Presidential Symposium:
The Changing Landscape of Epilepsy Surgery

Symposium Chairs:
Jacqueline French, M.D.

Saturday, December 7, 2013
Convention Center – Ballroom B, Level Three
8:30 a.m. – 11:45 a.m.
OVERVIEW
Epilepsy surgery is a very effective intervention for patients with treatment resistant epilepsy. The most successful epilepsy surgery is temporal lobectomy, which traditionally has produced seizure freedom in approximately two-thirds of patients. An AAN / AES guideline recommended temporal lobectomy as the treatment of choice for treatment resistant temporal lobe epilepsy. Yet, in a survey of centers with large epilepsy surgery programs, the number of overall surgeries, as well as the number of temporal lobectomies had decreased almost universally from their peaks. Moreover, surgeries for mesial temporal sclerosis have declined by half, whereas non-lesional cases have increased by a third.

This symposium will present the data from various sources that suggest a shift in epilepsy surgery type and possibly location (from established to emerging centers) and will provide available evidence for the theories that may account for these changes. Also, future directions related to these changes, including basic science considerations (should the neocortex receive as much attention as the hippocampus?) will be discussed.

LEARNING OBJECTIVES
- Recognize epilepsy syndromes other than temporal lobe epilepsy and evaluate such patients for epilepsy surgery
- Evaluate all patients with refractory epilepsy syndromes including extratemporal and non-lesional epilepsy to provide optimal treatment, identify surgical candidates, and perform epilepsy surgery for those with syndromes other than temporal lobe epilepsy when indicated.

TARGET AUDIENCE
Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, “mid-level” providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Advanced: Symposium will address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques, advanced treatment modalities, including surgery).

PROGRAM
8:30 – 9:30 am Research Awards Presentation
9:30 – 9:45 am Introduction
   Jacqueline A. French, M.D.
9:45 – 10:05 am Who Was I Treating Then? Who am I Treating Now?
   Dennis D. Spencer, M.D.
10:05 – 10:30 am The Changing Surgical Landscape in Kids
   Howard L. Weiner, M.D.
10:30 – 11:00 am What Is the Evidence that the Landscape is Changing? Theories of Change
   Dale C. Hesdorffer, Ph.D.
11:00 – 11:25 am Perspective of Basic Science: Is There Life Outside the Hippocampus?
   Jeffrey A. Loeb, M.D., Ph.D.
11:25 – 11:45 am Conclusions
   Jacqueline A. French, M.D.

ACCREDITATION
The American Epilepsy Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION
Physicians: The American Epilepsy Society designates this live activity for a maximum of 2.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistant: AAPA accepts certificates of participation for educational activities certified for AMA PRA Category 1 Credit™ from organizations accredited by ACCME or a recognized state medical society. Physician Assistants may receive a maximum of 2.5 hours of Category 1 credit for completing this program.

Nurses: EDUPRO Resources LLC is an approved provider of continuing nursing education by Pennsylvania State Nurses Association, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation. EDUPRO is also an approved provider by the California Board of Registered Nursing, provider number CEP-14387. Nurses who participate in selected AES programs can receive up to 30.75 contact hours. To successfully complete the activities, nurses are required to complete the evaluations for each session attended and to access the Medical Education Evaluator to claim Credit.

Nurses may claim up to 2.5 contact hours for this session.

International Credits: The American Medical Association has determined that non-U.S. licensed physicians who participate in this CME activity are eligible for AMA PRA Category 1 Credit™.

ABPN Core Competencies
The American Board of Psychiatry and Neurology has reviewed the Presidential Symposium and has approved this program as part of a comprehensive lifelong learning program, which is mandated by the ABMS as a necessary component of maintenance of certification.

Core Competencies: Comprehensive Patient Care, System-Based Practice, and Practice-Based Learning

FACULTY/PLANNER DISCLOSURES
It is the policy of the AES to make disclosures of financial relationships of faculty, planners and staff involved in the development of educational content transparent to learners. All faculty participating in continuing medical education activities are expected to disclose to the program audience (1) any real or apparent conflict(s) of interest related to the content of their presentation and (2) discussions of unlabeled or unapproved uses of drugs or medical devices. AES carefully reviews reported conflicts of interest (COI) and resolves those conflicts by having an independent reviewer from the Council on Education validate the content of all presentations for fair balance, scientific objectivity, and the absence of commercial bias. The American Epilepsy Society adheres to the ACCME’s Essential Areas and Elements regarding industry support of continuing medical education; disclosure by faculty of commercial relationships, if any, and discussions of unlabeled or unapproved uses will be made.

