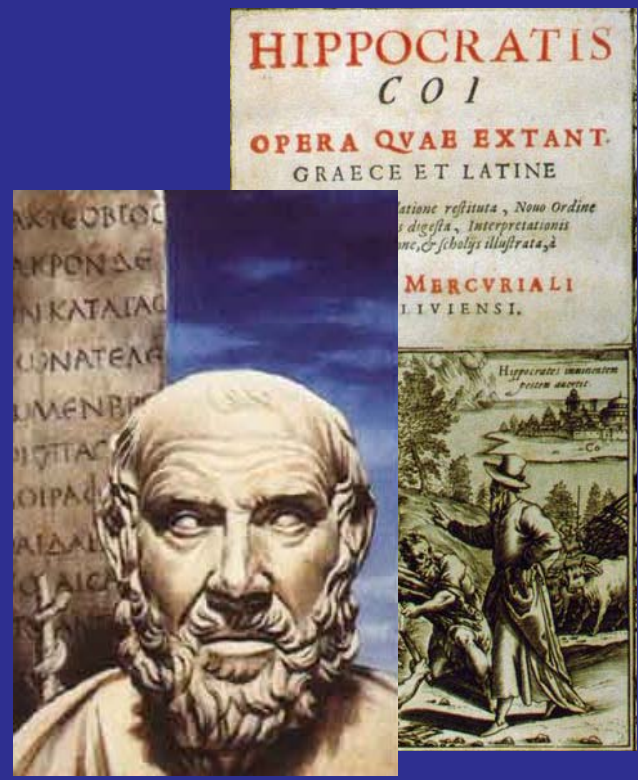
Epilepsy Benchmarks and Beyond: NIH and the Future of Medicine

Elias A. Zerhouni, M.D.
Director
National Institutes of Health

Historical Understanding of Epilepsy

- In ancient Greece, epilepsy was known as the “Sacred Disease”: thought to be caused by the gods
- Hippocrates disagreed: epilepsy was “nowise more divine nor more sacred than other diseases, but has a natural cause”
- Hippocratic vision of epilepsy:
  - Cause located cause in brain
  - “Curable”—by proper diet and regimen
  - “Origin is hereditary, like that of other diseases”
- Thousands of years later, we are still chasing down the hereditary basis of—and seeking a cure for—this disease



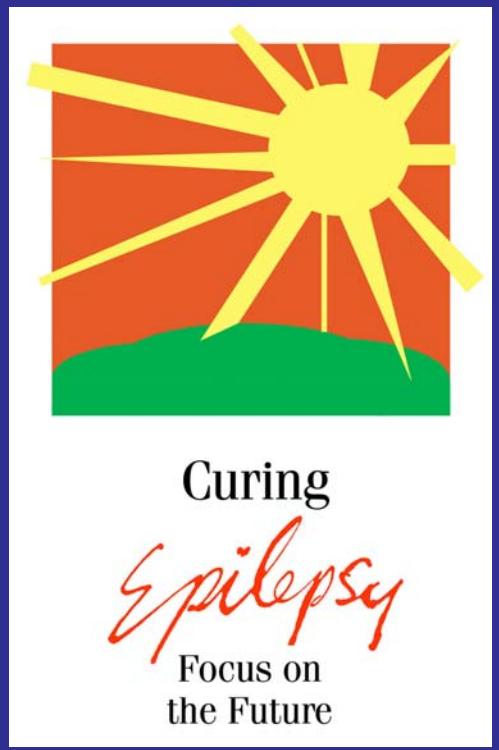
Impact of Epilepsy

CURING EPILEPSY 2007
Translating Discoveries Into Therapies

- Epilepsy affects an estimated 3 million Americans
- About 200,000 people in this country are diagnosed each year
- 25,000 – 50,000 deaths each year are due to seizures and seizure-related problems
- Estimated total cost of epilepsy in the U.S. is $12.5 billion/year

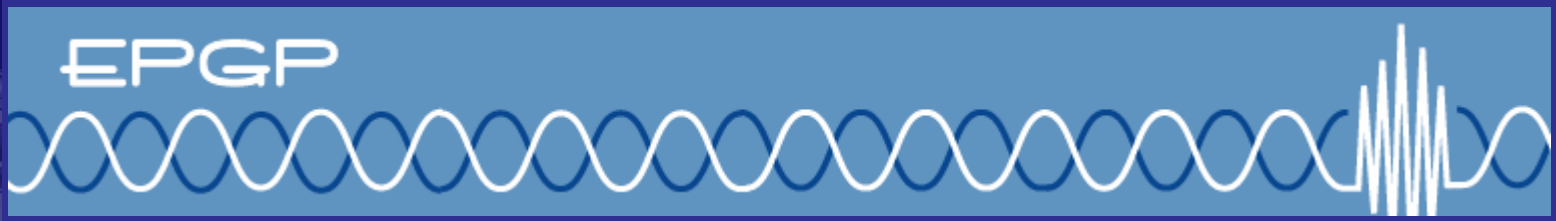
Epilepsy Benchmarks: 2000

"Epilepsy Benchmarks" developed after first *Curing Epilepsy* conference (2000); identified critical areas to be explored in search for cure



- 17 specific benchmarks in three main areas:
  - Understanding how epilepsy develops
  - Finding ways to prevent seizures from developing in at-risk individuals
  - Finding better ways to stop seizures without side effects in those who have epilepsy
- Benchmarks help to focus research; serve as milestones to measure progress. Several have been largely achieved:
  - Epilepsy Phenome/Genome Project (EPGP)
  - Increased/improved use of surgery
  - Responsive neurostimulator

Understanding Epilepsy: Epilepsy Phenome/Genome Project



- Collaborative project involving 15 medical centers; thousands of people with epilepsy
- Project: collect wide array of patient information, including genes and brain abnormalities; medical and family history; seizure types and frequency
- Goals: use improved understanding to:
  - Identify new genes that influence epilepsy
  - Identify genes that affect responsiveness to epilepsy medications
  - Improve epilepsy diagnosis, treatment, and prevention

Treating Epilepsy: Drug Development

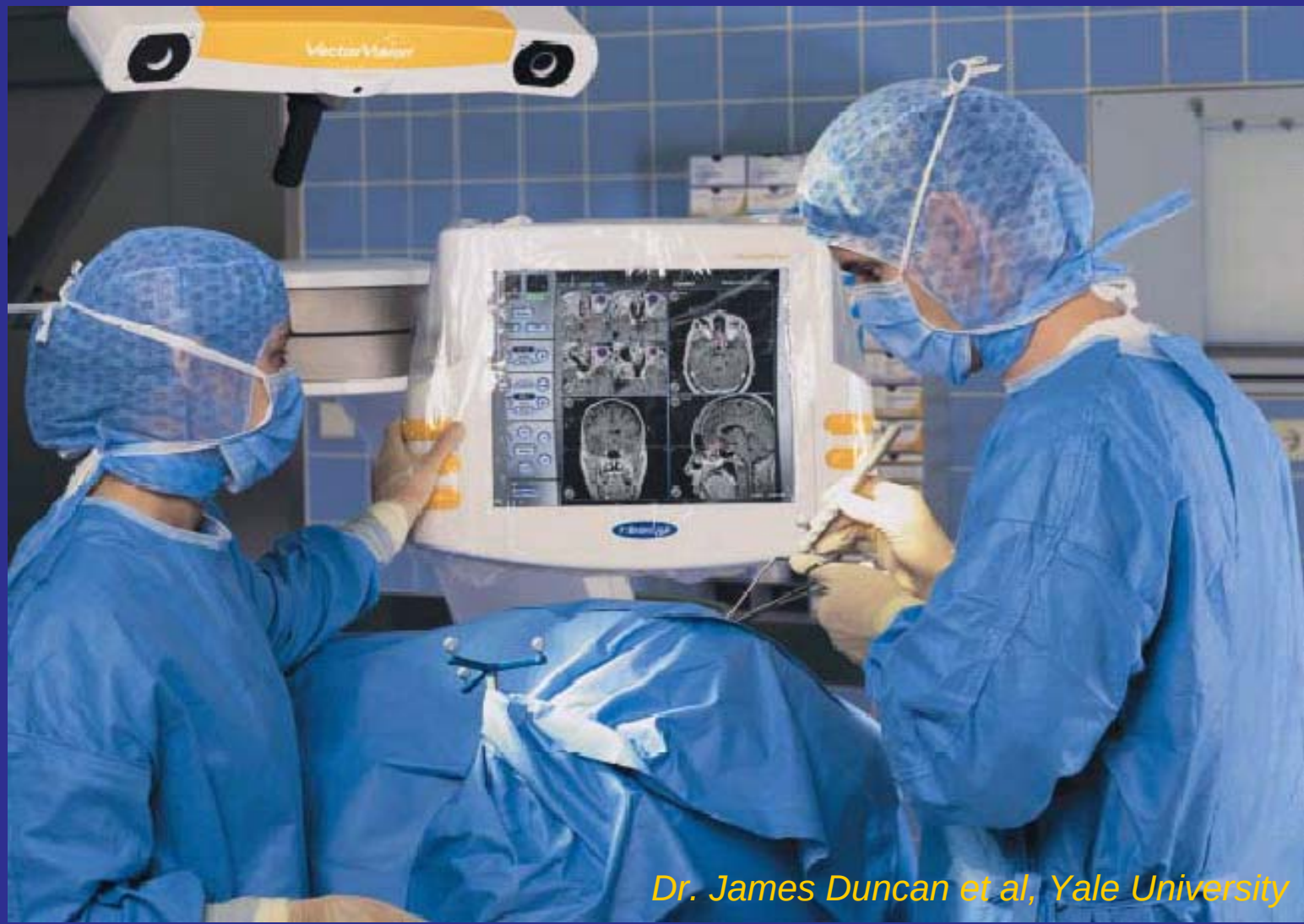
30 years ago, only 5 drugs were approved for epilepsy; today, there are 20

