographic recordings were made at monthly intervals for 6 months. Recordings were scored by an electroencephalographer unaware of which treatment group was being recorded. In 48 recordings made during 6 months, no epileptiform activity was observed in any animal. Seizure threshold was evaluated by continuous intravenous injection of the convulsant drug, pentylenetetrazole (2 mg/kg/min), with continuous electroencephalographic recording. Time to

spiking for the nonsurgical control group was 327 mean seconds +/- 181 standard deviation (SD), 216 mean seconds +/- 135 SD for the titanium group, and 389 mean seconds +/- 290 SD for the cobalt group. There were no significant differences among the groups (P = 0.17). Latency to behavioral tonicoclonic seizure was 1031 seconds +/- 537 SD for the group not operated on, 875 seconds +/- 334 SD for the titanium group, and 1267 seconds +/- 764 SD for the cobalt group. This study suggests that titanium clips are well tolerated within the brain and will not induce seizures.

View details for Web of Science ID A1996UM76300046

View details for PubMedID 8727148

- Cognitive effects of resecting basal temporal language areas *EPILEPSIA* Krauss, G. L., Fisher, R., Plate, C., Hart, J., Uematsu, S., GORDON, B., Lesser, R. P. 1996; 37 (5): 476-483

Abstract

Electrical stimulation of the basal temporal region of the dominant hemisphere before partial temporal lobectomy for epilepsy sometimes produces temporary interruption of language function, but the significance of removal of this area is unknown. We evaluated the correlation between resection of the basal temporal language areas (BTLA) and certain types of postoperative language deficits. In a population of 25 patients, we mapped the inferolateral temporal lobe with cortical electrical stimulation, verifying the positions of the stimulating electrodes with three-dimensional computed tomography (CT). Eighty percent of the patients developed transient language deficits with stimulation, particularly with tests of confrontation naming and comprehension. BTLA was primarily located in the fusiform gyrus, from 1 to 9 cm from the temporal tip. At testing 6-12 months after operation, patients with BTLA resection performed worse (mean 9% decrease) than those with no BTLA resection (mean 4% improvement) on tests of confrontation naming ($p = 0.03$). Resection size accounted for less of the variance in decrease in confrontation naming than did resection of the BTLA. Tests of performance I.Q. (PIQ), verbal I.Q. (VIQ), or recognition memory for word and verbal learning showed no significant difference between these groups. Most patients do not have language decrease with removal of basal temporal lobe 5-6 cm from the tip, even with removal of BTLA. Some patients, however, have persistent decrease in naming.

View details for Web of Science ID A1996UJ86700009

View details for PubMedID 8617177

- Open label pilot study of oxcarbazepine for inpatients under evaluation for epilepsy surgery *DRUG DEVELOPMENT RESEARCH* Fisher, R. S., ESKOLA, J., Blum, D., Kerrigan, J. F., Drazkowski, J., Duncan, B. 1996; 38 (1): 43-49
  View details for Web of Science ID A1996VF05000005
- Titanium aneurysm clips: part II - seizure and electroencephalographic studies in implanted rabbits *Neurosurgery* Fisher RS, T, Smith K, Lawton MT, Bichard WD, Spetzler RF 1996; 38: 1165-9
- Sensitivity and specificity of paired capillary prolactin measurement in

diagnosis of seizures *Journal of Epilepsy* Ehsan T, RS, Johns D, Lukas RJ, Blum D, Eskola J 1996; 9: 101-105

- Ethical use of placebos and provocative testing in diagnosis of epilepsy *Neurology* Devinsky O, Fisher RS 1996; 47: 866-870
- DIFFERENTIAL RESPONSE CHARACTERISTICS IN NONEPILEPTIC AND EPILEPTIC SEIZURE PATIENTS ON A TEST OF VERBAL-LEARNING AND MEMORY *NEUROLOGY* Bortz, J. J., Prigatano, G. P., Blum, D., Fisher, R. S. 1995; 45 (11): 2029-2034