FACULTY / PLANNER BIO AND DISCLOSURES
Jacqueline French, M.D. (Chair)
Dr. Jacqueline French is a professor in the Department of Neurology NYU, in the Comprehensive Epilepsy Center, and Director of the Clinical Trials Consortium, an academic group that has performed a number of early phase clinical trails in epilepsy, and has developed new methodologies for epilepsy trials. Dr. French trained in Neurology at Mount Sinai Hospital in New York, and did her fellowship training in EEG and epilepsy at Mount Sinai hospital and Yale University. Dr. French is the current president of the American Epilepsy Society. She has focused her research efforts on development of new therapeutics for epilepsy, and new methodologies for clinical trials.
Jacqueline French, M.D. discloses receiving support as Consulting/Advisory Board Activity from Consulting (on behalf of the Epilepsy Study Consortium) Acorda Therapeutics, Aprecia, Avanir, Biotie, Catalyst, Concert, Cyberonics, Eisai Medical Research, Electrocore, Eli Lilly, GlaxoSmithKline, Icaigen, Inc., Johnson & Johnson, LGCH Inc, Mapp Pharmaceuticals, Marinus, Neurelis, Neurotherapeutics, Neuropace, NeuroVista Corporation, Novartis, Ono Pharma USA, Inc., Lundbeck, Pfizer, Sepracor, Sunovion, SK Life Science, Supernus Pharmaceuticals, UCB Inc/Schwarz Pharma, Upsher Smith, Valeant, Vertex, Vivus Advisory board: UCB, Biotie, Electrocore, Eli Lilly, Acorda Therapeutics, Sunovion, Upsher-Smith.; as Research Funding from For Profit Commercial Sources/Principle Investigator from Principle investigator on multicenter trials for UCB, Impax, LGCH, Mapp Pharmaceuticals, Upsher Smith Vertex Funding to support the HEP study: UCB, Pfizer; as Federal/State/Not-for Profit Funding from Investigator (co-PI K Meador, P Pennell) NINDS 2U01NS038455-11A1 8/01/2012-7/31/2017 Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs This is a multicenter study assessing outcomes of pregnancy in women with epilepsy Co-PI-J French Epilepsy Study Consortium 7/1/2012-7/1/2017 Human Epilepsy Project This is a 26-center prospective observational study to determine clinical, blood and EEG biomarkers of resistance to antiepileptic drugs Support provided by UCB, Pfizer, Lundbeck, FACES Co-PI: J French 7/1/2010-7/1/2013 Milken Foundation WEPOD (Women with Epilepsy, Pregnancy, Outcomes and Delivery) This is a 3-center study of fecundity in epilepsy R01 NS053998 (PI Lowenstein) 05/01/07-04/30/2012 NINDS The Epilepsy Phenome Genome Project (EPGP) The EPGP is a large-scale, national, multi-institutional, collaborative research project aimed at advancing our understanding of the genetic basis of the most common forms of idiopathic and cryptogenic epilepsies and a subset of asymptomatic epilepsy. The Epilepsy Study Consortium 09/01/09-8/31/10 As director of the Epilepsy Study consortium, Dr French receives 25% ongoing salary support for various activities performed; as Participation in Foundation or Not-for-Profit Organizations from President, Epilepsy Study Consortium Head of Scientific Advisory Board Epilepsy Therapy Project Board of Directors: Epilepsy Foundation (until 5/2013; as Other Revenue Source - Are there other revenue/benefits that might be perceived as a conflict? from 25% salary support Salary Support from the Epilepsy Study Consortium (a non-profit organization).

Dale Hesdorffer, Ph.D.
Dale Hesdorffer, Associate Professor in the Sergievsky Center at Columbia University, serves on several editorial boards, the professional advisory board of the Epilepsy Foundation of America, the American Epilepsy Society Task Force on psychiatric aspects of epilepsy, the American Academy of Neurology SUDEP guidelines workgroup, and is an associate editor of Epilepsia. She was a member of the Institute of Medicine Committee on the Public Health Dimensions of the Epilepsies and the IOM Committee on Gulf War and Health: Long-Term Consequences of Traumatic Brain Injury. Her work focuses on the epidemiology of epilepsy.

Dale Hesdorffer, Ph.D. discloses receiving support as Consulting/Advisory Board Activity from UCB pharma. Gave a webinar and they paid me $1,000; as Federal/State/Not-for Profit Funding from the University receives the grants. I get salary from them.

Jeffrey Loeb, M.D., Ph.D.
Dr. Loeb is professor and head of the Department of Neurology and Rehabilitation at the University of Illinois in Chicago. He received his M.D. and Ph.D. from the University of Chicago, completed a residency in Neurology at the Massachusetts General Hospital and fellowship training in epilepsy at Harvard's Beth Israel Hospital. Dr. Loeb conducted postdoctoral work in the Department of Neurobiology at Harvard Medical School with Dr. Gerald Fischbach where he became interested in how understanding brain development can teach us what goes wrong in human disease and suggest new treatments. He directs a multidisciplinary program in human systems biology of epilepsy.
Jeffrey Loeb, M.D., Ph.D. discloses receiving support as Consulting/Advisory Board Activity from Consulting for Takeda pharmaceuticals and Neuropace; as Intellectual Property Ownership from submitted a patent through wayne state university on non-coding RNAs as a treatment for epilepsy.