- 1970s: NINDS-funded clinical trials led to approval of valproic acid, carbamazepine, clonazepam

Despite available medicines and surgical therapies, 25 to 30% of epilepsy sufferers still have no treatment that can control seizures without troubling side effects

- Eight new ASP-evaluated compounds now in active clinical tests; several others with novel targets in earlier stages of preclinical optimization and development

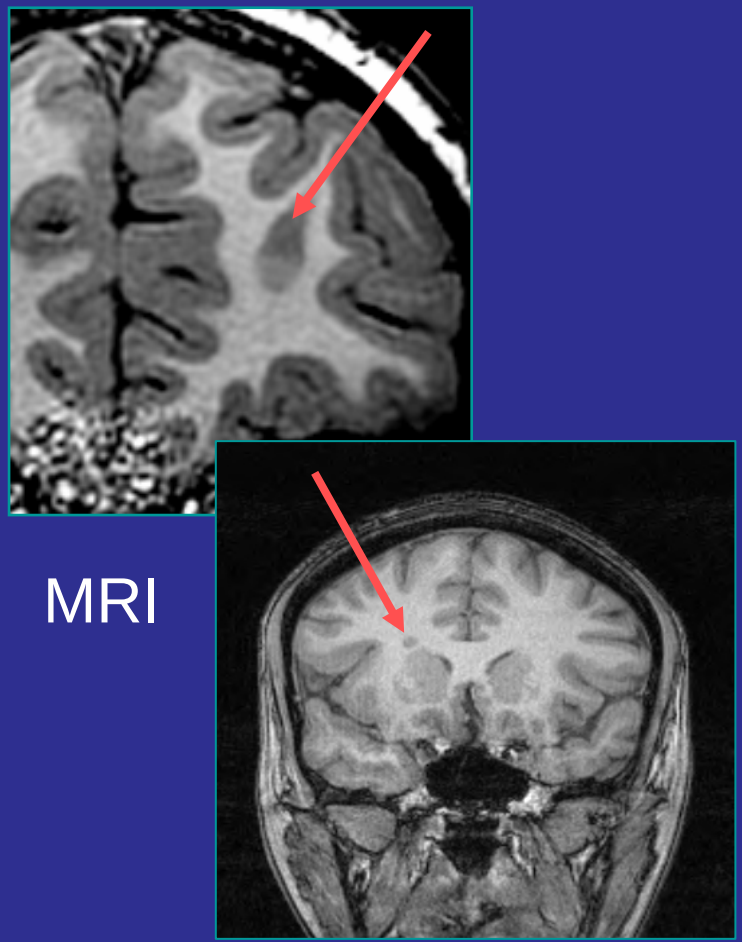
Treating Epilepsy: Bioimaging Improves Surgical Intervention



Dr. James Duncan et al, Yale University

Imaging: Perspectives on Epilepsy

Heterotopia



MRI

SPECT

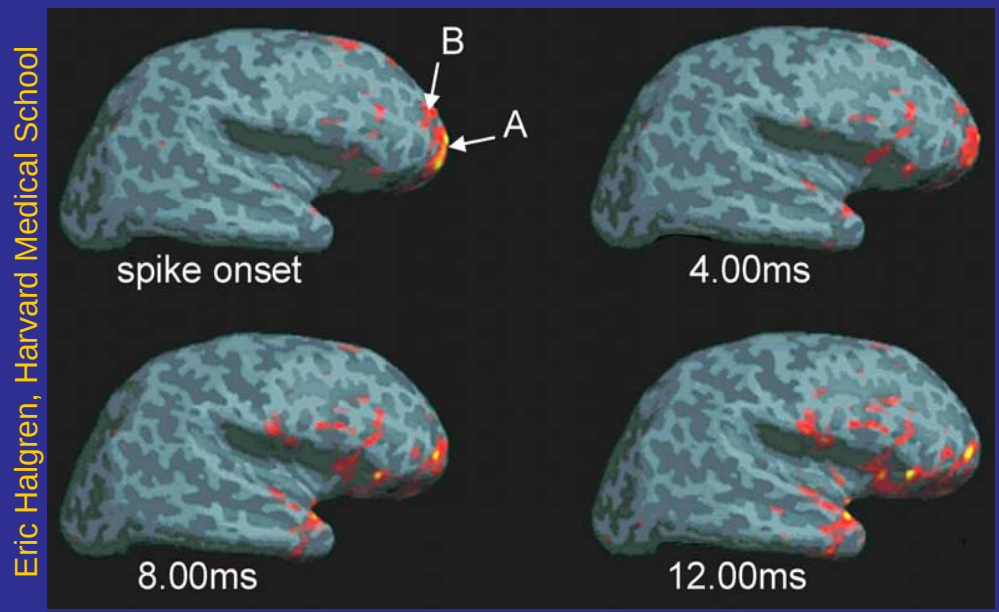
Imaging increases precision of surgical interventions

Andrew Cole/Sydney Cash, Massachusetts General Hospital

Greg Cascino, Mayo Rochester

Imaging: Perspectives on Epilepsy

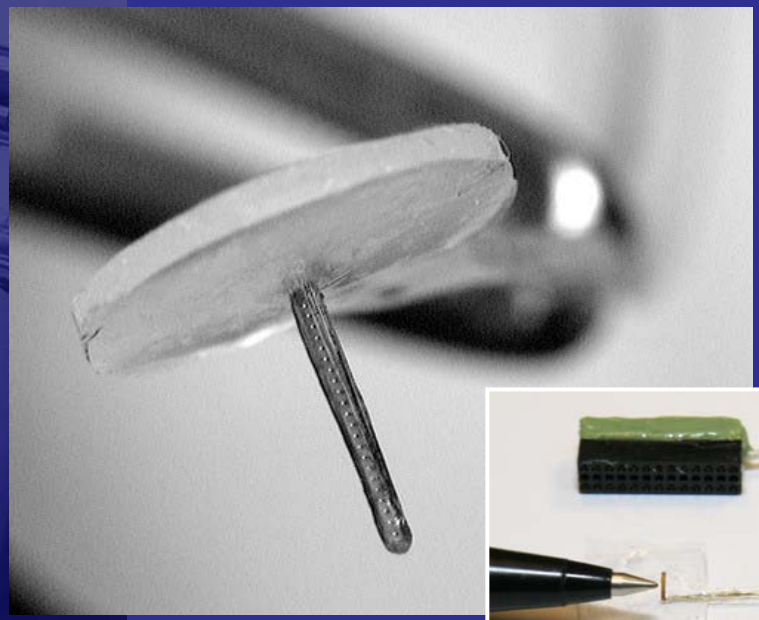
- Advances in recording and analysis of abnormal electrical discharges enable mapping source and spread of seizures in brain
- Overlay of structural and electrical maps provides directions for surgical removal of seizure-generating brain areas



Interictal spike propagation recorded with MEG; 'A' shows origin of spike

Cutting Edge Technologies –
Microelectrode Recordings in Human Cortex to better understand, detect and predict seizures

(to be discussed by John Donoghue on Friday afternoon section and some results presented by Sydney Cash at Junior Investigator Program)

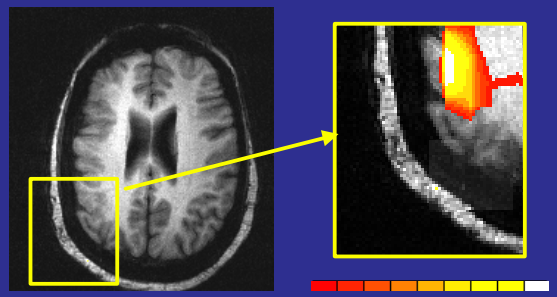


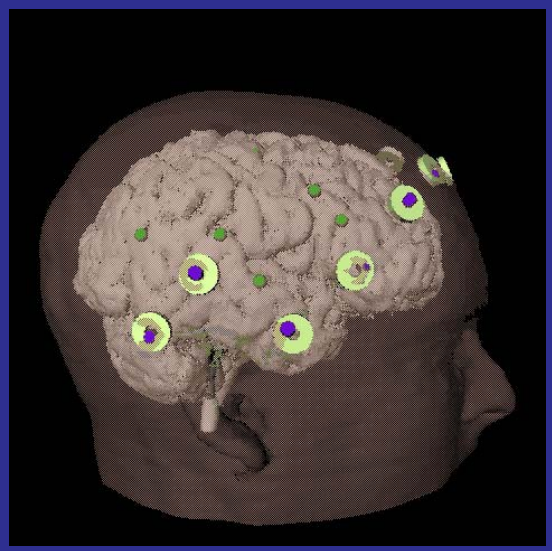
Laminar Microelectrode Array developed by Istvan Ulbert and George Karmos and in use by a collaboration led by Eric Halgren and Sydney Cash at UCSD, New York University and Harvard Medical School.

