Annual Fundamental of Symposium
Neuroimaging in Epilepsy: Focusing On the Focus and Outside the Focus

Symposium Co-Chairs:
Mohamad Koubeissi, M.D.

and

Michael Sperling, M.D.

Friday, December 6, 2013
Convention Center – *Ballroom C, Level Three*
12:30 p.m. – 3:00 p.m.
OVERVIEW
The Annual Fundamentals of Epilepsy Symposium will address standard and novel neuroimaging techniques used in the evaluation of epilepsy. Presentations will address recent advances in structural and functional MRI, tractography, PET, SPECT, and MRS. In addition, newer techniques of potential use in epilepsy will be presented. Two interactive sessions will allow the audience to read MRIs and submit their answers using Audience Response System.

LEARNING OBJECTIVES
• Use technical and interpretation key points to improve the quality and quantity of information extracted from neuroimaging studies in epilepsy
• Use state of the art structural and functional imaging modalities in the diagnostic work-up of patients with epilepsy
• Use new technologies such as fMRI and diffusion tensor imaging in presurgical evaluations.

TARGET AUDIENCE
Basic: Those new to epilepsy treatment or whose background is limited, e.g., students, residents, general physicians, general neurologists and neurosurgeons, other professionals in epilepsy care, administrators.

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.

PROGRAM
12:30 – 12:45 pm  Introduction
Mohamad Z. Koubeissi, M.D.
12:45 – 1:10 pm  Seizure Protocol MRI
Barbara Dworetzky, M.D.
1:10 – 1:35 pm  PET & SPECT in Epilepsy
William H. Theodore, M.D.
1:35 – 2:00 pm  Functional MRI in Epilepsy
Matthias J. Koepp, M.D., Ph.D.
2:00 – 2:25 pm  Diffusion Tensor Imaging
Beate Diehl, M.D.
2:25 – 2:50 pm  New MRI Techniques in Epilepsy
Graeme D. Jackson, M.D.
2:50 – 3:00 pm  Conclusions
Michael R. Sperling, 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 Annual Fundamentals 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 and Medical Knowledge

**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**

**Beate Diehl, M.D.**
Beate Diehl is a Clinical Senior Lecturer at University College London, UK. She completed Neurology training in Germany and the US (CCF 2003), and subspecialized in Epilepsy/Clin. Neurophysiology at the Cleveland Clinic. She is a Diplomate of the ABPN and ABCN. Beate worked at the CCF Epilepsy Center until 2008, since has joined the National Hospital, Queen Square, London. She holds the clinical lead at the EMU, and focuses on presurgical evaluation including intracranial EEG. Her research centres on improved characterization of the ictal onset zone, using novel imaging techniques and advanced neurophysiological methods, and to correlate electrical cortical stimulation with imaging.

Beate Diehl, M.D. has nothing to disclose.

**Barbara Dworetzky, M.D.**
Barbara Dworetzky MD is Chief of the Division of Epilepsy and EEG at the Brigham and Women's Hospital in Boston and directs the Edward B. Bromfield Comprehensive Epilepsy Center and Clinical Neurophysiology Fellowship there. She is an Associate Professor of Neurology at Harvard Medical School. Dr. Dworetzky is the chair of the American Epilepsy Society's Practice Management Committee. Her research interests are in psychogenic nonepileptic seizures, clinical epilepsy, SUDEP, and safety in monitoring units. She is a site PI for the EQUIGEN trial.
Barbara Dworetzky, M.D. discloses receiving support as Salary from Commercial Sources generating W-2 from Best Doctors, consulting SleepMed/ Digitrace EEG consulting; as Federal/State/Not-for Profit Funding from FDA grant for EQUIGEN; as Participation in Foundation or Not-for-Profit Organizations from American Epilepsy Society Epilepsy Foundation of New England./

Graeme Jackson, M.D., FRACP
Professor Graeme Jackson is a clinical neurologist and clinical researcher at the Austin Hospital in Melbourne Australia. He is a clinical fellow of the National Health and Medical Research Council of Australia, Senior Deputy Director of the Florey Institute of Neuroscience & Mental Health, and a Professorial Fellow of the University of Melbourne. His major research focus is in defining focal abnormalities of the brain including hippocampal sclerosis, understanding Malformations of Cortical Development, and using advanced structural, functional, and diffusion based MRI to define whole brain networks, functional reorganisation and subtle pathology in epilepsy.

Graeme Jackson, M.D., FRACP discloses receiving support as Participation in Foundation or Not-for-Profit Organizations from Neurosciences Victoria (Director) Chairman Scientific Advisory Committee.

Matthias Koepp, M.D., Ph.D.
Matthias Koepp qualified from the Free University Berlin in 1991. In 1993 he moved to London to pursue further training in neurology, with particular focus on neuroimaging in epilepsy, at the Institute of Neurology, and completed his PhD in 'Functional Imaging of the Epilepsies'. In 1999, he was appointed Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, and promoted to Professor of Neurology at the Institute of Neurology, University College London, in 2008. His particular clinical interests are functional and structural imaging of epilepsy and comorbidities (depression).

Matthias Koepp, M.D., Ph.D. discloses receiving support as Honoraria from Commercial Sources from UCB; as Company Ownership (incl. personally managed stocks and stock options, excluding mutual and managed funds) from GSK; as Federal/State/Not-for Profit Funding from EU-FP7, Wellcome Trustoses.