Dennis Spencer, M.D.
Dr. Spencer is the Harvey and Kate Cushing Professor and Chair of the Department of Neurosurgery at Yale University School of Medicine. He is a graduate of Washington University School of Medicine and completed his neurosurgical residency at Yale in 1977. He joined the Yale neurosurgery faculty following his residency, and became Chief of neurosurgery in 1987. He has an international reputation in the surgical treatment of neurological diseases causing epilepsy and developed a widely used neocortical sparing surgical approach for patients with temporal lobe epilepsy.

Dennis Spencer, M.D. has nothing to disclose.

Howard Weiner, M.D.
Howard L. Weiner, MD is a Professor of Neurosurgery and Pediatrics at the NYU Langone Medical Center, is a Diplomate of the American Boards of Neurological Surgery and Pediatric Neurological Surgery, holds an endowed chair, and is the pediatric epilepsy surgeon in the NYU Epilepsy Center. His clinical and research interests have included novel approaches in epilepsy surgery, Tuberous Sclerosis Complex, and pediatric brain tumors. He has published on these topics, has been invited to speak both in the US and abroad, has been consistently named in Castle Connolly, NY Magazine, and the NY Times Top Doctors lists, and was a recipient of the Van Wagenen Fellowship from the AANS.

Howard Weiner, M.D. has nothing to disclose.

Ajay Gupta, M.D. (CME Reviewer)
Ajay Gupta, M.D., is Head or Pediatric Epilepsy at the Cleveland Clinic Foundation. He is a Professional Staff in the Epilepsy Center/Neurological Institute at The Cleveland Clinic Foundation. He is Associate Professor at The Cleveland Clinic Lerner College of Medicine, Case Western Reserve University. He is also the founder director of multidisciplinary Tuberous Sclerosis Program at the Cleveland Clinic.

Ajay Gupta, M.D. discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from Lundbeck Inc; as Consulting/Advisory Board Activity from Questcor; as Federal/State/Not-for Profit Funding from Tuberous Sclerosis Alliance; as Participation in Foundation or Not-for-Profit Organizations from Epilepsy Foundation Editorial Board - Pediatric Neurology Editorial Board - Epileptic disorders.

Paul Levisohn (Medical Content Specialist, AES)
Dr. Levisohn is a member of the faculty of the section of Pediatric Neurology at The University of Colorado School of Medicine and Children's Hospital Colorado Neuroscience Institute, having joined the faculty over 15 years ago following a similar period of time in the private practice of pediatric neurology. His academic career has focused on clinical care for children with epilepsy with particular interest in clinical trials and on the psychosocial impact of epilepsy. Dr. Levisohn is currently a consultant on medical content for CME activities to staff of AES. He is a member of the national Advisory Board of EF and has been chair of the advisory committee for the National Center of Project Access through EF.

Paul Levisohn, M.D. discloses receiving support as Consulting/Advisory Board Activity from CME medical content consultant to AES staff.; as Research Funding from For Profit Commercial Sources/Principle Investigator from Eisai (clinical trials); as Federal/State/Not-for Profit Funding from NIH/NINDS: Childhood Absence Epilepsy, PI. NeuroNEXT, PI.; as Participation in Foundation or Not-
for-Profit Organizations from Professional Advisory Board, Epilepsy Foundation; Co-chair, Advisory Committee National Center for Project Access; Consultant to AES.

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The Medical Education Evaluator® is an online system that allows any attendee to self-manage the process of completing course evaluations, tracking educational credits and printing out the CME or nursing certificate.

Log on to the Evaluator via the AES website at www.AESnet.org. Once you are on the Evaluator, you will be asked to enter your MyAES ID # and password. You must then complete the evaluations and claim credit for the sessions you attended. The certificate(s) are saved to your personal account page and you may print the certificate(s) in PDF format at any time.

To help support this process, attendees who want CME will be asked to pay the following rates:

- **Member Fees**: $50 through January 17, 2014
  $75 January 18 – February 28, 2014
- **Non-member Fees**: $75 through January 17, 2014
  $100 January 18 – February 28, 2014

The online Evaluator will be left open through February 28, 2014. You must complete the evaluations and credit tracking by that date.

By completing this information online, attendees greatly assist the Council on Education and Annual Meeting Committee with important needs assessment data whereby the AES can further plan and address educational gaps to meet the needs of our learners.

A meeting attendance certificate will be available for international meeting attendees at the registration desk.

**Handouts**
Handouts for the educational symposia are available to print in the AES virtualToteBag. Paper handouts will not be provided on site.
The Changing Landscape of Epilepsy Surgery
December 7, 2013
Jacqueline A French MD
Comprehensive Epilepsy Center
NYU School of Medicine

Number of Surgeries performed worldwide between 1986-1990

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>Number (% of surgeries performed)</th>
<th>Totals</th>
</tr>
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<tr>
<td>Anterior Temporal lobectomy</td>
<td>4862 (59%)</td>
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Are Times Changing?