Abstract

Investigators have found it difficult to separate patients with nonepileptic seizures (NES) from those with true epileptic seizures (ES) using quantitative measures of neuropsychological test performance. We examined qualitative response characteristics on the California Verbal Learning Test of 41 patients undergoing continuous video/audio-EEG monitoring in an effort to distinguish these patient groups (12 patients with left temporal [LT] foci, 11 with right temporal [RT] foci, and 18 with NES). NES patients explicitly recognized fewer target words compared with ES patients. In addition, NES patients rarely made false-positive errors, which resulted in failure to endorse a significant number of items on the recognition list. This response tendency is called a negative response bias. In contrast, LT patients endorsed a high number of items on the recognition test, which resulted in a positive response bias. RT patients demonstrated no consistent response tendency. In our sample, a negative response bias index (ie, a cutoff score < 0) showed a sensitivity of 61% and a specificity of 91%. We propose that failure to explicitly recognize words following repeated exposure may reflect aspects of psychological denial in NES patients. Response bias indices may thus help identify patients with NES and may begin to explain the psychological mechanisms underlying this complex disorder.

View details for Web of Science ID A1995TG31200016

View details for PubMedID 7501154

- COMPLEX PARTIAL STATUS EPILEPTICUS ACCOMPANIED BY SERIOUS MORBIDITY AND MORTALITY *NEUROLOGY* Krumholz, A., Sung, G. Y., Fisher, R. S., Barry, E., Bergey, G. K., Grattan, L. M. 1995; 45 (8): 1499-1504

Abstract

Nonconvulsive status epilepticus (NCSE) accounts for approximately 20% of all status epilepticus (SE). Although convulsive SE is recognized as a medical emergency, prompt diagnosis and treatment of patients with NCSE is often not emphasized because its consequences are thought to be benign. We report 10 patients with persistent neurologic deficits or death after well-documented NCSE in the form of complex partial status epilepticus (CPSE). All patients had prolonged CPSE lasting 36 hours or longer, as documented by clinical and EEG findings. Causes for CPSE were preexisting epilepsy with partial and secondarily generalized seizures (3 patients), vascular disease (2 patients), encephalitis (2 patients), and metabolic disease (1 patient); causes were unknown for two patients. Poor outcomes identified included persistent (lasting at least 3 months) or permanent

cognitive or memory loss (5 patients), cognitive or memory loss plus motor and sensory dysfunction (3 patients), and death (3 patients). NCSE in the form of CPSE is not a benign entity. Serious morbidity and mortality may occur due to the adverse effects of prolonged seizures and as a result of acute brain disorders that precipitate the seizures.

View details for Web of Science ID A1995RP30400013

View details for PubMedID 7644048

- CLOBAZAM, OXCARBAZEPINE, TIAGABINE, TOPIRAMATE, AND OTHER NEW ANTIEPILEPTIC DRUGS Fisher, R., Blum, D. LIPPINCOTT-RAVEN PUBL. 1995: S105-S114

Abstract

Clinical investigators recently have studied at least 21 new antiepileptic drugs (AEDs) in people with epilepsy. This review briefly examines 15 of these new AEDs: clobazam (CLB), dezinamide, flunarizine (FNR), loreclezole, milacemide (MLM), MK-801, nafimidone, ORG-6370, oxcarbazepine (OCBZ), progabide (PGB), ralitoline, stiripentol, tiagabine (TGB), topiramate (TPM), and zonisamide (ZNS). CLB, PGB, and TGB represent agents that act on the GABA system, and MLM acts on the glycine system. MK-801 and ZNS (in part) are excitatory amino acid antagonists, and FNR is a calcium-channel antagonist. OCBZ is a keto analogue of carbamazepine, which is not metabolized to the epoxide and may have fewer side effects. The remaining agents are novel compounds with a variety of suspected mechanisms. TPM appears especially effective for intractable partial seizures but has a high incidence of cognitive side effects. None of these new AEDs is useful for all patients with inadequate seizure control or ongoing toxicity. The role of each will require further clinical study and experience.