Mohamad Koubeissi, M.D. (Co-Chair)
Dr. Koubeissi is an Associate Professor of Neurology and Director of the Epilepsy Center at George Washington University. Dr. Koubeissi earned his Bachelor's Degree with honors in mathematics and his medical degree from the American University of Beirut, and pursued his clinical training at Upstate Medical University and New York University in Neurology, and at Johns Hopkins University for epilepsy fellowship. He was on faculty at Case Western Reserve University in Cleveland, OH before he joined George Washington University. Dr. Koubeissi has conducted a number of research projects in epilepsy, published his papers in major journals, and edited a book on epilepsy surgery.

Mohamad Koubeissi, M.D. discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from Speakers' Bureau of UCB pharma; as Research Funding from For Profit Commercial Sources/Principle Investigator from A device grant from Medtronic to conduct a DBS trial in intractable epilepsy.

Michael Sperling, M.D. (Co-Chair)
Dr. Michael Sperling is Baldwin Keyes Professor of Neurology at Thomas Jefferson University in Philadelphia where he serves as Director of the Jefferson Comprehensive Epilepsy Center and Vice Chair of Neurology. He has published extensively about epilepsy, with over 175 peer-reviewed publications, 80 chapters and reviews, and has written two books and edited several journal supplements. He has been president of the American Clinical Neurophysiology Society, the Philadelphia Neurological Society, and lectures widely about epilepsy.
Michael Sperling, M.D. discloses receiving support as Consulting/Advisory Board Activity from Accorda Therapeutics, electroCore; as Research Funding from For Profit Commercial Sources/Principle Investigator from Eisai, UCB, Neuronex, Medtronics, SK Life Sciences, Vertex, Marinus, Sunovion, Visualase; as Participation in Foundation or Not-for-Profit Organizations from Epilepsy Foundation of Eastern Pennsylvania.

**William Theodore, M.D.**

Dr Theodore, Chief, Clinical Epilepsy Section, NINDS and Professor of Neurology, Uniformed Services University of the Health Sciences, received BA degrees from Harvard and MD from Columbia University College of Physicians and Surgeons. He received the AES Outstanding Clinical Investigator Award in 1991. Past AAN Epilepsy Section Chair, he served on the AES Board of Directors, numerous editorial boards, and as Epilepsy Research Co-Editor-in-Chief. He worked with PAHO, WHO, and WFN on international projects and was Visiting Professor at the University of Zambia. His research focuses on functional imaging in epilepsy using MRI and PET.

William Theodore, M.D. discloses receiving support as Honoraria from Commercial Sources from Honorarium from Elsevier for editing Epilepsy Research through 12/2012; as Company Ownership (incl. personally managed stocks and stock options, excluding mutual and managed funds) from CSCO, GE, HON, IBM, PG, SJM, XOM.; as Federal/State/Not-for Profit Funding from NIH salary and research support.

**Lara Jehi, M.D. (CME Reviewer)**

Dr. Lara Jehi is an adult epileptologist at the Cleveland Clinic Epilepsy Center. She serves as the head of the Outcomes Research Program, and the Director of Research. She also serves as the Associate Program Director of the Clinical Research Unit at Cleveland Clinic within the auspices of the NIH-funded Clinical and Translational Science Collaborative. In these various roles, she has focused on advancing the understanding of the mechanisms of seizure recurrence after epilepsy surgery, and expanding the vision of treatment outcomes in clinical practice.

Lara Jehi, M.D. discloses receiving support as Research Funding from For Profit Commercial Sources/Principle Investigator from research funding from UCB pharma to investigate the relationship between interictal EEG findings and epilepsy refractoriness. I get no salary support from this project.; as Participation in Foundation or Not-for-Profit Organizations from board of trustees for Cleveland Chapter of Epilepsy Association. This is an unpaid contribution (I volunteer my time).

**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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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.
Seizure Protocol MRI

December 6, 2013

Barbara Dworetzky, MD
Brigham and Women’s Hospital
Harvard Medical School

Learning Objective

Understand the importance of having the appropriate seizure protocol MRI to enhance clinical diagnosis and management of seizures/epilepsy (because not all MRIs are created equal)

Ideal or optimal MRI

- 3D acquisition of data to allow reformatting
- Thin slices with no gaps or skip
- High signal to noise ratio (SNR)
- High spatial resolution
- Good tissue contrast
- No artifacts
- Short duration

Understand the MRI Test

- Sensitivity/specificity depends on the use
- MRI data are gathered over time (~1 bit q5-10usec)
- Pts tolerate only certain amount time in scanner
- Time is costly so shorter sequences are more economical and more feasible
- MRI is a diagnostic tool that varies in quality, technique, and the interpretation
- MRI is normal in many seizure cases
- And, even if abnormal, the finding(s) may be unrelated to the cause of the seizure

Different types of MRI for different seizure presentations

1. Acute seizure or probable seizure
2. Epilepsy in an adult
3. Epilepsy in a child/early onset

**Having a carefully defined MRI protocol substantially increases the sensitivity of finding a lesion**


Disclosures

Name of Commercial Interest | Type of Financial Relationship
--- | ---
Sleep Medicine | Consultant
Best Doctors | Consultant
1. **Acute seizure or probable seizure**  
Tumor, hemorrhage, stroke, infection, trauma

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**MRI features and Brain Tumors**
- Location: Parenchymal vs Pial vs Dural
- Multiple vs. single
- Enhancing vs Non-enhancing
- Shape and Pattern of enhancement & edema
- Hypocellular vs Hypercellular
- High vs. Low Blood Volume
- Intra-tumoral calcium or hemorrhage