To determine whether physicians felt that MTLE was still the most common type of surgical candidate, we used the new “Q-PULSE” mechanism

Intro to Q-Pulse

- New AES effort
- 2 epileptologists invited from every NAEC epilepsy center make up q-pulse panel
  - Each filled out a survey providing demographics (age, pediatric vs adult, years in practice, primary interest, geographic location)
- Q-Pulse questions pushed to panel via Survey Monkey
- All responses anonymized, but demographics can be linked with responses
- We received 97 replies to the survey
At your center, how many of the treatment resistant epilepsy patients have mesial temporal lobe epilepsy?

- The majority: 51%
- <10% (very few): 35%
- 10-50% (the minority): 11%
- Don't know: 4%

*No-one endorsed "all patients" or "no patients"

Compared to 10 years ago, your epilepsy center sees _____ pts with mesial temporal lobe epilepsy

- Not practicing then but more: 64%
- More: 10%
- Not practicing then but less: 16%
- Less: 3% (very few)

The majority Don't know

If the landscape is changing, how can we know for sure?

- Epilepsy centers may behave in different ways:
  - They may elect to perform only temporal lobe surgeries
    - In this case, the absolute number of surgeries at the center might fall, but the percent of the total made up of TLE would not change
  - They may attempt to perform increasing number of neocortical surgeries
    - In this case, the absolute number of surgeries at a center may stay the same, rise or fall, but the percent of temporal lobectomies would fall

Absolute number of surgeries in Bonn

Epilepsy program

This Symposium

- A Surgeon's view of the changing landscape (Spencer)
- What about Children? (Weiner)
- If things are changing, why is it happening? (Hesdorffer)
- What is the implication for Basic Science? (Loeb)
- Where do we go from here? (French)
Who Was I Treating Then? Who Am I Treating Now?
December 7, 2013
Dennis Spencer, M.D.
Yale University School of Medicine

Disclosure
Nothing to disclose.

Yale epilepsy surgery 1983-2009

Single Program: Adults, pediatrics, inclusive of all surgery types
Single Surgeon
Database designed in 1982 and implemented in 1983
1022 total cases
648 temporal resections
65 callosoomies
41 hemispherectomies
329 neocortical resections
7 pure MST’s

What does one program tell us about the changing landscape of epilepsy surgery over time, in particular the medial temporal lobe thought to be the most common source of surgically remediable epilepsy


• The authors record the stories of 82 patients through the 60’s
• Discharges all medial
• Correlated with MTS in 65%, describes fields
• No neocortical involvement
• Using Falconer’s approach but talking about neocortical sparing
ANTEROMEDIAL TEMPORAL RESECTION

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Decline in medial temporal resections for MTS

- Proportionate to decline in all surgeries
- Reflection of increased demand for intracranial studies for neocortical epilepsy

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- Is there more decline in MTS than other temporal substrates?
Decline in medial temporal resections for MTS

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- Is there more decline in MTS than other temporal substrates?
- Are more patients studied but not going to resection?
Decline in medial temporal resections for MTS

• Proportionate to decline in all surgeries

• Reflection of increased demand for intracranial studies for neocortical epilepsy

• Is there more decline in MTS than other temporal substrates?

• Are more patients studied but not going to resection?

• Is there a change in referral base?

Research in this decade included several NIH grants studying human temporal lobe epilepsy clinically and the hippocampus anatomically, immunohistochemically and electrophysiologically.

At the end of this decade our human research required combining temporal and extratemporal studies still emphasizing temporal lobe but less stress on medial structures for example with microdialysis comparing neocortical and temporal lobe substrates
In the past decade human research is balanced with animal models and involves all etiologies with much less emphasis on the hippocampus and much more on developmental issues and neocortical network localization using intracranial studies.

Average Number of Contacts per Patient

Present Research Focus

Pub Med review:
- Temporal Lobe Epilepsy----14,998 articles
- Temporal Lobe Surgery----8,493 articles
- Hippocampal Research and Epilepsy----9,361 articles
- Neocortical Epilepsy Surgery----434 articles
- Neocortical Epilepsy Research----772 articles

Yale Experience Summary

- Single Center thirty year experience
- Taking into account:
  - dispersion of cases
  - change in referral base
  - new medications
  - better treatment of complex febrile seizures
  - Appears to be a decline and flattening in the incidence of MTS
  - Our clinical and basic research efforts need to recognize this and refocus
The Changing Surgical Landscape in Kids

December 7, 2013

Howard L. Weiner, MD
NYU Langone Medical Center

American Epilepsy Society | 2013 Annual Meeting

Learning Objectives

• To appreciate two fundamental changes that have led to the expanding surgical landscape in children with epilepsy