Neuroport® Array developed by Cyberkinetics Neurotechnology Systems Inc. and in use at Columbia Univ. and Harvard Medical School.

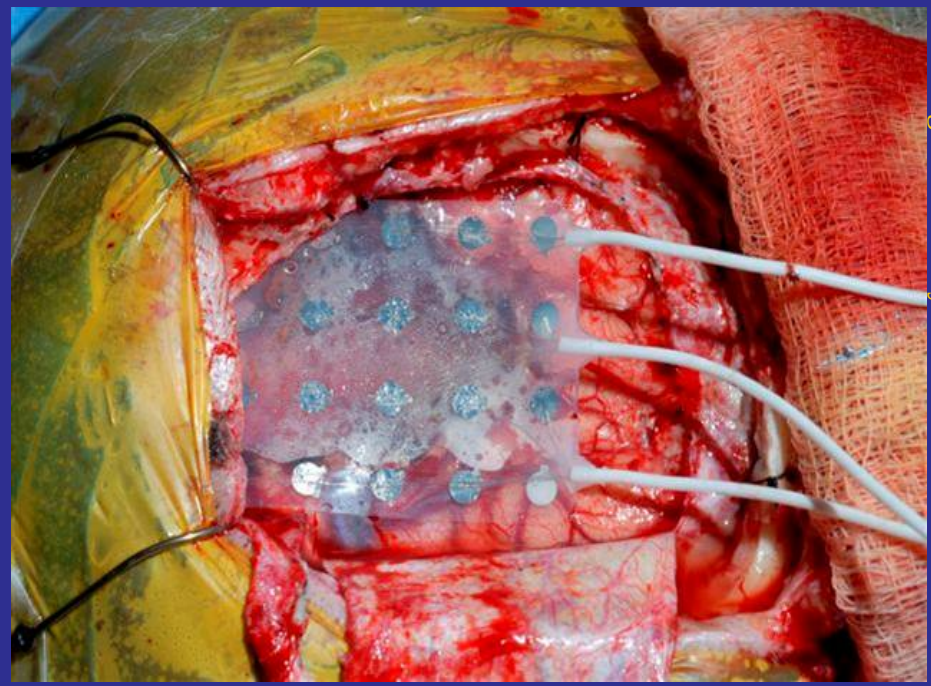
Epilepsy: Imaging to Operation

Preoperative Images



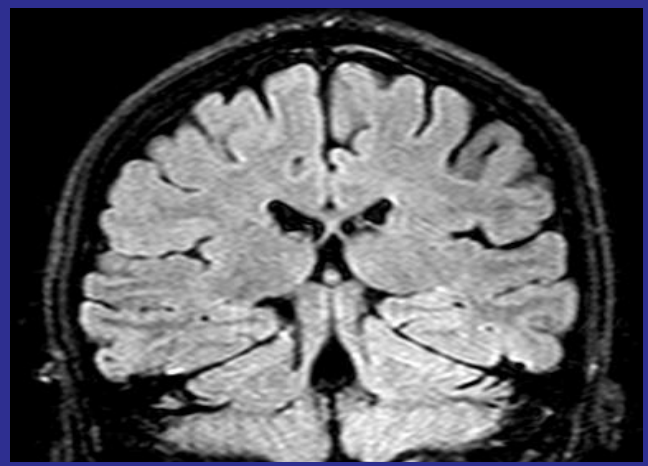


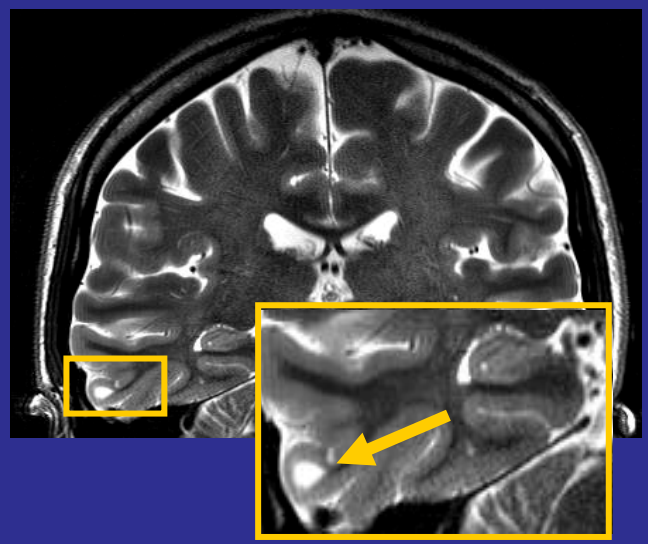
Intra-operative Grid



Greg Cascino Mayo Clinic Rochester

Application: Bioimaging and Intervention in Neocortical Epilepsy





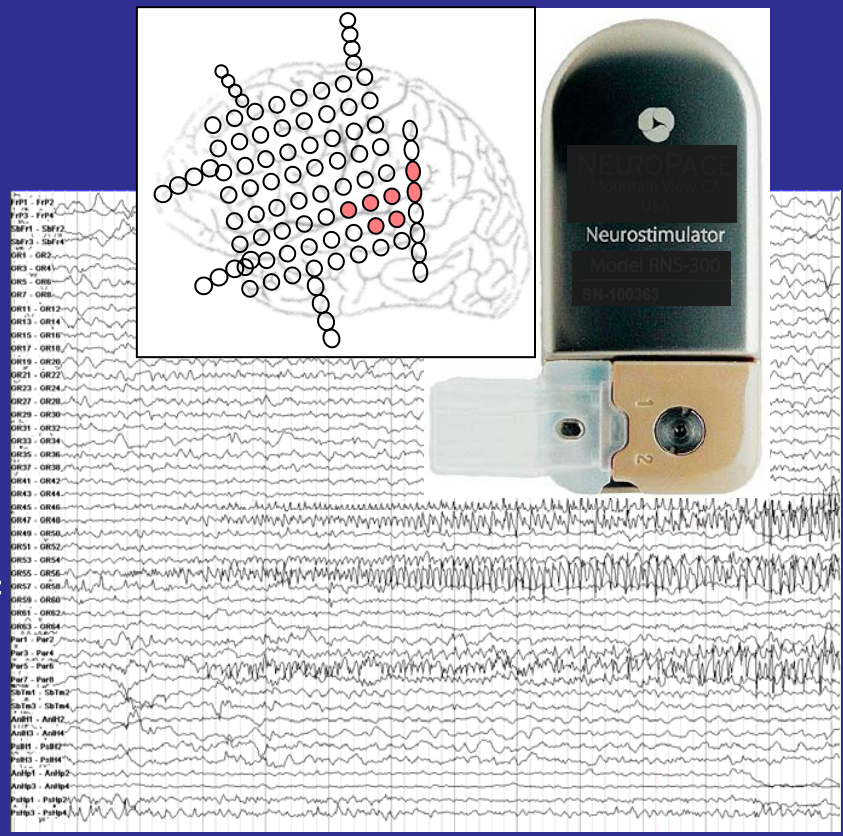
- Dramatic improvements in Bioimaging technology allows intervention in Neocortical Epilepsy
- Today:
  - 60% Increase in Seizure Foci Identification
  - Successful image-guided epilepsy surgery
  - Reduce or eliminate major post-op neurologic deficits

BWH E. Bromfield, P Black

Responsive Neurostimulator

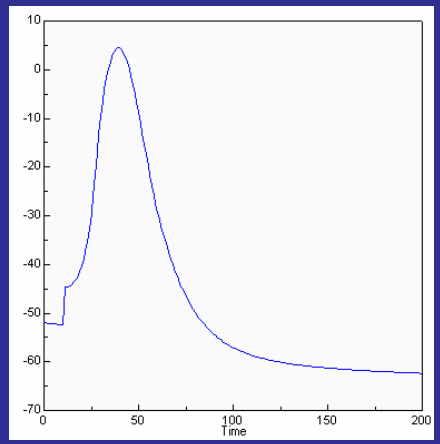
Epilepsy Benchmark (2000): Create a device "that, in at least one type of epilepsy, will detect an oncoming seizure and apply treatment to stop the seizure before it begins"

- Responsive neuro-stimulator system now being tested clinically in people with partial seizures
- System includes pacemaker-like device implanted in brain
  - Continuously monitors electrical activity for signs of seizure onset
  - Delivers brief electrical stimulation to suppress seizure