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**52 yo F w/ lung lesion and 3 GTCs found to have metastatic melanoma**

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**64 yo M presenting with sz and progressive left arm weakness: GBM**

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**21 yo M w/ hydrocephalous and daily seizures: callosal lipoma**

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**MRI and Hemorrhage**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time</th>
<th>Blood products</th>
<th>T1WI</th>
<th>T2WI</th>
<th>SWI/GRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>&lt;24 hrs</td>
<td>Oxyhemoglobin, Intracellular</td>
<td>Iso- or Hypo</td>
<td>Hyper</td>
<td>Iso</td>
</tr>
<tr>
<td>Acute</td>
<td>1-3d</td>
<td>Deoxyhemoglobin, Intracellular</td>
<td>Hypo</td>
<td>Hypo</td>
<td>Hypo</td>
</tr>
<tr>
<td>Early Subacute</td>
<td>&gt;3d</td>
<td>Methemoglobin, Intracellular</td>
<td>Hyper</td>
<td>Hypo</td>
<td>Iso</td>
</tr>
<tr>
<td>Late Subacute</td>
<td>&gt;7d</td>
<td>Methemoglobin, Extracellular</td>
<td>Hyper</td>
<td>Hyper</td>
<td>Iso</td>
</tr>
<tr>
<td>Chronic</td>
<td>&gt;14d</td>
<td>Ferritin/hemosiderin Extracellular</td>
<td>Hypo</td>
<td>Hypo</td>
<td>Hypo</td>
</tr>
</tbody>
</table>

57 yo F with sz found to have a cavernoma

75 yo M w/ HTN presenting w/ confusion

MRI and Ischemic Stroke

<table>
<thead>
<tr>
<th>Time</th>
<th>MRI APPEARANCE</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 hrs</td>
<td>DWI bright, ADC dark, ni FLAIR</td>
<td>Pure cytotoxic cell swelling</td>
</tr>
<tr>
<td>6hrs-1 week</td>
<td>DWI bright, ADC dark, FLAIR bright, gyral swelling</td>
<td>Predominantly cytotoxic edema, increasing vasogenic edema</td>
</tr>
<tr>
<td>3d–months</td>
<td>Gadolinium enhancement</td>
<td>BBB breakdown</td>
</tr>
<tr>
<td>~1-2 wks</td>
<td>DWI bright, ADC normal or bright, FLAIR bright, gyral swelling, variable enhancement</td>
<td>Decreasing cytotoxic edema Predominantly vasogenic edema</td>
</tr>
<tr>
<td>&gt;2 wks</td>
<td>DWI normal, ADC bright, FLAIR bright, decreased gyral swelling, variable enhancement</td>
<td>Resolving vasogenic edema Increasing gliosis</td>
</tr>
<tr>
<td>Month(s)</td>
<td>DWI normal, ADC bright, FLAIR bright, volume loss, no enhancement</td>
<td>Gliosis and encephalomalacia</td>
</tr>
</tbody>
</table>

MRI and Infections

MRI findings
- T1 post gado (BBB breakdown)
- DWI (cellular swelling)
- FLAIR (edema)
- SWI (hemorrhage, calcification)
- Pattern of appearance is important

Types of Infections
- Bacterial meningitis/cerebritis/abscess
- Fungal meningitis/cerebritis/abscess
- Viral meningitis/encephalitis
- Prions

28 yo F, 30 wks pregnant, presents w/ sz, mutism and R HP

58 yo presented rigors and confusion 5d after a camping trip: CSF 330 WBCs, Viral panel: EEE
69 yo man w/ 2 mo progressive mental status changes and szs

54 yo Haitian farmer presenting with sz

MRI and Trauma
Often normal in setting of mild trauma, but useful for axonal or vascular injury, contusions

<table>
<thead>
<tr>
<th>Technique</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWI</td>
<td>Cell Swelling</td>
<td>Cell Loss</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Edema, Mass Effect</td>
<td>Gliosis</td>
</tr>
<tr>
<td>GRE</td>
<td>Deoxyhemoglobin, Hemosiderin</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Mass effect, (Focal) Atrophy, Encephalomalacia</td>
<td></td>
</tr>
</tbody>
</table>

55F w/ sz and history of TBI 2 years ago

MRI Protocol: Acute Seizure
- Sagittal T1: this study acts as a survey to look at entire brain (mass effect, herniation)
- AX T1: pre-contrast
- Axial T2 FLAIR: sensitive to brain edema, hemorrhage, or abnormal protein concentration
- DWI: infection, stroke
- Gradient echo (GRE) OR susceptibility weighted image (SWI): hemorrhage, brain mineralization
- T1 post-gadolinium (tumor, infection, altered BBB)
TIME= (40 min)

Normal MRI: Now what?
- Maybe it wasn’t a seizure
- Maybe it is non-lesional epilepsy
- Maybe the brain isn’t normal even though you have a “negative test” (false negative)
- Maybe the scan isn’t really normal
You have 5 seconds to find Waldo...