American Epilepsy Society | 2013 Annual Meeting

Hypothesis

• In contrast to adult epilepsy surgery, the change in surgical landscape in kids does not appear to be epidemiological but, rather, likely reflects a change in us and how we look at the problem

The Changing Surgical Landscape in Kids

Hypothesis

• The landscape is expanding

• This is based on two fundamental changes:
  -- a change in our understanding of the risk-benefit profile of pediatric epilepsy surgery
  -- a change in our overall approach to the evaluation and treatment of children with epilepsy

The Established Landscape in Kids

• cortical dysplasia (1)
• epilepsy-associated tumor (3, 4)
• cavernoma (4)
• hemispheric pathology (4)
• MTS (5)
• temporal/frontal resections (2)
• 20-35% intracranial electrodes (5)
• unifocal, older age (1)

Harney L et al, Epilepsia 2009 (1); Cossu M et al Epilepsia 2008 (2); Southwell DG et al, Neurosurgery 2012 (2); Maistros CR et al Epilepsia 2007 (3); Palmini A et al Neurology 1995 (3); Thorn MJ et al, Brain Pathology 2012 (2); Smyth MD et al, Neurology 2007 (7); Moosa M et al, Neurology 80:253-60, 2013 (8)
Pediatric Epilepsy Surgery
Novel Concept

The Changing Surgical Landscape in Kids--the default presumption is one of reluctance--as it should be

- Dangerous--especially in young children
- Too invasive
- Not better than medical therapy
- Costs too much

“pediatric epilepsy surgery” PubMed search

- pre-1993 (first in 1949) n=97
- 1993-2003 n=387
- 2003-2013 n=901

My practice the last 12 months

- 78 craniotomies for children with epilepsy

Uncontrolled epilepsy is bad for the developing brain, quality of life, life expectancy

- “Uncontrolled seizures impair cognitive function with effects being most severe in infancy and lessening with increasing age at onset. These findings further emphasize the need for early aggressive treatment and seizure control in infants and young children.” 

- “Relative to the population...sudden and seizure related deaths alone double overall mortality...mortality is significantly higher compared with the general population in children with complicated epilepsy...the SUDEP rate was similar to or higher than sudden infant death syndrome rates.”

A change in our understanding of the risk-benefit profile of pediatric epilepsy surgery

In general, weighing the risk of the current course vs. the risk of surgery

- uncontrolled epilepsy is bad for the developing brain, quality of life, life expectancy
- effective epilepsy surgery in kids can improve development, quality of life
- surgery in kids is safe - comparable to other aspects of pediatric neurosurgery
- effective epilepsy surgery can be cost effective in kids

“Dangerous” especially in young children

“Too invasive”
Effective epilepsy surgery in kids can improve development, quality of life

• “After surgery, seizure frequency and developmental quotient improved.”

• “Developmental status before surgery predicted developmental function after surgery.”

• “Patients who were operated on at younger age and with epileptic spasms showed the largest increase in developmental quotient after surgery.”


Surgery in kids is safe - comparable to other aspects of pediatric neurosurgery

• “...carefully selected pediatric patients with intractable epilepsy can benefit from subdural invasive monitoring procedures that entail definite but acceptable risks” Onal C et al J Neurosurg 98:1017-26, 2003

• “There were no surgical complications related to intracranial EEG monitoring...The supplemental depth electrodes conferred an extra dimension of depth to the analysis, which allowed for successful outcome...” Kim H et al J Neurosurg Pediatr 8:49-56, 2011

• “Placement of subdural grid and strip electrodes...is generally well tolerated in the pediatric population...not associated with higher rates of...complications” Johnston JM Jr et al J Neurosurg 105:343-7, 2006

Safety

• Roth J, Carlson C, Devinsky O, Harter DH, MacAllister WS, Weiner HL.

• Safety of Staged Epilepsy Surgery in Children

• Neurosurgery (in press)

• 161 children (Mean age 7 yo, 8 mos-16 yo), 200 admissions, 496 surgeries

• No mortality

• Neuro deficit 2%, infection 1.5%, bleed 0.5%

• Learning curve: complications down in second half of study (1st v. 2nd 6 yrs, 100 admissions)

Effective epilepsy surgery in kids can be cost effective

• “Surgical treatment resulted in greater reduction in seizure frequency compared to medical therapy and was a cost-effective treatment option in children with intractable epilepsy.” Widjaja E et al Epilepsy Research 94:61-68, 2011

• Cleveland Clinic, Neurologic Institute, 2011 Outcomes

A change in our overall approach to the evaluation and treatment of children with epilepsy

In general, kids who previously would not have been candidates for surgery are being considered

• Improved diagnostic evaluations pre-operatively (MRI, PET, MEG, SPECT, fMRI)

• More comfort with invasive EEG monitoring in kids in challenging cases

• More willingness to consider aggressive surgical resections even in the face of anticipated neurologic deficits
• "Epilepsy surgery may be successful for selected children... with a congenital or early-acquired brain lesion, despite abundant generalized or bilateral epileptiform discharges on EEG. The diffuse EEG expression may be due to an interaction between the early lesion and the developing brain"


• "This approach can help to identify both primary and secondary epileptogenic zones in young TSC patients with multiple tubers. Multiple or bilateral seizure foci are not necessarily a contraindication to surgery."