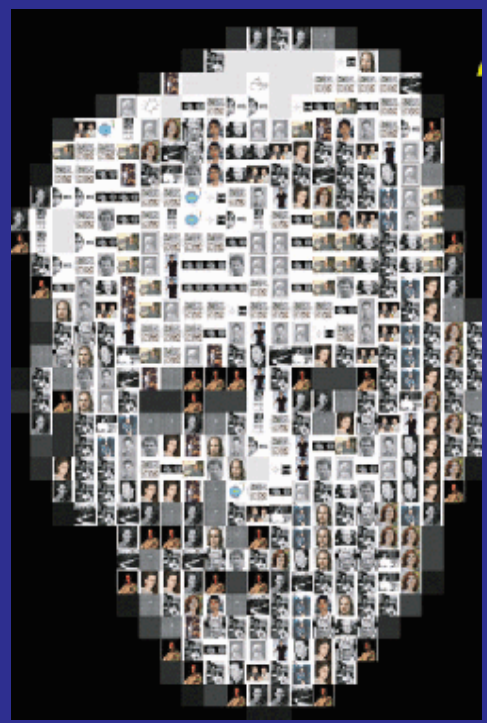


Sydney Cash, Massachusetts General Hospital

Hodgkin-Huxley … Computational Neuroscience

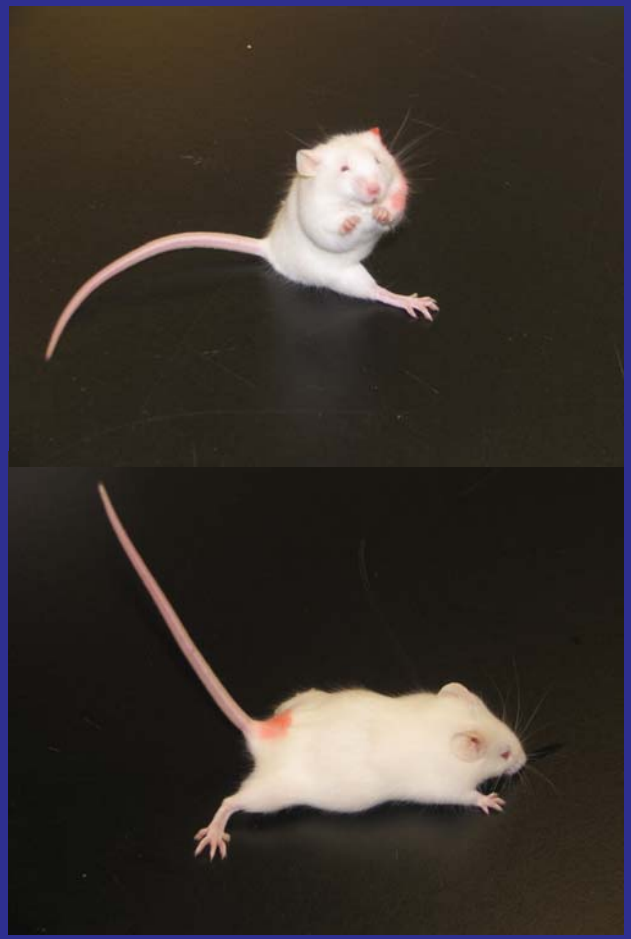


" … collaboration between experimentalists and theoreticians is thriving." --Floyd Bloom, Oct. 6 *Science*



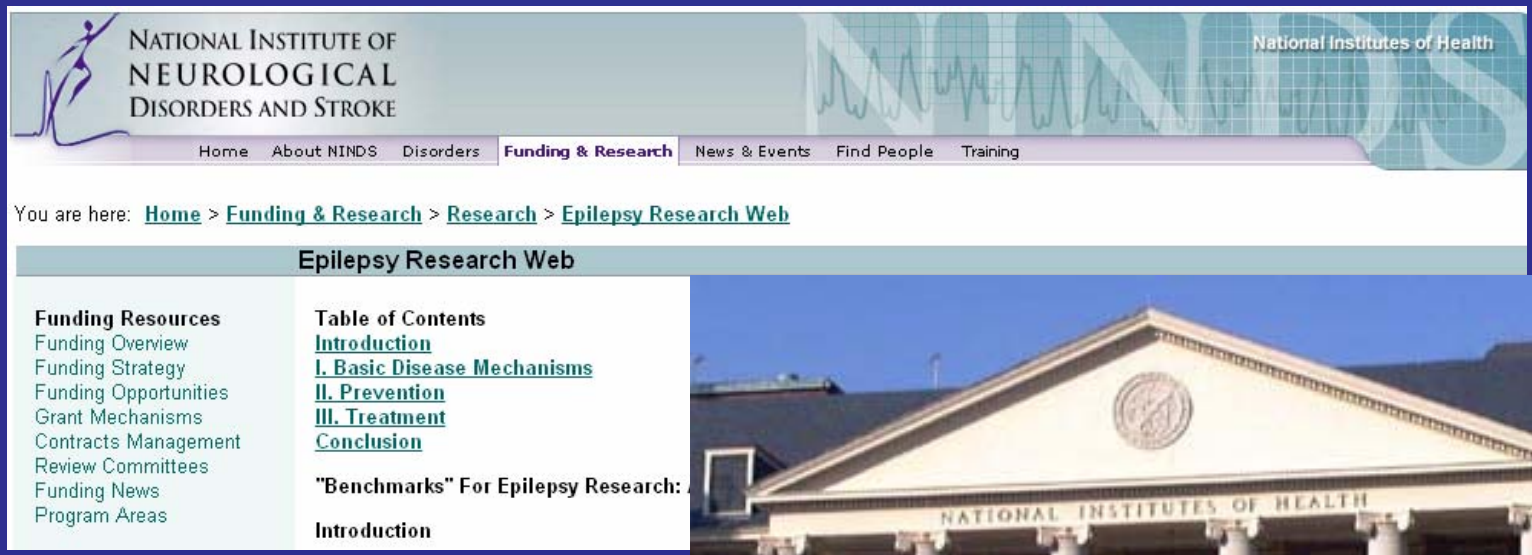
Neuroscience Database Gateway
http://ndg.sfn.org/

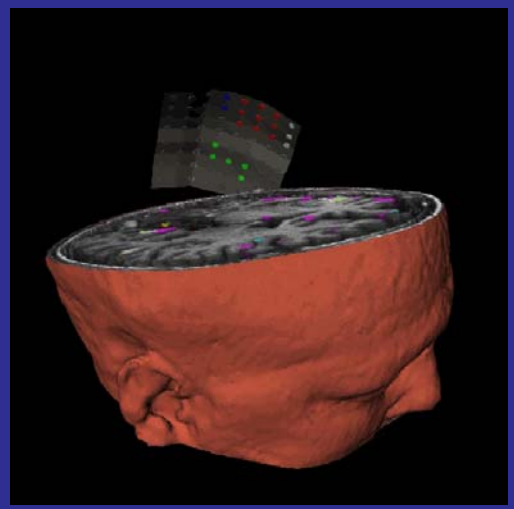
Advancing Our Understanding: Epilepsy and Animal Models



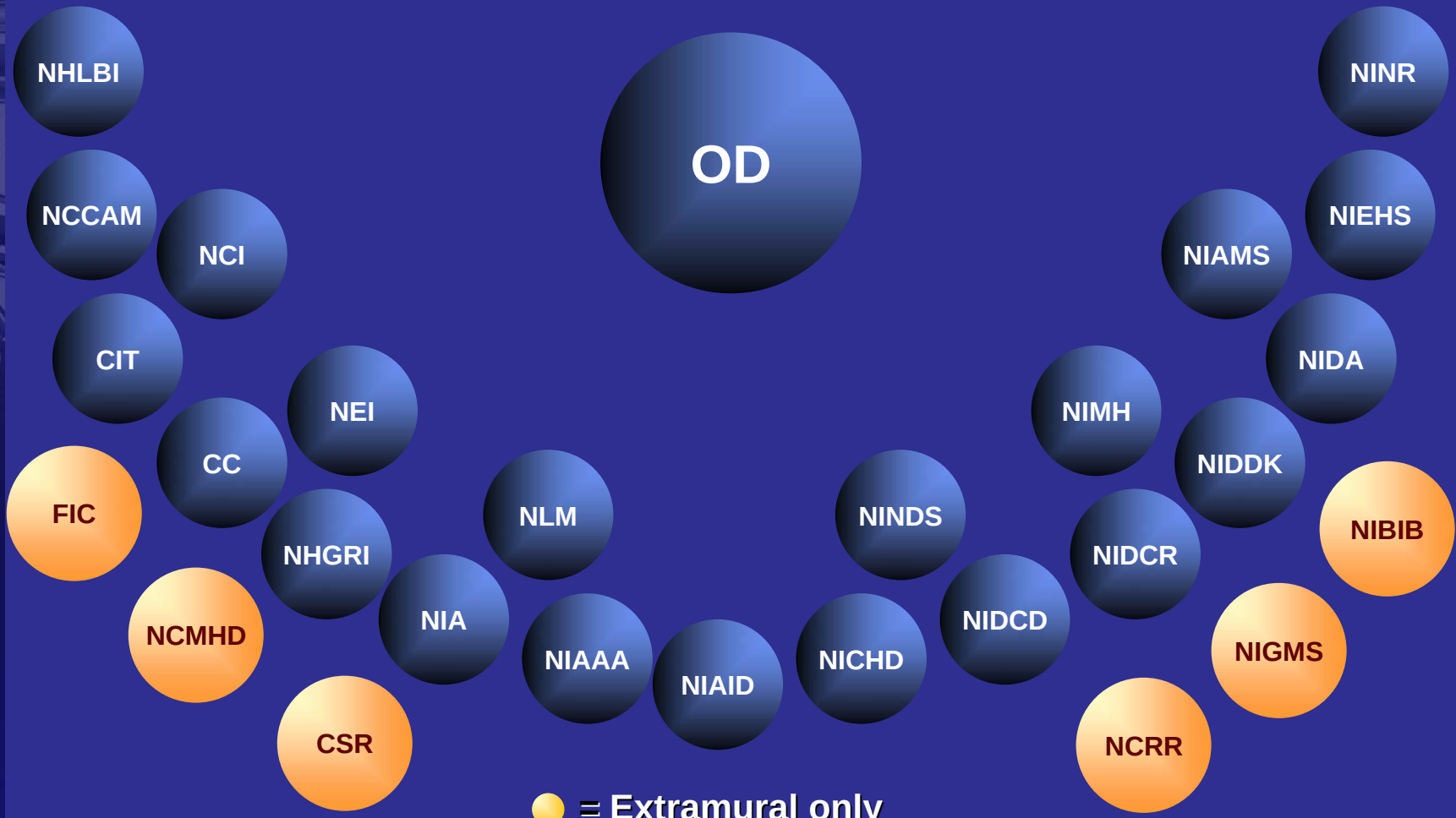
- Collaborative network identifying genetic programs common to multiple animal models of epilepsy
- Research should lead to new theories about genetic basis of epileptogenesis
- Many new animal models have been developed in past decade, including:
  - New models of drug-resistant epilepsy
  - New models for febrile seizures and infantile spasms
  - Models of nerve toxin exposure