View details for Web of Science ID A1995RD91100011

View details for PubMedID 8784219

- ELECTRICAL-STIMULATION OF THE MAMILLARY NUCLEI INCREASES SEIZURE THRESHOLD TO PENTYLENETETRAZOL IN RATS *EPILEPSIA* Mirski, M. A., Fisher, R. S. 1994; 35 (6): 1309-1316

Abstract

High-frequency electrical stimulation of mammillary nuclei (MN) of rat posterior hypothalamus resulted in a significant increase in seizure threshold induced by pentylenetetrazol (PTZ). The anticonvulsant effect was frequency and intensity specific. Stimulation at 100 Hz (1-5 V, 30-200 microA) afforded protection against EEG and behavioral manifestations of PTZ seizures. Stimulation of either low frequency (5 Hz), high intensities (8-20 V, 300-800 microA), or outside the histologically verified MN target region did not increase seizure threshold. In some instances, high-intensity stimulation of MN alone elicited spike-wave epileptiform EEG activity accompanied by either arrest of behavior or myoclonic seizures. In animals with ongoing seizure activity, electrical stimulation of MN disrupted the high-voltage synchronous wave forms on cortical EEG. These data support the concept that electrical perturbation of MN in hypothalamus may functionally

inhibit generalization of paroxysmal activity required for expression of the EEG and, in particular, the behavioral component of PTZ seizures. These studies provide additional insight into forebrain-brainstem interactions mediating generalized seizure expression.

View details for Web of Science ID A1994PX21600028

View details for PubMedID 7988525

- CLINICAL AND ELECTROENCEPHALOGRAPHIC EVIDENCE FOR SITES OF ORIGIN OF SEIZURES WITH DIFFUSE ELECTRODECREMENTAL PATTERN *EPILEPSIA* Arroyo, S., Lesser, R. P., Fisher, R. S., Vining, E. P., Krauss, G. L., BANDEENROCHE, K., Hart, J., GORDON, B., Uematsu, S., Webber, R. 1994; 35 (5): 974-987

Abstract

A diffuse electrodecremental ictal pattern (DEP) has been associated with tonic seizures and, less often, with other forms of epilepsy and has been considered to reflect a generalized seizure disorder of diffuse cortical or subcortical (brainstem) origin. In some seizures associated with DEP, however, focal ictal manifestations have been observed. We reviewed the records of all patients admitted to our seizure monitoring unit for 3 years and detected 39 patients with seizures associated with DEP. In 23 of 39 patients, clinical ictal behaviors resembled seizures of unilateral supero/mesiofrontal lobe origin and interictal EEG showed a prominent unilateral frontal component. Nine of 39 had complex absences (CA)/complex partial seizures (CPS); 4 of them were of unilateral frontal lobe origin. Seven of 39 patients had tonic or atonic seizures. Seven patients were studied further with subdural electrodes. Ictal onsets showed a high-frequency frontal lobe discharge. We conclude that in a subgroup of patients a generalized electrodecremental pattern on scalp EEG results from a regional cortical high-frequency ictal discharge originating in a single frontal lobe.

View details for Web of Science ID A1994PP61200010

View details for PubMedID 7925169

- ELECTROENCEPHALOGRAPHIC CHANGES DURING SIMPLE PARTIAL SEIZURES *EPILEPSIA* Bare, M. A., BURNSTINE, T. H., Fisher, R. S., Lesser, R. P. 1994; 35 (4): 715-720

Abstract

We analyzed retrospectively the clinical and EEG data in 13 patients with simple partial seizures (SPS). All EEGs were recorded with surface electrodes with the standard 10-20 system and additional closely spaced scalp and subfrontotemporal skin electrodes. Seventy-seven seizures were recorded. We detected electrographic correlates with SPS in 10 of 13 patients (77%) and in 47 of 77 seizures (61%). The most common ictal correlates were rhythmic theta waves or spikes. Of the SPS with EEG changes, 58% were motor, 14% were sensory, and 28% were psychic seizures. Use of additional electrodes and recording channels may account for the higher incidence of EEG changes in this study than has been reported previously in the literature.