Improved diagnostic evaluations pre-operatively (MRI, PET, MEG, SPECT, fMRI)

The ability of high field strength 7-T magnetic resonance imaging to reveal previously uncharacterized brain lesions in patients with tuberous sclerosis complex


More comfort with invasive EEG monitoring in kids in challenging cases

1) Non-concordant or non-localizing non-invasive studies (implies that complicated cases may still have resectable seizure focus)

2) Normal MRI in setting of refractory partial epilepsy (define resection)

3) Presumed seizure focus overlaps eloquent cortex (define resection)

4) Multiple potential (multifocal) seizure foci with non-localizing non-invasive studies (which one?)

5) Structural lesion on MRI (define relationship of seizure focus to MRI lesion)

More willingness to consider aggressive surgical resections even in the face of anticipated neurologic deficits

• Would you agree with resecting a seizure focus in eloquent cortex (motor, visual) if you were confident it could render child seizure free?

• Painful decision with parents

• QOL intervention--Trade off of potential physical deficit for seizure freedom and developmental improvement

• Unique to pediatric medicine

Do tubers contain foci? A review of epileptogenic foci in perilesional cortex in children with tuberous sclerosis complex

Yaron A, Friedling, Robert Stroink, Patricia Tumak, Jennifer Blatteis, Ulrich Carbone, Tim Ebersole, Jane Whalen, Wesley


Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings

• "Epilepsy surgery may be successful for selected children... with a congenital or early-acquired brain lesion, despite abundant generalized or bilateral epileptiform discharges on EEG. The diffuse EEG expression may be due to an interaction between the early lesion and the developing brain"
Speculation about future

- Will numbers go down?
- Are local community neurologists more willing to refer young patients for presurgical evaluations earlier?
- Will long term benefits outweigh natural history?
- Minimally invasive approaches (diagnostic and therapeutic)

Conclusion

- In contrast to adult epilepsy surgery, the change in surgical landscape in kids does not appear to be epidemiological but, rather, likely reflects a change in us and how we look at the problem.

Impact on Clinical Care and Practice

- a change in our understanding of the risk-benefit profile of pediatric epilepsy surgery
- a change in our overall approach to the evaluation and treatment of children with epilepsy
What Is the Evidence that the Landscape is Changing? Theories of Change

December 7, 2013

Dale C Hesdorffer, PhD
GH Sergievsky Center
Columbia University

Learning Objectives

• To understand changes in epilepsy surgery for MTS over time
• To understand the possible reasons for these changes

Anterior temporal lobectomy

• 1980’s epilepsy surgery became popular
  – Shown to render 60%-90% of patients seizure-free
• 2001 RCT showed efficacy for seizure freedom for patients with seizures impairing awareness
• 2003 AAN, AES, AANS practice parameter published on temporal lobe and localized neocortical resections

What has happened since 1980?

UK-wide trends in epilepsy surgery to control epilepsy

Disclosure

Upsher Smith Consultant
Esai Consultant

Wiebe et al, NEJM 2001; Engel et al, Neurology 2003

Number of epilepsy surgeries in Sweden

Proportion of total temporal lobectomies 1993-2009, Olmsted County

Incidence of temporal lobectomies in Olmsted County 1993-2009


Have the etiologies of MTS changed over time?
Etiology of MTS: Patients with intracranial electrodes, surgery, and seizure freedom

- **67% Febrile seizures**
  - 73% were SE, repeated or with Todd’s
    - (75% among children in Falconer)
- **14.9% Head Trauma**
  - With LOC (70%)
- **9% Birth trauma**
  - 33% with significant birth trauma
- **6% Other**
- **7% No risk factors**

Trends in incidence of hospitalized TBI in the US

![Graph showing trends in incidence of hospitalized TBI in the US from 1980 to 2003](image)

Trends in incidence of birth asphyxia in California

![Graph showing trends in incidence of birth asphyxia in California from 1955 to 1990](image)

Proportion with febrile seizures in focal epilepsy of unknown etiology, Olmstead County

![Bar graph showing proportion with febrile seizures in focal epilepsy of unknown etiology](image)

Proportion of first febrile seizures stopped by a drug in Rochester, MN

![Bar graph showing proportion of first febrile seizures stopped by a drug](image)

How many patients with MTS could be expected each year in the US?