NIH, Biomedical Research, and Curing Epilepsy



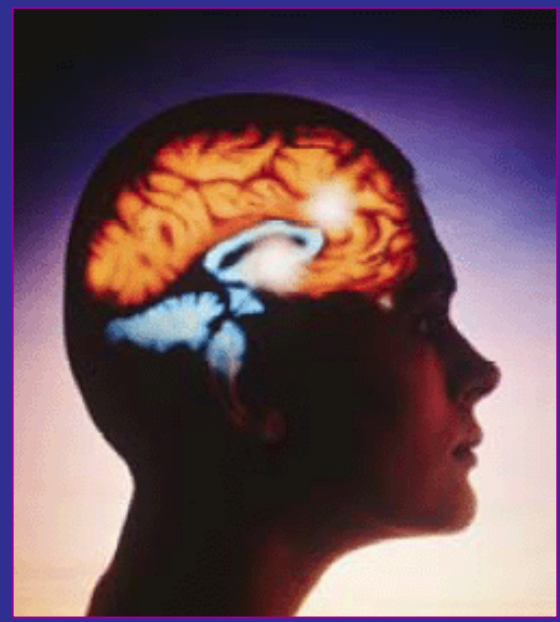


NIH Consists of 27 Institutes and Centers

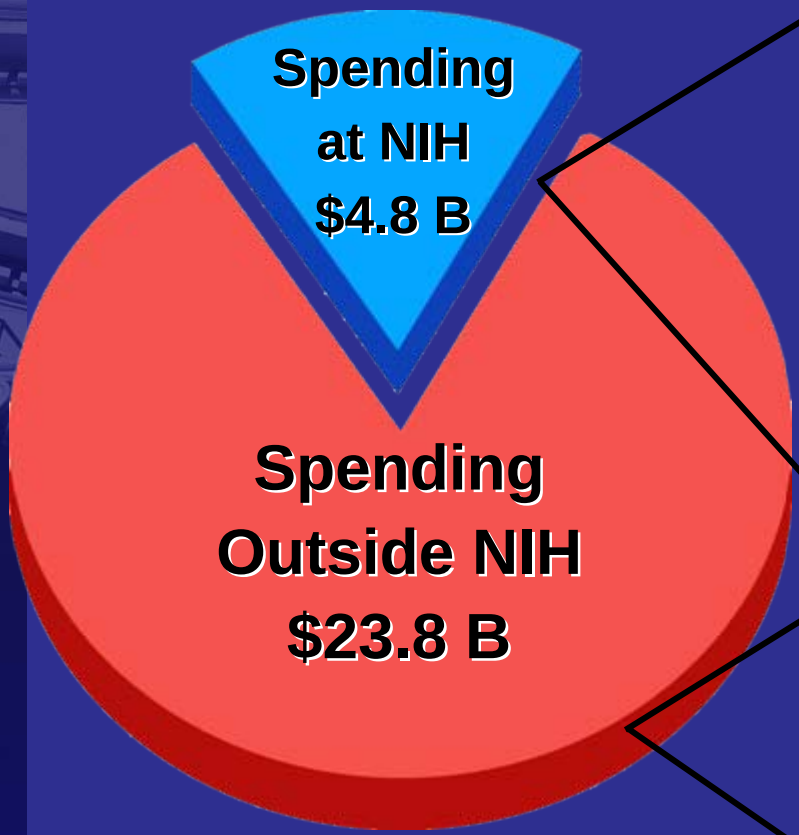


Collaboration at NIH

- **Interagency Epilepsy Working Group**
  - 8 NIH institutes and centers (ICs) plus CDC
  - *Goal*: increase communication among institutes and agencies sponsoring epilepsy-related research; explore opportunities for increased coordination
- **NIH Blueprint**
  - Collaboration among 15 ICs
  - Areas of study: neurodegeneration, neurodevelopment, and neuroplasticity: *all highly relevant to epilepsy research*
  - *Goal*: develop new tools, resources, training opportunities to accelerate pace of discovery in neuroscience research



NIH Budget in FY 2006: $28.6 Billion



17%	Amount	Expenditure
10%	$2.8B	6000 Intramural Scientists & Research Personnel
3.8%	$1.1B	R M & S
3.2%	$1.0B	NLM, OD, etc.

83% of the total NIH budget supports an estimated 325,000 Extramural Scientists and Research Personnel at more than 3,000 Institutions Nationwide.

FY 2005 NIH Extramural Grants by Research Institution

Data: Assoc of University Technology Managers (AUTM) Survey 2004

Evolving Public Health Challenges

Shift from Acute to Chronic Conditions

Aging Population

Health Disparities

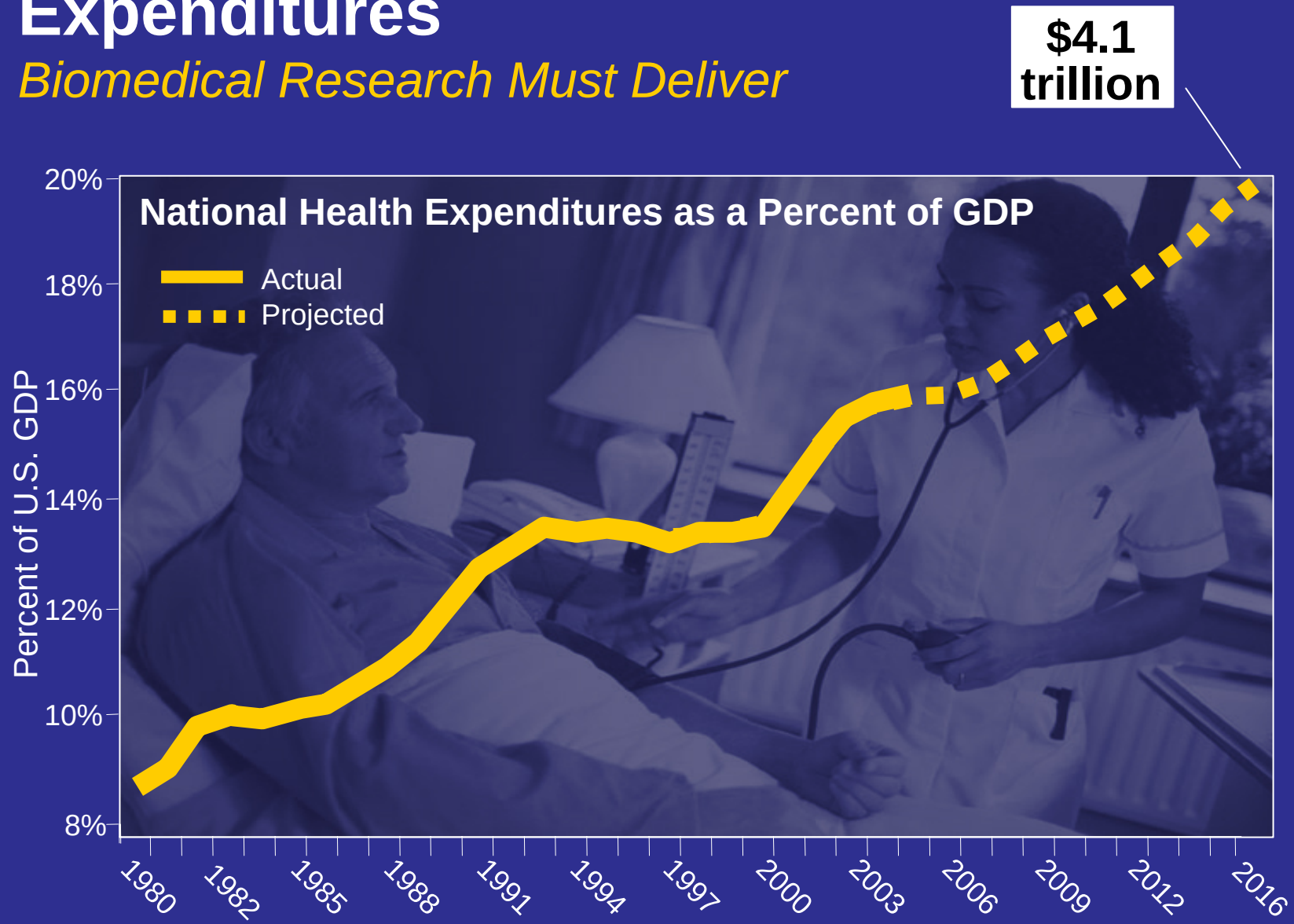
Emerging and Re-emerging Infectious Diseases