“Now what” algorithm
- Confirm whether images were optimal
- If not optimal, have an additional more optimal MRI protocol performed
- If you have optimal 1.5T imaging and still no dx, then consider a 3T MRI (discuss protocol directly with the subspecialist who will interpret it)

High Resolution MRI

2. Epilepsy, adult onset

Mesial Temporal Sclerosis (MTS)
- Accurate diagnosis critical as surgery is curative in 70-90%
- Atrophy of the hippocampus (T1)
- Loss of internal structure (T1 or T2)
- Increased signal intensity (T2 or FLAIR)
- Excellent pathological correlation
Coronal oblique

24 yo w/ complex partial szs/weekly

Chronic Epilepsy Protocol: Adult onset

- Retrieve old scan for comparison (especially if it was normal)
- Thin slices, no gaps, COR oblique perpendicular to axis of hippocampi
  - T2 FLAIR med temp lobes
  - T1 3D SPGR med temp lobes or COR inversion recovery
- Selected whole brain sequences, if needed
- (40 min)

3. Epilepsy, early onset

Suspect Malformation of Cortical Development (MCD)

- History of early onset or childhood epilepsy, or in retrospect, spells that were likely to be seizures
- Seizures refractory to polytherapy
- “normal MRI”
Developmental/Glioneuronal Tumors

Chronic Epilepsy Protocol: Early onset

- Retrieve old scan, even if normal
- 3D Whole Brain high spatial resolution imaging of the gray white junction
  - Spoiled gradient recalled echo (SPGR) volumetric dataset, thin slices (≤1.2mm), no gaps
  - Or inversion prepared 3D T2
- AX 2D FLAIR T2 whole brain
- AX 2D proton density
- Selected whole brain sequences, if needed
- (40-60 min)

The Role of Repeating the MRI

Ticks and Fleas

SEIZURE/EPILEPSY PROTOCOL

- AX T1 pre and post gado
- AX FLAIR
- AX DWI/ADC
- AX GRE or SWI
- COR oblique T2 FLAIR (thin cuts)
- COR T1 thin cuts (SPGR)
  (40-60 minutes)

Advanced MRI: MR Spectroscopy (MRS)

- Noninvasive technique to measure metabolic act.
- No further hardware needed
- Focus on only one area in question
- Used for distinguishing tumors from radiation necrosis
- Most common use in epilepsy is to determine lateralization of MTS
Magnetic Resonance Spectroscopy

- N-acetyl-aspartate (NAA) is a neuronal marker
- NAA/Creatine ratio is an index of neuronal loss
- Reduced NAA/Cr occurs in the region of the epileptogenic zone
- Choline peak is increased where membrane turnover is found

MRS Confirms the Dysplastic Lesion

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chol</td>
<td>Cr</td>
</tr>
<tr>
<td>NAA</td>
<td></td>
</tr>
</tbody>
</table>

Sz Protocol MRI: Key Lessons

- Imaging and review should be hypothesis-driven
- Modalities inform each other: iterative process
- Not all lesions seen on MRI are epileptogenic
- May need to repeat the MRI (not all are equal)
- Communication with the neuroradiologist is key
- Think about which protocol you need for the patient in front of you
Learning Objectives

- To understand the value of ictal SPECT and FDG-PET in presurgical evaluation for epilepsy
- To understand the potential of PET neurotransmitter receptor ligands
SPECT Statistical Thresholding

SISCOM

Difference Compared to normal Variation P<0.001

Ictal SPECT

- SISCOM localization
  - Hyperperfusion images 66%
  - Hypoperfusion 74%
  - Combined 83% (67% in non-lesional ETLE)
- Prediction of outcome
  - 63% (58% ETLE) good outcome if concordant with resection
  - 20% (17%) if non-concordant

So and O'Brien 2012

Utility of Ictal SPECT in MTLE with hippocampal atrophy

- 124 patients with SPECT
- 116 without SPECT
- No difference in # offered surgery, invasive monitoring
- Mean duration of hospital stay 1 day longer for SPECT group (P<0.001).
- SGS occurred in 51% of the SPECT and 26% of the non-SPECT group (P<0.001)
- Cost of presurgical evaluation 35% higher with SPECT (P<0.001)
- Proportion of patients seizure-free after surgery similar in SPECT (59%) and non-SPECT group (54%).

Velasco et al 2010

SPECT in Surgery Decisions

<table>
<thead>
<tr>
<th>Table 1: Utility of SPECT in different epilepsy subgroups</th>
</tr>
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<tbody>
<tr>
<td>SPET results</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Proportion of good outcome (%)</td>
</tr>
<tr>
<td>SGS occurred (%)</td>
</tr>
<tr>
<td>Cost of presurgical evaluation (%)</td>
</tr>
<tr>
<td>Proportion of patients seizure-free after surgery (%)</td>
</tr>
</tbody>
</table>

Rathore et al 2011

FDG-PET

Ipsilateral PET hypometabolism:
- 86% predictive value for good outcome
  - Does it add anything to lesional MRI?
- 80% with normal MRI
  - Predicts outcome
- 72% in patients with non-localized ictal scalp EEG

Willmann et al 2007

FDG Meta-analysis
- 46 Studies 1992-2006
- Ipsilateral PET hypometabolism:
  - 86% predictive value for good outcome
    - Does it add anything to lesional MRI?
  - 80% with normal MRI
    - Predicts outcome
  - 72% in patients with non-localized ictal scalp EEG

Willmann et al 2007
Extent of Hypometabolism

- Depends on analysis method
- Bilateral hypometabolism
  - Bilateral EEG
  - More frequent secondary generalization
  - Worse contralateral memory on Wada
  - Worse temporal lobectomy outcome in most studies
- Widespread ipsilateral hypometabolism
  - Frontal
  - Insula
  - No clear relation to surgery outcome
- In TLE, resection of hypometabolic zone beyond MTS may improve outcome