- Assuming 61 million children <15 years in 2010
  - 1,220,000 (2%) with febrile seizure annually
- Febrile SE is 2%-4% of all febrile seizures in Rochester
  - 24,400 – 48,800 with FSE annually
- FEBSTAT shows that 10% with increased T2 on MRI and at 1 year 86% have hippocampal atrophy
  - 2,440 – 4,880 with increased T2
  - 2,098 – 4,157 with hippocampal atrophy
The prevalence - incidence effect
What is the role of the new AEDs on decreases in epilepsy surgery?

Timeline: ASD approvals by FDA since 1990
RCTs of adjunctive therapy for focal epilepsy resistant to standard AEDs

The proportion with treatment resistant focal epilepsy has not changed

• 3% to 37% of treatment resistant focal epilepsy in RCT have a \( \geq 50\% \) reduction in seizures

HOWEVER

• Few stop having seizures

The role of new AEDs

• If seizure frequency in treatment resistant focal epilepsy has decreased due to the new AEDs

• Then the proportion of patients who wish to have surgery may have decreased over time

Effect of treatment changes in 139 patients with drug-resistant epilepsy

Has the profile of surgical referrals changed over time?
What is the influence of patient refusal of surgery after pre-surgical evaluation?

Outcomes of presurgical evaluations for epilepsy surgery

Opinions about surgery in adult epilepsy patients

Risk factors for positive and negative opinions about surgery in adult epilepsy patients

Patient education

- Education about epilepsy surgery is needed
  - Most particularly in patients with
    - below a high school education
    - disability
    - a lack of trust in their doctor
      - Erba et al. Epilepsy Behav 2012
    - Racial minorities and those with medicaid, medicare and no insurance
      - Englot et al. Neurology 2012
  - Otherwise......
Effect of treatment changes in 139 patients with drug-resistant epilepsy

![Graph showing the number of AED changes over 6 years](Behavior 2008)

What do neurologists think about epilepsy surgery?

Swedish study of neurologist who treat epilepsy regularly

- Response rate 66%  
  - 81% from hospitals  
  - 57% from private practices
- Referral to surgery  
  - 36% 2-5 patients  
  - 32% 6 patients  
  - 32% Never referred

Michigan study of neurologists’ views of epilepsy surgery in 2006

- Response rate 20% (N=84)
- 11% never discussed epilepsy surgery with their patients
- Among those with patients who had surgery, 70% were seizure free  
  – 31% of those with surgery had serious complications
- ~50% did not get appropriate feedback from the epilepsy center  
  – For 76%, this was an important factor for further referrals
- 38% said their patient never returned to the practice  
  – 48% said this was very important when considering referrals

Italian study of barriers towards epilepsy surgery among adult and child neurologists caring for epilepsy

- Neurologists need surgery education  
- Lack of experience in patient referral for surgery  
- Variability in understanding epilepsy surgery  
- Lack of alignment with experts about epilepsy surgery

Communication between epilepsy centers and neurologists

- Lack of feedback from the surgical center  
- Failure of neurologists’ patients to return to them

What are the barriers?
Why is surgery for MTS decreasing?

• Prevalence – incidence effect

• Decrease in the occurrence of risk factors for MTS
  – And the possibility that patients with febrile seizures who
    receive drugs to stop seizures, have shorter duration
    seizures than they would have had without drugs

• Increasing patient refusal rates

What factors can be addressed?

• Lack of patient education

• Lack of outreach to poorer communities

• Lack of neurologist education

• Lack of communication between epilepsy centers
  and neurologists

Impact on Clinical Care and Practice

To benefit patients with treatment resistant
epilepsy:
• It is important to educate patients with
  treatment resistant epilepsy about surgery
• Neurologists treating epilepsy patients also
  need education about surgery
• Surgical centers need to develop protocols for
  communication with neurologists about surgery
  and return of their patients to the referring
  practice
Perspective of Basic Science: Is There Life Outside the Hippocampus?
December 7, 2013

Jeffrey A. Loeb, M.D., Ph.D.
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Learning Objectives

• The neocortex is not the hippocampus

• Reverse Translational Research and Systems Biology to understand and develop treatments for human neocortical epilepsy

Disclosure

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UCB Research collaboration (no financial support)

The neocortex is not the hippocampus
Number of Articles in PubMed:

“Epilepsy + Hippocampus” → 12,464 hits

“Epilepsy + Neocortex” → 1,620 hits

The neocortex is not the hippocampus

- Many Lesions Associated with Neocortical Epilepsy
- Epileptogenic Zones are most often normal.

Neocortex

GFAP

Reverse Translational Research

Intercital spiking is far more frequent than seizures

Interictal spiking is far more frequent than seizures

What is different about brain regions that produce seizures?