View details for Web of Science ID A1994PF80800002

View details for PubMedID 8082613

- EPILEPSY AND DRIVING - AN INTERNATIONAL PERSPECTIVE Fisher, R. S., PARSONAGE, M., Beaussart, M., Bladin, P., MASLAND, R., Sonnen, A. E., Remillard, G. LIPPINCOTT-RAVEN PUBL. 1994: 675-684

Abstract

Individuals with a history of seizures may be granted driving privileges if the risks of future seizure while driving are relatively low. Different nations have defined these risks in a wide variety of ways. Some countries, e.g., Japan, Greece, Brazil, India, and Russia, preclude driving after a single seizure. Other countries, such as Canada and the United States, allow driving < or = 3 months after certain types of seizures. A Joint Commission of the International Bureau for Epilepsy/International League Against Epilepsy has summarized regulations in several countries. From a consideration of medical literature and existing practices, a series of proposed guidelines for driving and epilepsy is recommended. In general, these guidelines suggest use of a seizure-free interval, generally 1-2 years but less in particular instances, to determine fitness to drive. Required physician reporting is discouraged, but physicians should report patients whom they believe pose a danger to themselves and to public safety. Individualized consideration should be given to special circumstances that may modify a general driving prohibition. Education and information programs are necessary for medical and regulatory authorities to develop a rational approach to driving and epilepsy worldwide.

View details for Web of Science ID A1994NW29100028

View details for PubMedID 8026417

- ADVANCES IN EPILEPSY *CURRENT OPINION IN NEUROLOGY* Blum, D., Fisher, R. S. 1994; 7 (2): 96-101

Abstract

Recent advances in clinical epilepsy have included improved systems for classifying seizures and epileptic syndromes, better definition of nontemporal seizures, improved methods for distinguishing syncope and pseudoseizures from epilepsy, and new approaches in the management of pregnant women with epilepsy. There has been continued development of the concept that epilepsy is a heterogeneous disorder with many imitators. Treatment is most successful when tailored to the particular seizure type, epileptic syndrome, and special needs of the individual patient.

View details for Web of Science ID A1994ND72400002

View details for PubMedID 8019668

- AUTOMATIC EEG SPIKE DETECTION - WHAT SHOULD THE COMPUTER IMITATE *ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY* Webber, W. R., Litt, B., Lesser, R. P., Fisher, R. S., Bankman, I. 1993; 87 (6): 364-373

Abstract

We conducted a study to explore how electroencephalographers (EEGers) read EEGs and reach clinical impressions based upon them. Eight EEGers and a rule-based computerized "spike" detector marked epileptiform discharges ("EDs") in 12 test records. Of all marked events, 18% were marked by all readers and 38% were marked by only one reader. Readers agreed on basic clinical features of the records, such as whether a record demonstrated EDs, the rank order of ED sources by location, and the ranking of test records in order of the number of EDs detected. Readers marked records in a consistent pattern that was independent of an objective measure of expertise and experience. Our computerized ED detector had lower sensitivity and selectivity than human readers, but either parameter could be adjusted to be comparable to human EEGers at the expense of the other. We propose that EEGers employ reproducible, quantitatively different styles of reading EEG tracings to reach qualitatively similar clinical impressions. In practice, EDs are not absolutely defined, but appear to represent a continuum of activity which lends itself better to description and rank ordering than to absolute quantitation. More than just counting EDs, a successful computerized ED detector should be adaptable to the style of individual readers in order to help them efficiently formulate their clinical impressions.

View details for Web of Science ID A1993MR14000003

View details for PubMedID 7508368

- EMERGING ANTIEPILEPTIC DRUGS *NEUROLOGY* Fisher, R. S. 1993; 43 (11): S12-S20

Abstract

The introduction of several new antiepileptic drugs in the United States is likely in 1993. Many new drugs have undergone testing, but the four currently considered the most important are felbamate, gabapentin, lamotrigine, and vigabatrin. When these drugs are used as add-on therapy for patients with intractable epilepsy, 20 to 60% of patients show at least a 50% improvement in seizure frequency and 7% become seizure free. An overview of these agents is presented.