Kumar et al. 2012

Comparative Meta-analysis

<table>
<thead>
<tr>
<th>PET Modality</th>
<th>Overall (n=118)</th>
<th>Good Surgical Outcome %</th>
<th>Invasive EEG %</th>
<th>Normal MR (n=208) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR</td>
<td>72</td>
<td>77</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>FDG-PET</td>
<td>85</td>
<td>88</td>
<td>58</td>
<td>80</td>
</tr>
<tr>
<td>Ictal SPECT</td>
<td>73</td>
<td>78</td>
<td>56</td>
<td>55</td>
</tr>
</tbody>
</table>

Wot et al. 1999

Some SPECT-PET Comparisons

<table>
<thead>
<tr>
<th>Author</th>
<th>Syndrome</th>
<th>PET</th>
<th>SPECT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuce 2013</td>
<td>Nonlesional extratemporal (14)</td>
<td>75% +</td>
<td>95% +</td>
<td>Complete resection of functional ABN +</td>
</tr>
<tr>
<td>Deou 2013</td>
<td>Varied location (105)</td>
<td>55% + IDEEG (87% for TLE)</td>
<td>85% + IDEEG (87% for TLE)</td>
<td>85% + IDEEG (87% for TLE)</td>
</tr>
<tr>
<td>Kriegel 2012</td>
<td>Orbito-frontal (10)</td>
<td>63% +</td>
<td>85% +</td>
<td>Contralateral</td>
</tr>
<tr>
<td>von Oertzen 2011</td>
<td>Varied location non-lesional (18)</td>
<td>82% + surgery site</td>
<td>75% multilobar SPECT + Iodine IDEEG</td>
<td></td>
</tr>
<tr>
<td>Sei et al 2011</td>
<td>Varied location non-lesional Pd (14)</td>
<td>15% bilateral</td>
<td>71% hemispheric</td>
<td>IDEEG concordance</td>
</tr>
<tr>
<td>Kim 2001</td>
<td>OLE (15)</td>
<td>66% localized</td>
<td>76% localized</td>
<td>SISCOM HMPAO</td>
</tr>
<tr>
<td>Sturm 2000</td>
<td>OLE (5)</td>
<td>54% localized</td>
<td>54% localized</td>
<td></td>
</tr>
</tbody>
</table>

Lee et al. 2003

FDG-PET and SISCOM in non-Lesional Neocortical Epilepsy

Lateral Temporal Foci (n=22) Extra Temporal Foci (n=11)

All patients had scalp ictal TL onset, grids, good surgical outcome

Lee et al. 2003
**11C Flumazenil-PET**

- Occasionally + when FDG, MRI -
- Localization > FDG
- Multiple regions showing ↑ or ↓ binding may predict worse outcome
  - ↑ = periventricular nodular heterotopia?
- 40-50% + in MRI – focal epilepsy
- No value if lesion present

**FMZ FDG MRI**


**Serotonin 1A Receptor PET**

**PET and Temporal Lobectomy Outcome**

Stepwise variable selection in logistic regression

**FCWAY PET**

Significant additional 18F-FCWAY effect (β = 9.8796, p<0.01) after seizure-free probability explained by FDG.

Significant 18F-FDG (β = 8.64, p<0.02) effect After seizure-free probability explained by 18F-FCWAY PET.

Theodore et al 2012

**11C PK11195 in FCD**

(A) Ictal FDG-PET showing right frontal hypometabolism.
(B) Interictal FDG-PET showing right frontal hypometabolism.
(C) (C) PK11195-PET overlay on CT showing increased tracer uptake in right frontal lobe.

Hirvonen et al 2012

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Functional Imaging Pitfalls

- Ictal SPECT
  - Very sensitive to injection time
  - Sensitive to seizure spread
  - Reflects only one seizure

- FDG PET
  - Averages activity over 30-40 minutes
  - May be sensitive to time since last seizure (< 2 days)
  - May be sensitive to most recent seizure type

- Flumazenil PET
  - Effect of seizures may be long-lasting

- Other Ligands
  - No data

So and O’Brien 2012; Kumar et al 2012

Presurgical Evaluation: Cost-Effectiveness

18F-FDG-PET (n=178)
- Localization rates:
  - MRI 35.8%
  - Video-EEG 62.2%
  - Ictal SPECT 60.0%
  - (18)F-FDG PET 75.0%
  - Intracranial EEG 93.8%
- EEG/MRI had lowest cost per class I/II outcome
- PET had lower cost than SPECT per class I/II outcome

Markov Decision Analysis
- Data from Knowlton
- PET, ictal SPECT, MEG, PET+SPECT, PET+MEG, SPEC+MEG
- PET+MEG cost $95,612 / 16.30 QALY gained.
- SPECT cost $97,479 / 16.45 QALY gained.
- PET+MEG had lower cost than SPECT per class I/II outcome
- PET+MEG favored when willingness to pay <$10,000
- SPECT favored when willingness > $10,000

O’Brien et al 2008

Impact on Clinical Care and Practice

- PET and SPECT * sensitivity and specificity for MTLE
  - Uncertain value if MRI shows MTS
  - SPECT possibly more useful in extratemporal epilepsy
  - Both may have false positives
  - It is amazing what we still don’t know
  - Independent role of imaging hard to assess
  - Surgery in the end usually based on EEG
- Before imaging evaluation, know the question you want to answer
FUNCTIONAL MRI IN EPILEPSY
December 6th 2013