**Internal Control:** *Epileptic vs. “Less-Epileptic”*

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**Genomics:**

*Genome-wide transcriptome analysis*

- **Microarray**: Each spot measures mRNA levels of a single gene from a sample of tissue.
- Covers 43,000 genes across the entire Human Genomic Target Set.
Area of Overlap Suggests Common Pathophysiology

Seizure Onset vs. Interictal Spiking

Validation:

1. Where in the human genome?
2. What Pathways are involved?
3. Where in the neocortex?
   - Layers
   - Cells

Seizure Onset vs. Interictal Spiking


Validation:

1. Where in the human genome?
2. What Pathways are involved?
3. Where in the neocortex?
   - Layers
   - Cells

Why Layer 2/3 Neurons?

Hypothesis: Layer 2/3 neurons have cortical connections that lead to hypersynchrony

Validation:

1. Where in the human genome?
2. What Pathways are involved?
3. Where in the neocortex?
   - Layers
   - Cells
Seizure Onset vs. Interictal Spiking

Gene Correlation Profiles

Identify Cell Types Using Pubmed

Layer-specific activation of MAPK-CREB in neocortical epilepsy linked to epileptic spiking and microlesions.

How to prove MAPK-CREB is necessary and translate (forward) this into therapeutics?

Tetanus Toxin Somatosensory Cortex Interictal Spiking Model
Focal interictal spiking

Chronic and progressive

CREB is phosphorylated on spiking side in layers 2/3.

Identification of drug candidates to test in this model:

MAPK

Identification of drug candidates to test in this model:

MAPK Inhibitor Blocks the Development of Epileptic Spiking (Intercital)

MAPK Inhibitor Blocks the Development of Epileptic Spiking (Intercital)

MAP Kinase inhibition blocks the development of interictal spiking

"Morning after pill"

Conclusions

• The hippocampus is not the neocortex
• Reverse Translation: Systems biology of well-characterized human cortex generates new hypotheses
• Chromosomal Hotspots of epileptic gene transcription
• Biomarkers of epileptic spiking localized to Layer 2/3
• A new gene clustering method predicts novel ‘Microlesions’ in deeper layers of epileptic spiking
• Animal models (forward translation) turn biomarkers into new Drug Targets
Where do we go from Here?
December 7, 2013

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American Epilepsy Society | Annual Meeting

Learning Objectives
Learn to provide optimal treatment, identify surgical candidates, and perform epilepsy surgery for those with syndromes other than temporal lobe epilepsy when indicated.

American Epilepsy Society | 2013 Annual Meeting

The changing landscape

• There are clear trends towards
  – A reduction in surgery for mesial temporal lobectomy at major epilepsy centers
  – A reduction in epilepsy surgery overall

• There are no clear trends towards
  – A reduction in treatment resistant epilepsy patients overall


The world as seen in 2000

• Many patients with treatment resistant epilepsy, “The majority” with temporal lobe epilepsy
• Not enough surgical programs
• Conclusion: If we could increase the number of surgeries, we could make a serious dent in the number of treatment resistant patients

The world as seen in 2013

• There are probably still a substantial number of patients who have not been referred for epilepsy surgery who are good candidates, however....
• The majority of treatment resistant epilepsy patients at most epilepsy centers
  – Do not have clear surgically remediable epilepsy
  – Do not have temporal lobe epilepsy

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Within the past year, The Epilepsy Study Consortium received payments for research services from:
• Acorda, Eisai Medical Research, GlaxoSmithKline, Impax, Johnson & Johnson, Mapp Pharmaceuticals, Merck, Neuro, Lundbeck, Pfizer, Sepracor, Supernus, UCB, Vertex, and Wyeth.
• I am an investigator at NYU on studies for Eisai Medical Research, LLC, Impax, Mapp Pharmaceuticals, Neuro, Lundbeck, UCB Inc/Schwarz Pharma, Upsher Smith, and Vertex.
• The HFIP project receives research support from UCB, Pfizer, and Lundbeck. The AREST trial (completed) Received support from UCB, Supernus, Eisai, GSK, Lundbeck, & J. Upsher Smith, and Pfizer.
What does this mean?

• We need to:
  – Continue efforts to find TLE patients (who most benefit from resective surgery) and promote early referral
  – Identify better methods of improving the lives of those who are not currently candidates for surgery
    • Better strategies for evaluating patients who currently are considered poor surgical candidates
    • Enhanced basic research on non-temporal lobe epilepsy
    • Continued search for non-surgical effective therapies

What new strategies can we use?

• Ways to make “non-lesional” epilepsy “lesional”
  – SISCOM
  – Ictal Spect
  – Measurement of cortical thickness
  – PET
  – MR spectroscopy
Conclusion

- The landscape IS changing
  - Surgery for kids: Expanding
  - Surgery for adults: Shrinking (for now)
    - With better strategies, this can turn around

- It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change. - Darwin

Impact on Clinical Care and Practice

- New methods are needed to identify good candidates for surgery
  - Patients with lesions and/or temporal lobe epilepsy should be referred early
  - Neocortical (extratemporal) and non-lesional surgery is currently challenging