View details for Web of Science ID A1993MJ68300004

View details for PubMedID 8232982

- DECREASED HIPPOCAMPAL MUSCARINIC CHOLINERGIC RECEPTOR-BINDING MEASURED BY I-123 IODODEXETIMIDE AND SINGLE-PHOTON EMISSION COMPUTED-TOMOGRAPHY IN EPILEPSY *ANNALS OF NEUROLOGY* MULLERGARTNER, H. W., Mayberg, H. S., Fisher, R. S., Lesser, R. P., Wilson, A. A., Ravert, H. T., Dannals, R. F., WAGNER, H. N., Uematsu, S., Frost, J. J. 1993; 34 (2): 235-238

Abstract

Regional binding of 123I-iododexetimide, a muscarinic acetylcholine receptor antagonist, was measured in vivo in the temporal lobes of 4 patients with complex partial seizures using single-photon emission computed tomography. In the anterior hippocampus ipsilateral to the

electrical focus, 123I-iododexetimide binding was decreased by 40 +/- 9% (mean +/- SD, p < 0.01) compared with the contralateral hippocampus; 123I-iododexetimide binding in other temporal lobe regions was symmetrical. The data indicate a regionally specific change of muscarinic acetylcholine receptor in anterior hippocampus in complex partial seizures of temporal lobe origin.

View details for Web of Science ID A1993LR02400019

View details for PubMedID 8338348

- MIRTH, LAUGHTER AND GELASTIC SEIZURES *BRAIN* Arroyo, S., Lesser, R. P., GORDON, B., Uematsu, S., Hart, J., SCHWERDT, P., Andreasson, K., Fisher, R. S. 1993; 116: 757-780

Abstract

Little is known about what pathways subserve mirth and its expression laughter. We present three patients with gelastic seizures and laughter elicited by electrical stimulation of the cortex who provide some insight into the mechanisms of laughter and its emotional concomitants. The first patient had seizures manifested by laughter without a subjective feeling of mirth. Magnetic resonance imaging showed a cavernous haemangioma in the left superior mesial frontal region. Ictal subdural electrode recording showed the seizure onset to be in the left anterior cingulate gyrus. Removal of the lesion and of the seizure focus rendered the patient virtually seizure free over 16 months of follow-up. The other two patients had complex partial seizures of temporal lobe origin. Electrical stimulation of the fusiform gyrus and parahippocampal gyrus produced bursts of laughter accompanied by a feeling of mirth. These cases reveal a high likelihood of cingulate and basal temporal cortex contribution to laughter and mirth in humans, and suggest the possibility that the anterior cingulate region is involved in the motor act of laughter, while the basal temporal cortex is involved in processing of laughter's emotional content in man.

View details for Web of Science ID A1993LT17900001

View details for PubMedID 8353707

- Cerebellar and thalamic stimulation for epilepsy. *Advances in neurology* Krauss, G. L., Fisher, R. S. 1993; 63: 231-245
  View details for PubMedID 8279308

- ANTERIOR CHEEK ELECTRODES ARE COMPARABLE TO SPHENOIDAL ELECTRODES FOR THE IDENTIFICATION OF ICTAL ACTIVITY *ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY* Krauss, G. L., Lesser, R. P., Fisher, R. S., Arroyo, S. 1992; 83 (6): 333-338

Abstract

Sphenoidal electrodes are used to localize epileptiform activity originating in the temporal lobe during complex partial seizures. Sphenoidal electrodes, however, are semi-invasive and uncomfortable to the patient. We compared skin electrodes placed on the cheek ("cheek electrodes") with sphenoidal electrodes for the detection of the side and site of complex partial seizure onset. In a masked, randomized comparison of single ictal recordings in 22

patients, there were no significant differences between sphenoidal and cheek electrode montages in detecting the side or site of ictal onset ($P < 0.01$). Signal/noise ratios for interictal spikes were a mean 16.5% greater at sphenoidal sites compared to cheek sites (paired t test, $t = 2.4$, $P < 0.05$). This difference, however, did not influence the detection of rhythmical ictal activity in cheek and sphenoidal montages in our study, nor the assignment of side, site or time of seizure onset by unbiased readers. Recordings from cheek electrodes are comparable to those from sphenoidal electrodes and are useful for localizing ictal activity.