Matthias J Koepp, MD, PhD
UCL Institute of Neurology
National Hospital for Neurology and Neurosurgery
London, UK

Learning Objectives

• compare fMRI and intracarotid amobarbital test
• sensitivity / specificity of fMRI for lateralization and localization of language and memory
• prediction of post-operative cognitive outcome
• role of simultaneous EEG-fMRI

Role of fMRI in epilepsy

Presurgical evaluation / mapping of eloquent cortex:
• motor function ⇒ ECoG
• interictal epileptiform activity ⇒ depth recording
• language lateralization ⇒ Wada test
• language localisation ⇒ fMRI
• memory function ⇒ Wada test ?

Language Localisation: fMRI

<table>
<thead>
<tr>
<th>Task</th>
<th>dorsolateral PFC</th>
<th>superior PFC</th>
<th>superior temporal</th>
<th>ventrolateral temporal</th>
<th>ventral occipital</th>
<th>angular gyrus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing sentences vs. Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Reading sentences vs. Rest</td>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>L-H</td>
<td>B</td>
</tr>
<tr>
<td>Object naming vs. Rest</td>
<td></td>
<td>B</td>
<td></td>
<td>L-H</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Semantic decision vs. Rest</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td></td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>Word generation vs. Rest</td>
<td>L-H</td>
<td></td>
<td>L-H</td>
<td></td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Word generation vs. Reading</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B</td>
</tr>
</tbody>
</table>

Language Localisation: fMRI vs WADA

"Atypical" language dominance
• epilepsy ~25%
• controls ~2%

High discordance between WADA / fMRI:
• bilateral language representation
• interhemispheric dissociation

Woermann et al, Neurology 2003
Janecek et al, Epilepsia 2013

Disclosure

Name of Commercial Interest | Type of Financial Relationship
-----------------------------|-----------------------------
GE-Healthcare               | Advisory board

American Epilepsy Society | Annual Meeting
"Atypical" language dominance
- epilepsy ~25%
- controls ~2%

Interhemispheric dissociation:
- Left (temporal) focus
- Left handedness

Berl et al.,
Annals of Neurology 2013

Prediction of post-op language: fMRI vs WADA

Language Localisation: fMRI vs WADA

Prediction of post-operative memory deficits
"holy grail" of clinical imaging

- ATLR leads to seizure freedom in up to 70% of patients with medically refractory TLE
- ATLR may lead to memory impairment
  - verbal memory
  - visual memory

Prediction of post-operative memory deficits
"holy grail" of clinical imaging

- ATLR leads to seizure freedom in up to 70% of patients with medically refractory TLE
- ATLR may lead to memory impairment
- Prognostic indicators for memory decline
  - preoperative memory performance
  - Structural MRI – hippocampal volume
  - Age at epilepsy onset
  - Language dominance on fMRI/ IAT
  - Functional MRI

Limitations of fMRI

- Noise
- Distortions/signal loss
- Subject movement
- Paradigm
  - stimulus: event-related vs blocked
  - performance: controlled vs variable
  - task: complicated vs simple
  - baseline: similar to task vs low level
  - subtraction: specific component vs entire system
- Subjects: groups vs individual

Subjects
  - Groups: patients > normals
  - Individual

Richardson, Nat Neurosci 2004
memory encoding fMRI

Study Design

<table>
<thead>
<tr>
<th>10 pictures</th>
<th>10 words</th>
<th>10 faces</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALARM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Post-scanning recognition test:
- outside scanner
- 60 min delay
- 50% novel items
- random

Button-press response:
- word
- face

Button-press response:
- “old” or “new”

Powell et al., Neuroimage 2005; Bonelli et al., Brain 2010

Prediction of post-op memory deficits

greater ipsilateral anterior HC activation correlated with greater verbal memory decline

greater ipsilateral (posterior) HC activation correlated with better verbal memory outcome

reorganisation within ipsilateral TL

Encoding words vs change in verbal learning

Bonelli et al., Brain 2010

Prediction of post-op memory deficits

Hippocampal connectivity in left TLE

Task positive network: DLPFC, hippocampus

Task negative network: Precuneus, anterior cingulate

Blue arrows: Decreased connectivity intra hippocampus.

Red arrows: Increased connectivity to posterior hippocampus

Encoding words vs change in verbal learning

Bonelli et al., Brain 2010

post-op memory encoding fMRI

post- > pre-operative L TLE

word encoding correlation with verbal learning outcome

Bonelli et al., Brain 2013

post-op memory encoding fMRI

post- > pre-operative L TLE

word encoding correlation with verbal learning outcome

Bonelli et al., Brain 2013
Summary: memory encoding in TLE
• hippocampal connectivity: decreased between hippocampi → poor outcome increased to posterior hippocampus → better outcome
• pre-op increased activity in posterior hippocampus: → better post-op outcome

Summary: memory encoding in TLE
• hippocampal connectivity: decreased between hippocampi → poor outcome increased to posterior hippocampus → better outcome
• pre-op increased activity in posterior hippocampus: → better post-op outcome
• Pre > post-op activation in posterior hippocampus: → better post-op outcome
• Post > pre-op activation in posterior hippocampus: → poor post-op outcome

language fMRI: effect of seizures

EEG-fMRI: common effects of interictal discharges

“ictal” EEG-fMRI

fMRI in Epilepsy: Summary
• Altered task-specific activations in TLE: intra-/inter hemispheric re-organization increased co-activation in hippocampus
• Seizures can disrupt networks partially and temporarily
• Evidence for common seizure-modulating site
fMRI in Epilepsy: Summary