Emerging Non-communicable Diseases - Obesity

Biodefense

Challenge of Rising U.S. Health Expenditures

Biomedical Research Must Deliver



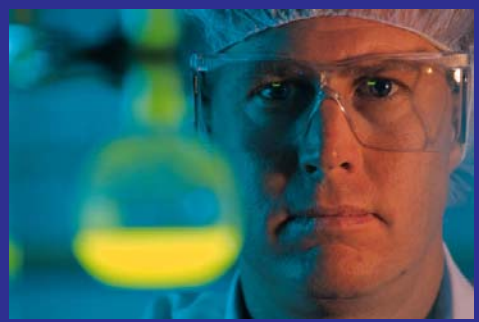
http://www.cms.hhs.gov/NationalHealthExpendData/downloads/proj2006.pdf

Challenges

Demand for Grants "Took Off" Just as NIH Budget Was "Landing"!

- Post doubling "boom" in applications has led to a *supply/demand imbalance*
- Success rate drop is due to
  - Near 100% increased demand for grants
  - 40% increased costs of grants
  - Decrease in inflation adjusted budget
- Budget cycling effect will slightly improve supply vs. demand of grants in 2007 and beyond

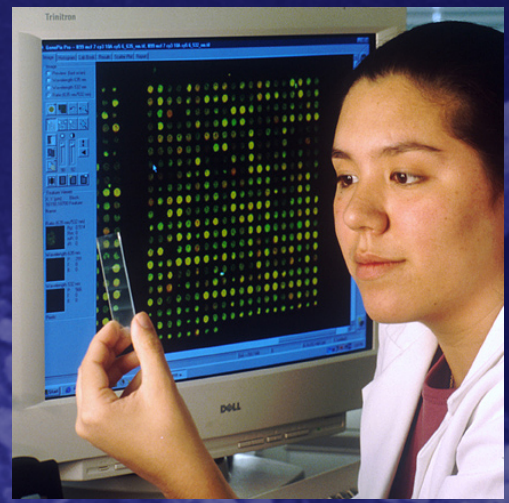
NIH: Adaptive Strategies for Tough Times



- **Our Approach**: No inflationary adjustments for non-competing renewal awards in FY2007
- **Our Goal:**
  - Stabilize number of competing grants
  - Strengthen support for at-risk populations:
    - New Investigators
    - First grant renewals
    - Well-established investigators with little or no additional support

The Future Paradigm: The 4 P's

Transform Medicine from Curative to Preemptive



Predictive ⟷ Personalized ⟷ Preemptive

Participatory

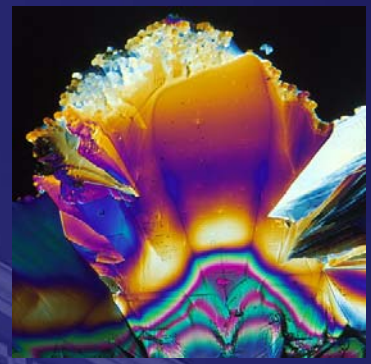
Era of Precision Medicine

Benchmarks and Beyond: Toward Pre-empting Epilepsy

- Personalized: Identifying molecular causes of epilepsy in all patients will allow personalized treatments
- Predictive: Technology to identify sub-clinical seizure-like activity in brain can predict when a seizure is about to occur
- Preemptive: Devices being developed that can stop seizures before they cause symptoms
- Participatory: People with epilepsy will participate in the Epilepsy Phenome/Genome Project, results will enhance disease understanding at many levels

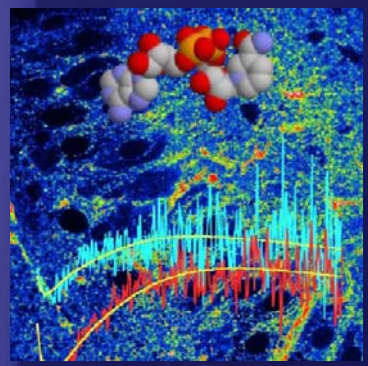
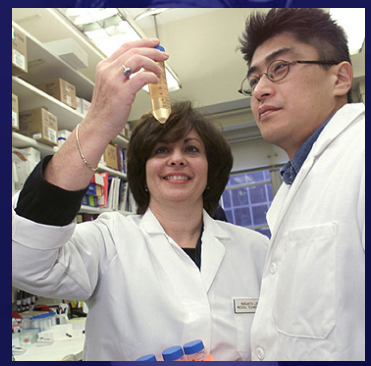
In the future, significant improvements in medicine will improve the quality of life for people with epilepsy and reduce the personal and economic costs of the disease






NIH

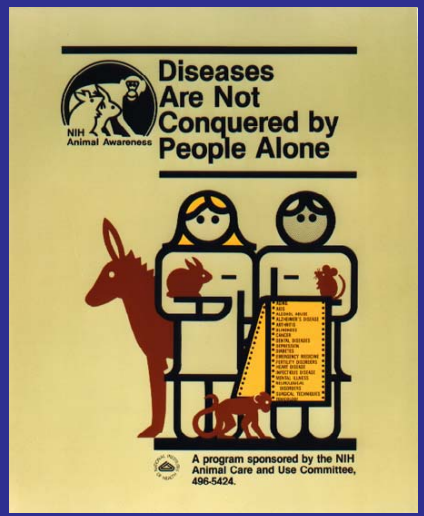
Transforming medicine and health through discovery

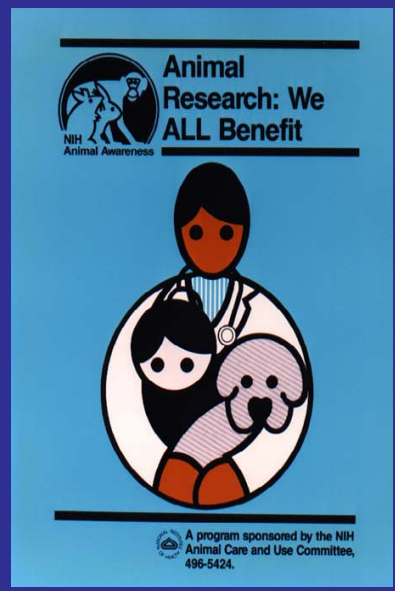




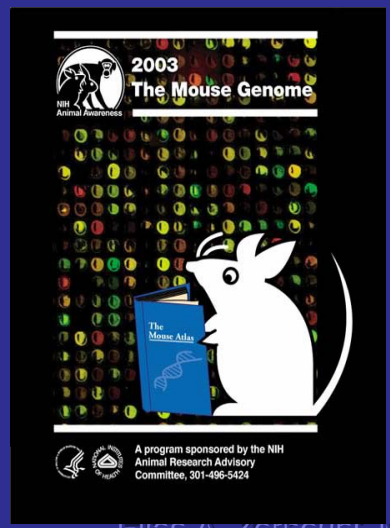

Extra Slides

Promote the Value of Ethical Animal Research for the Benefit of Humans and Animals.