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View details for PubMedID 1281078

- PLACEBO-CONTROLLED PILOT-STUDY OF CENTROMEDIAN THALAMIC-STIMULATION IN TREATMENT OF INTRACTABLE SEIZURES *EPILEPSIA* Fisher, R. S., Uematsu, S., Krauss, G. L., CYSYK, B. J., Mcpherson, R., LESER, R. P., GORDON, B., SCHWERDT, P., Rise, M. 1992; 33 (5): 841-851

Abstract

Stimulation of centromedian (CM) thalamic nuclei has been proposed as a treatment for seizures. We implanted programmable subcutaneous (s.c.) stimulators into CM bilaterally in 7 patients with intractable epilepsy to test feasibility and safety. Stimulation was on or off in 3-month blocks, with a 3-month washout period in a double-blind, cross-over protocol. Stimuli were delivered as 90-microseconds pulses at 65 pulses/s, 1 min of each 5 min for 2 h/day, with voltage set to half the sensory threshold. Stimulation was safe and well-tolerated, with a mean reduction of tonic-clonic seizure frequency of 30% with respect to baseline when stimulator was on versus a decrease of 8% when the stimulator was off. There was no improvement in total number of generalized seizures with stimulation, and treatment differences were not statistically significant. Stimulation at low intensity did not alter the EEG acutely, but high-intensity stimulation induced slow waves or 2-3 Hz spike-waves with ipsilateral frontal maximum. In an open-label follow-up segment with stimulator trains continuing for 24 h/day, 3 of 6 patients reported at least a 50% decrease in seizure frequency. There were no side effects. This pilot project demonstrated the feasibility of controlled study of thalamic stimulation in epilepsy, but further study will be needed to demonstrate efficacy.

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- HIGH-FREQUENCY EEG ACTIVITY AT THE START OF SEIZURES *JOURNAL OF CLINICAL NEUROPHYSIOLOGY* Fisher, R. S., Webber, W. R., Lesser, R. P., Arroyo, S., Uematsu, S. 1992; 9 (3): 441-448

Abstract

Frequencies above 35-40 Hz are poorly visualized on conventional EEG scalp recordings. We investigated frequency components up to 150 Hz in digitally recorded EEGs of seizures in five patients with implanted subdural grids, as part of their evaluation for epilepsy surgery. Amplifier bandpass

was set from 0.1 to 300 Hz, and EEG was digitized at 2,000 samples per second. Seizures with electrodecremental patterns at the start showed a significant increase in spectral power above 35 Hz, with a twofold increase in the 40-50-Hz range, and up to a fivefold increase in the 80-120-Hz portion of the spectrum. Activity above 40 Hz could represent summed action potentials, harmonics of synaptic potentials or transient sharp components of synaptic potentials. High-frequency increases were largely localized to the region of the seizure focus. Grid sites remote from the focus did not show significant energy in the EEG band above 40 Hz at baseline, nor at time of seizure onset. Our findings suggest that high-frequency recordings may be of use in localizing seizure foci.

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View details for PubMedID 1517412

- MOTOR AND SENSORY CORTEX IN HUMANS - TOPOGRAPHY STUDIED WITH CHRONIC SUBDURAL STIMULATION *NEUROSURGERY* Uematsu, S., Roberts, D. W., Lesser, R., Fisher, R. S., GORDON, B., Hara, K., Krauss, G. L., Vining, E. P., WEBBER, R. W. 1992; 31 (1): 59-72

Abstract

Classic neurosurgical teaching holds that once the Rolandic fissure (Rf) has been located, there are distinct differentiated primary motor and sensory functional units confined within a narrow cortical strip: Brodmann's Areas 4 and 6 for primary motor units in front of the Rf and 3, 1, and 2 for sensory units behind the Rf. To test this assumption, we examined in detail the records of cortical mapping done by electrical stimulation of the cerebral cortex via implanted subdural electrode grids in 35 patients with seizure disorders. Of 1381 stimulations of the electrode sites, 346 (25.1%) produced primary motor or motor-arrest and sensory responses in contralateral body parts: 56.8% were primary motor responses; 16.2% were motor-arrest; 22.5% were sensory; and the remaining 4.5% were mixed motor and sensory responses. Two-thirds (65.9%) of the primary motor responses were located within 10 mm of the Rf, and the remaining one-third (34.1%) were more than 10 mm anterior to the Rf or were posterior to the Rf. Furthermore, in the patient group with brain lesions, fewer than one-third (28.1%) of the responses were within the 10-mm narrow anterior strip. Our study reconfirmed that a significant number--at least one-third--of motor responses are distributed outside the classic narrow cortical strip. In patients with brain lesions, the motor representation is further displaced outside the narrow strip. This finding indicates that primary motor cortex may extend beyond the gyrus immediately anterior to the Rf.