- Altered task-specific activations in TLE: intra-/inter hemispheric re-organization increased co-activation in hippocampus
- Seizures can disrupt networks partially and temporarily
- Evidence for common seizure-modulating site
- fMRI allows exploration of specific effects at network level, complementing neuropsychological assessment

fMRI in Epilepsy: Impact on Clinical Care and Practice

Consider WADA, if
- fMRI is not possible (e.g. VNS, claustrophobia, LD, ...)
- L TLE and R MTL pathology on MRI/EEG
- R TLE and L MTL pathology and R language dominance

Consider fMRI, if
- patient can perform task
- overt responses (microphone, decision-making, ...)
- event-related, or bilaterally activating memory paradigms available in centers with experience in healthy controls

Consider EEG-fMRI, if
- patient has frequent inter-ictal discharges, or frequent focal seizures without significant movement
Diffusion Tensor Imaging
December 6, 2013

Beate Diehl, MD PhD FRCP
University College London, UK
National Hospital for Neurology and Neurosurgery,
Queen Square, London, UK

Learning Objectives
• To understand the basis of Diffusion Tensor Imaging (DTI), how it can be used to reconstruct white matter tracts (Diffusion Tensor Tractography, DTT) and its technical limitations.
• To appraise opportunities to improve our knowledge about the “epileptic brain” using DTI, and how structure and function relate to each other.
• To appraise the utility of DTT for surgical planning and resection.

Impact on Clinical Care and Practice
• Indications for obtaining DTI and DTT in clinical practice.
• Opportunity for translational clinical research for better prognostication of postoperative deficits and their prevention.

Diffusion Tensor Imaging

OUTLINE
• From DWI to DTI and DTT, Introduction to Technique
• DWI and DTI abnormalities in the epileptic network
  • DTI abnormalities and structure/function relationship
  • Role of DTT in perusing pathways of seizure spread
• Role of DTI in planning epilepsy surgery
• Postoperative findings of DTI after epilepsy surgery

Diffusion-weighted Imaging (DWI):
Non-invasive MR-technique that allows the measurement of molecular motion of water in tissue.

Diffusion Tensor Imaging (DTI):
Modification of DWI that measures water diffusion in more than 6 directions.

Disclosure
None
**Radial diffusion**

**Mean diffusivity**

---

**Results:**

- **Aim:**
  - Objectives included comparing white matter region of interest approach.

- **Methods:**
  - Studies included comparing TLE with control group.

- **Results:**
  - 13 cross-sectional studies
  - FA and mean diffusivity compared to controls [0]

---

**Diffusion Tensor Imaging**

**Diffusion Tensor Tractography (DTT): Techniques**

- Depending on the technique used for reconstruction, results differ.
- False positive and false negative results can be seen.
- Examples are shown illustrating regarding the optic radiation.

Tournier JD et al., 2011
Winston G et al., 2011

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**Diffusion Tensor Imaging**

**Metaanalysis: DTI in TLE**

- Aim: To obtain an estimate of white matter diffusion characteristics and relate these to the distance from the seizure focus.
- Methods: Studies included comparing TLE with control group. White matter region of interest approach.
- Results: 13 cross-sectional studies
- Compared to controls significant:
  - FA reduction in ipsilateral > contralateral WM.
  - MD increase in ipsi- and contralateral WM.
  - Tracts closely connected to sz onset zone most affected.

Otto WM et al, Epilepsy 2012

---

**Diffusion Tensor Imaging**

**Widespread DTI abnormalities in patients with Epilepsy: Mechanism and limitations**

- Axonal packing and myelin content are the primary predictors of FA [Baraha, 2002]
- Correlations between in vivo DTI and histology in humans [Carroll et al, 2013]
- Animal and recent human reports provide validation of DTI
- Most commonly seen pattern of DTI changes associated with focal epilepsy:
  - Unchanged parallel diffusivity
  - Increased perpendicular diffusivity as can be seen in Wallerian degeneration. (Gross O, 2011)
- Limitations: Image resolution, crossing fibers.
Diffusion Tensor Imaging
Structure-Function Relationship

• Integrity of white matter tracts relates to performance across a wide range of cognitive skills. Systematic investigations TLE only
• Memory performance in TLE: 28 patients (18 L) L TLE: Evidence of damage of the uncinate fasciculus based on abnormal ADC and/or FA measures relates to auditory memory (L UF) and visual memory (R UF) performance. Diehl et al., Epilepsia 2008

Diffusion Tensor Imaging
Structure-Function Relationship: Language

• Cryptogenic left FLE: Streamline DTI from both FLs. Right language dominant. Number of L arcuate fasciculus (AF) fibers reduced by 50%. Modified from Kilmartin and Diehl, chapter in Extratemporal Lobe Epilepsy Surgery, AJ Radiologists and Neuroradiologists
• DTI/FA of the AF predicted language laterality (determined by WADA test) in the majority (19 of 23) of patients. Ellmore TM et al., Neuroimage 2009

Diffusion Tensor Imaging
Structure-Function Relationship: Memory

• 18 patients, unilateral TLE, 10 healthy controls
• Tractography of parahippocampal connections
• Left TLE patients: connected regions ipsilateral to the epileptogenic region reduced in volume and mean FA compared to contralateral region, and left-sided connections in control subjects.
• Significant correlations in left TLE patients between left and right FA, and verbal and non-verbal memory respectively.