Stand by our Scientists







Understanding Epilepsy; Curing Epilepsy

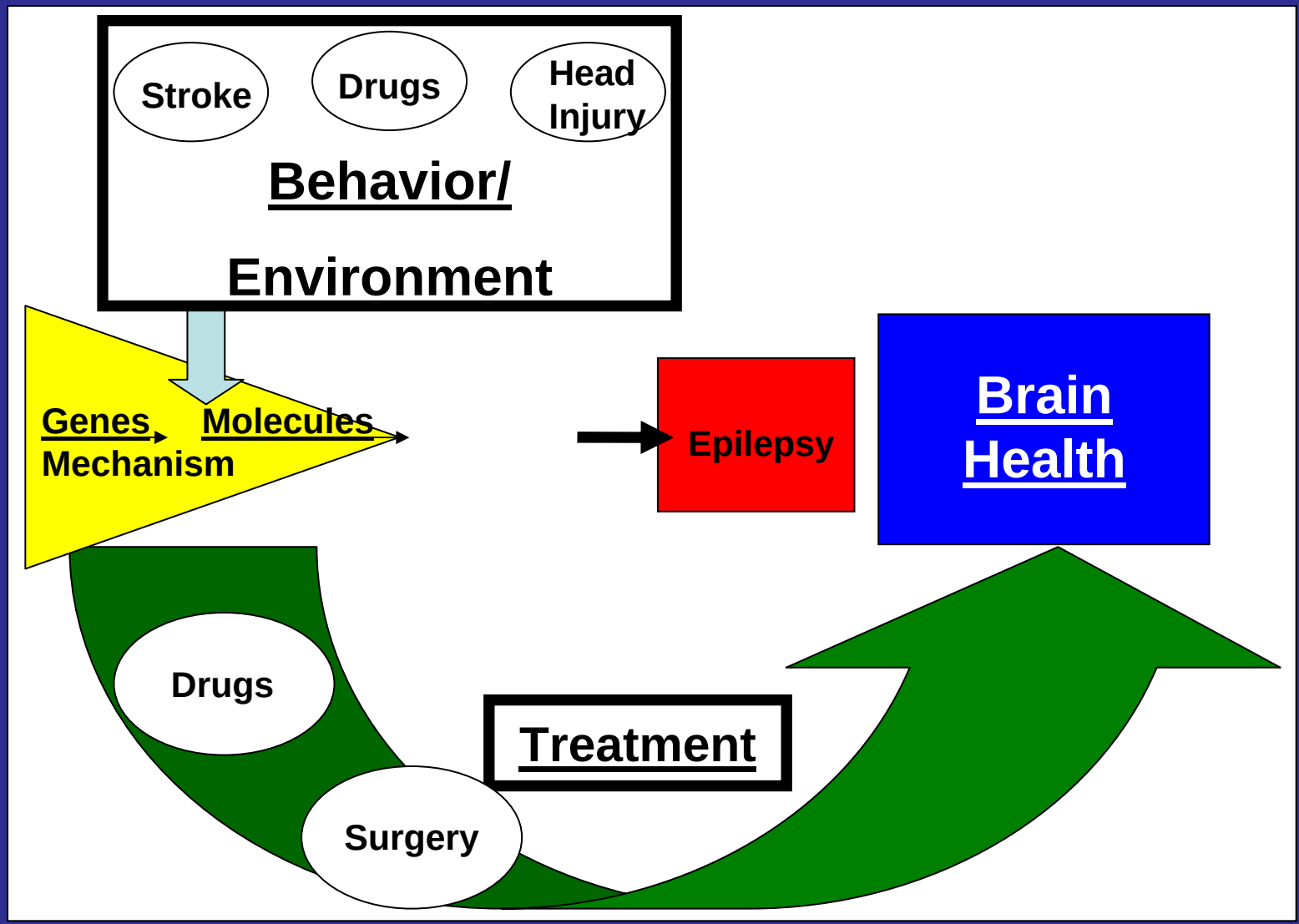
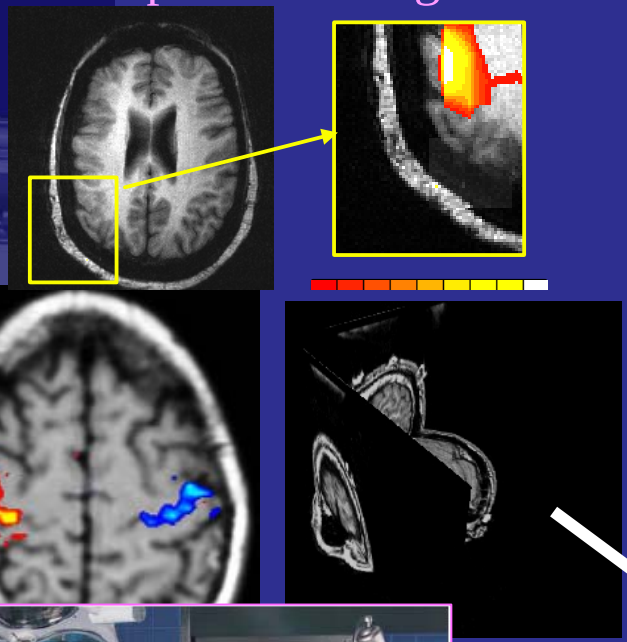
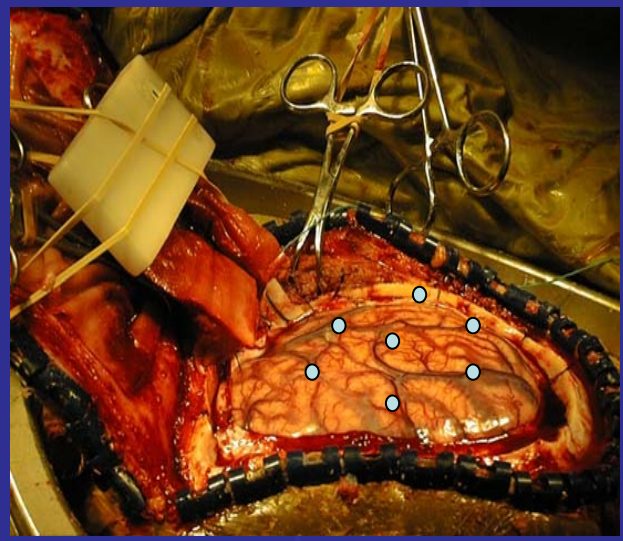