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- DESIGN PRINCIPLES FOR COMPUTERIZED EEG MONITORING *ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY* Lesser, R. P., Webber, W. R., Fisher, R. S. 1992; 82 (4): 239-247
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- APPARENT DESENSITIZATION TO GLUTAMATE - POSSIBLE ROLE IN EPILEPSY *EPILEPSY RESEARCH* Fisher, R. S., Cole, A. E., Pumain, R., Gale, K. 1992: 197-201
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- ASSESSMENT OF SURGICAL OUTCOME *EPILEPSY RESEARCH* Lesser, R. P., Fisher, R. S., Uematsu, S. 1992: 217-229

  ## Abstract

  Evaluation of outcome of epilepsy surgery is complex because of several factors. Epilepsy is itself a heterogeneous disorder. Different epilepsy centers encounter different referral mixes of patients. Institutions employ various methods for pre-operative evaluation and widely varying surgical techniques. Clear definitions of surgical success and reliable scales for its measurement are lacking. Few data are acquired prospectively and maintained in a format allowing inter-institutional collation of results. A better representation of surgical outcome could in the future be served by adherence to 4 principles: collection of common data in standard formats; comparison of like, rather than disparate, populations; maintenance of quantitative data in raw form; and measurement of outcome along several dimensions or scales. Psychosocial issues have been underemphasized in most prior analyses of outcome.

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- QUANTIFICATION OF MU-OPIATE AND NON-MU-OPIATE RECEPTORS IN

TEMPORAL-LOBE EPILEPSY USING POSITRON EMISSION TOMOGRAPHY *ANNALS OF NEUROLOGY* Mayberg, H. S., SADZOT, B., Meltzer, C. C., Fisher, R. S., Lesser, R. P., Dannals, R. F., Lever, J. R., Wilson, A. A., Ravert, H. T., WAGNER, H. N., Bryan, R. N., Cromwell, C. C., Frost, J. J. 1991; 30 (1): 3-11

Abstract

Alterations in a variety of neurotransmitter systems have been identified in experimental models of epilepsy and in brain tissue from patients with intractable temporal lobe seizures. The availability of new high-affinity radioligands permits the study of some neuroreceptors in vivo with positron emission tomography (PET). We previously characterized the in vivo binding of 11C-carfentanil, a potent and selective mu opiate receptor agonist, and described increases in 11C-carfentanil binding in the temporal neocortex of patients with unilateral temporal lobe epilepsy. These studies have been extended to 11C-diprenorphine, which labels mu, kappa, and delta opiate receptor subtypes. Paired measurements of opiate receptor binding were performed with PET using 11C-carfentanil and 11C-diprenorphine in patients with unilateral temporal lobe seizures. Carfentanil binding, reflecting changes in mu opiate receptors, was increased in the temporal neocortex and decreased in the amygdala on the side of the epileptic focus. Diprenorphine binding, reflecting mu as well as non-mu opiate subtypes, was not significantly different among regions in the focus and nonfocus temporal lobes. Regional glucose metabolism, measured using 18F-2-fluoro-2-deoxyglucose, was decreased in the mesial and lateral aspects of the temporal lobe ipsilateral to the epileptogenic focus. The variation in pattern of carfentanil and diprenorphine binding supports a differential regulation of opiate subtypes in unilateral temporal lobe epilepsy.

View details for Web of Science ID A1991FV10200001

- EPILEPSY *JOURNAL OF NUCLEAR MEDICINE* Fisher, R. S., Frost, J. J. 1991; 32 (4): 651-659

Abstract

As surgical treatments for adult and pediatric forms of epilepsy have become more refined, methods for noninvasive localization of epileptogenic foci have become increasingly important. Detection of focal brain metabolic or flow abnormalities is now well recognized as an essential step in the presurgical evaluation of many patients with epilepsy. Positron emission