Diffusion Tensor Imaging
Validating DTT of the Arcuate Fasciculus

Comparison with language stimulation for Electrical cortical mapping. Colocalization significantly better in anterior than posterior language regions.

Using Cortico-cortical evoked potentials, connectivity via the arcuate fasciculus can also be shown.
Diffusion Tensor Imaging
Diffusion changes in new onset childhood epilepsy

- 35 children (23 with focal seizures)
- Diffusion changes can already be found shortly after seizure onset.
- Reduced fractional anisotropy in the left post central white matter (after correction for multiple comparisons).

Widjaja et al., 2013
American Epilepsy Society | 2013 Annual Meeting

Diffusion Tensor Imaging
Diffusion changes and epileptogenicity

Diffusion abnormalities in cortex and white matter in different depths in the seizure onset zone of children undergoing intracranial EEG recordings.

- 18 children, focal neocortical epilepsy, normal MRI compared to 18 age-matched healthy controls.
- Analysis of ADC and FA of cortex and white matter in different depths (surface based/laminar analysis).
- Different patterns of diffusion abnormalities found in seizure onset and normal cortex:
  - Seizure onset region: increase in diffusivity, mostly outer fraction of gray matter and in white matter underlying the epileptic cortex.

Govindan RM et al., Epilepsia 2013
American Epilepsy Society | 2013 Annual Meeting

Diffusion Tensor Imaging
OUTLINE
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- Role of DTI in planning epilepsy surgery
- Postoperative findings of DTI after epilepsy surgery

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Diffusion Tensor Imaging
DTT and pathways of seizure spread

- Aim in Epilepsy surgery: NO SEIZURES, NO SIDE EFFECTS.
- Requires best possible definition of the epileptogenic zone.
  - Possible benefit of understanding early propagation
- Reduce risk to function
  - Cortical mapping (MRI/electrical stimulation)
  - Preserve connectivity – Role for DTT?

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Diffusion Tensor Imaging
DTT and pathways of seizure spread

American Epilepsy Society | 2013 Annual Meeting

Modified from Dieth B et al., Epil Res 2010
American Epilepsy Society | 2013 Annual Meeting
Diffusion Tensor Imaging
DTI and presurgical planning
Left postcentral cortical dysplasia (red) and pyramidal tract (blue) seeded from the hand sensory area as defined by fMRI.
Four electrode contacts representing the ictal onset zone as per intracranial EEG.

Also see: Catani M et al., Cortex 48 (2012)
Courtesy R Rodionov PhD, M Nowell MD

Diffusion Tensor Imaging
DTT for presurgical planning
Visual field deficits after anterior temporal lobe resections
European guidelines *the horizontal visual field should be at least 120 degrees, the extension should be at least 50 degrees left and right and 20 degrees up and down.

Four electrode contacts representing the ictal onset zone as per intracranial EEG.

Also see: Catani M et al., Cortex 48 (2012)
Courtesy R Rodionov PhD, M Nowell MD

Diffusion Tensor Imaging
DTT for presurgical planning
DTT of the optic radiation to plan lesionectomy of cavernous haemangioma

Winston G et al., 2012
American Epilepsy Society | 2013 Annual Meeting

Winston G et al., Ann Neurol 2012
American Epilepsy Society | 2013 Annual Meeting

Diffusion Tensor Imaging
Before and after surgery
• Little is known what happens to diffusion changes after surgery.
• Comparing 8 pts with TLE pre and post surgery, and to 22 controls; preop observed FA reductions in fornix, cingulate and external capsules, did not normalise (Concha et al., 2007)
• Several reports of FA increase postoperatively
  – in contralateral fornix (Hogen et al., 2011)
  – in the inferior and superior longitudinal fasciculi (Faber et al., 2013)
• Significance of such increases is currently not well understood
  – Structural reorganization?
  – Artefactual?

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Diffusion Tensor Imaging
Before and after surgery

- 26 left, 20 right TLE patients, before and after anterior TLE resection (mean 4.5 months)
- Whole-brain analysis, tract-based spatial statistics, compare pre/post
- In right and left TLE, postop decreased FA in tracts adjacent to resection
- In left TLE: Increased FA in the ipsilateral external capsule, posterior limb of the internal capsule
  - Corresponding to ventro-medial language network
  - May represent structural reorganization in response to resection

Modified from Yogarajah M et al., Brain 2010

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Diffusion Tensor Imaging
Conclusions

- DTI is a novel imaging technique that provides insight into the structural integrity of cerebral white matter.
- There are significant technical limitations to reconstruct tracts from DTI, and validation of findings is an ongoing effort.
- Widespread abnormalities have been found in patients with focal epilepsy, and tracts closely connected to seizure onset zone are most affected in TLE.
- Some structure-function relationship exists, but networks underpinning cognition are complex.
- DTT may contribute to our understanding of ictal onset and spread.
- DTT has the potential to improve prediction of postsurgical outcome and improve functional outcome.

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Annual Fundamentals of Epilepsy Symposium:
Neuroimaging in Epilepsy:
Focusing On the Focus and Outside the Focus

New MRI Techniques in Epilepsy

Graeme D. Jackson, M.D.

Slides Not Available