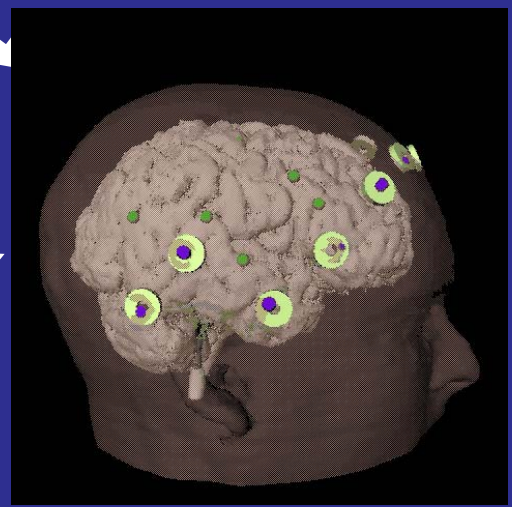
Image-Guided Epilepsy Surgery

Preoperative Images



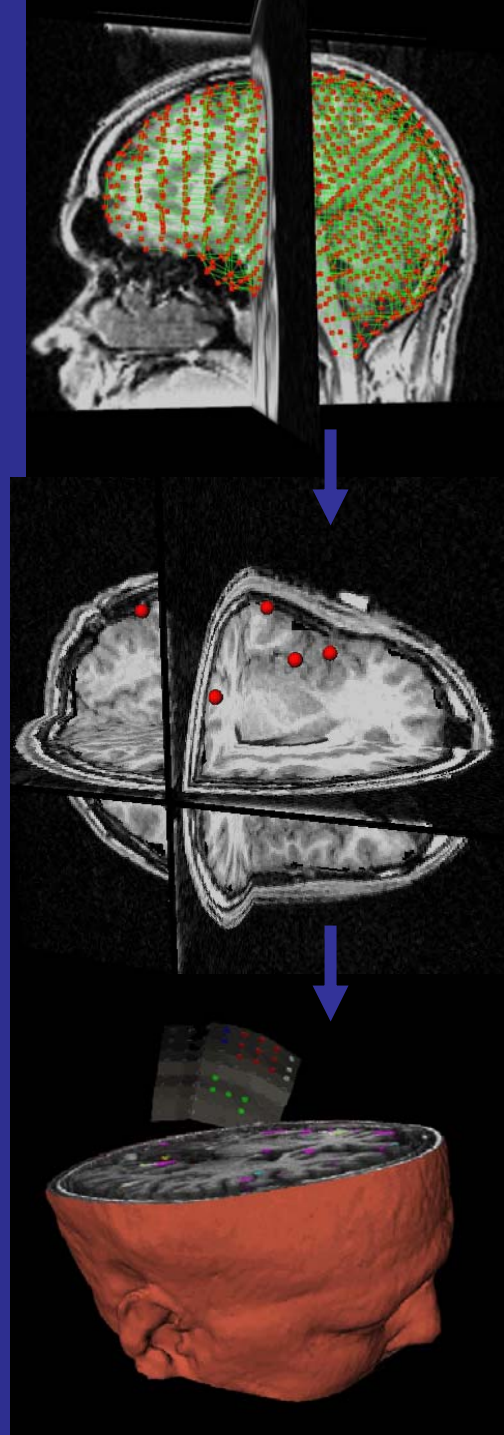


But the brain deforms



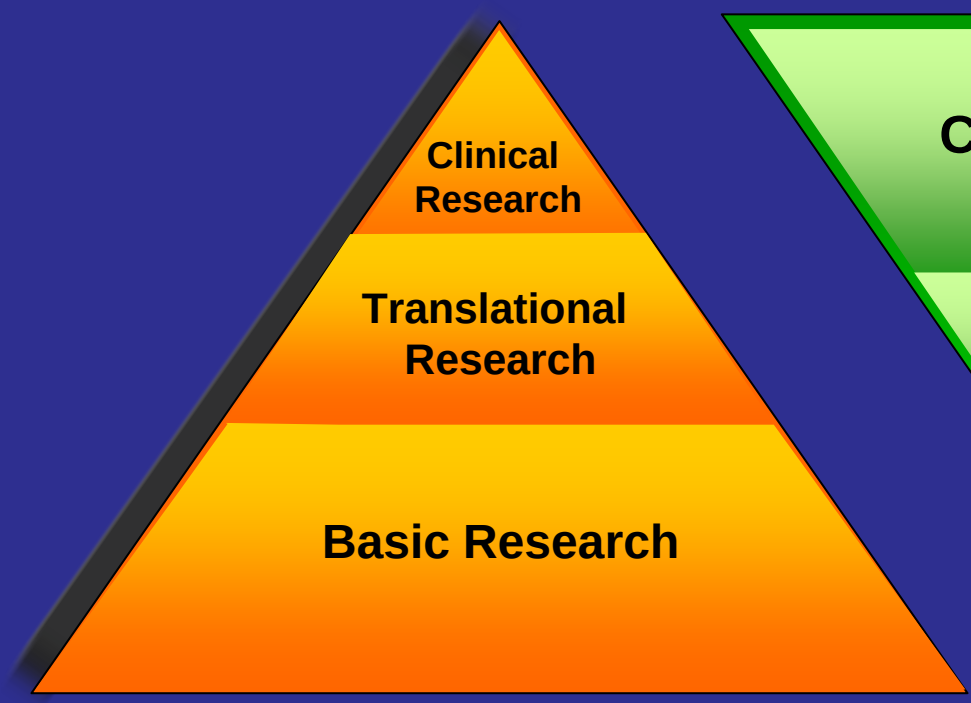
Marker-registered frames

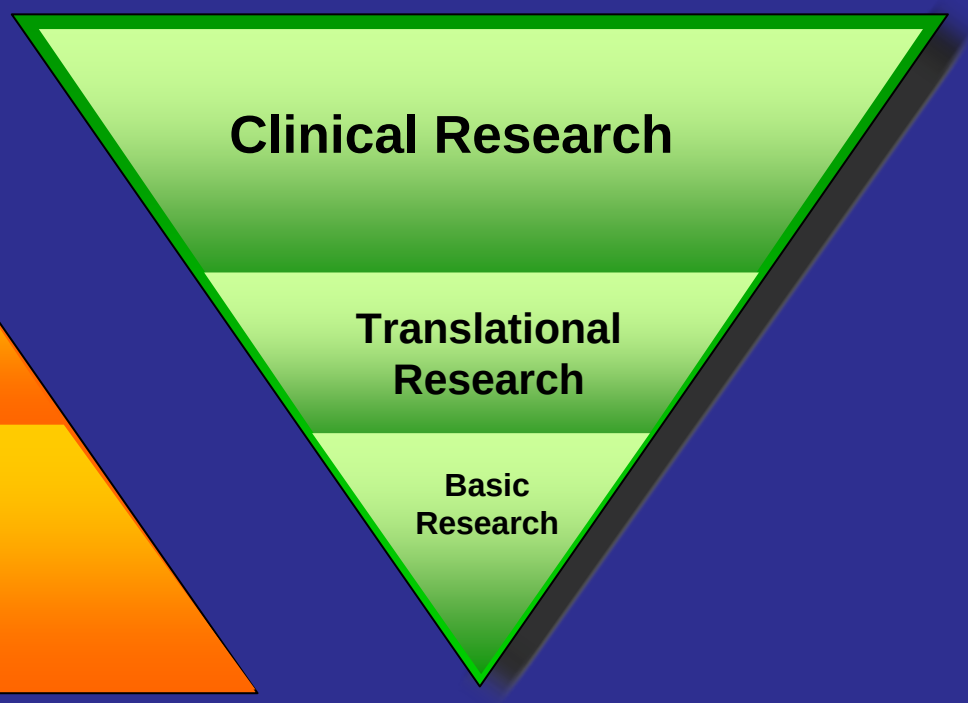
Intraoperative Stereotactic Frame



Elias A. Zerhouni, M.D.

Balanced National Biomedical Research Portfolio





NIH – $28 B

Private Sector – $59 B

Need to Transform Health and Medicine in the 21st Century

20th Century	21st Century
Treat disease when symptoms appear and normal function is lost	Intervene before symptoms appear and preserve normal function for as long as possible
Did not understand the molecular and cellular events that lead to disease	Understanding preclinical molecular events and ability to detect patients at risk
Expensive in financial and disability costs	Orders of magnitude more effective

NIH and its Partners

Congress

FDA

Public

NATIONAL INSTITUTES OF HEALTH

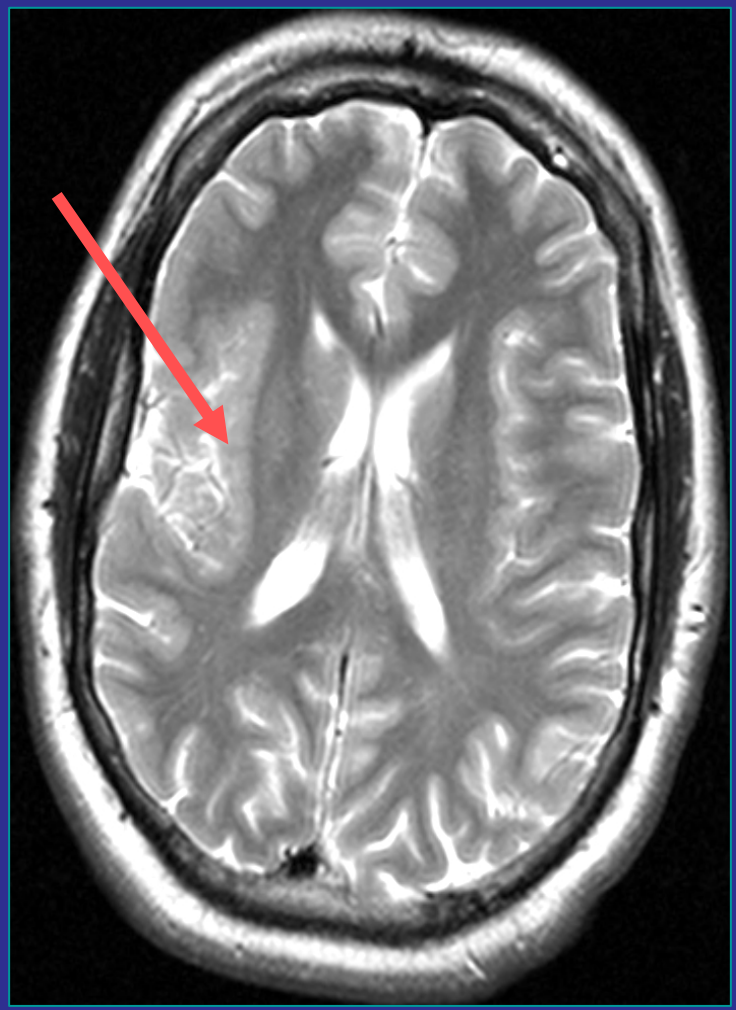
Industry

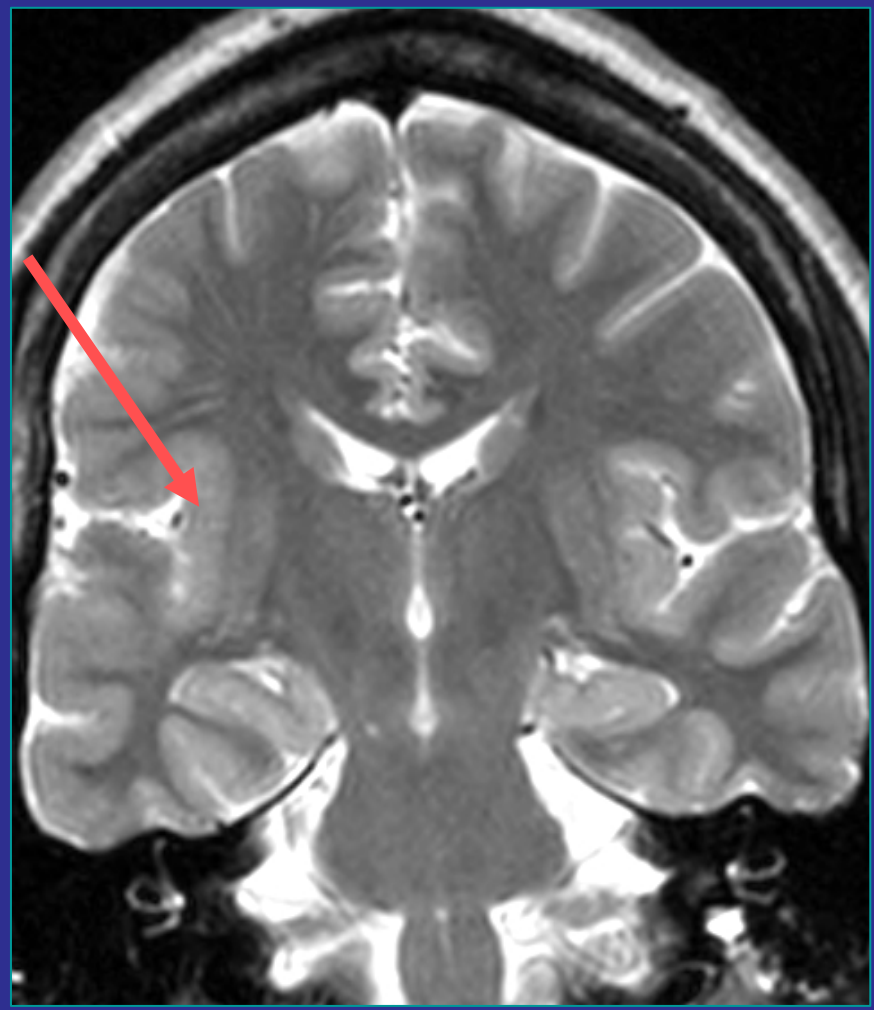
Products

Universities

Start-up Company

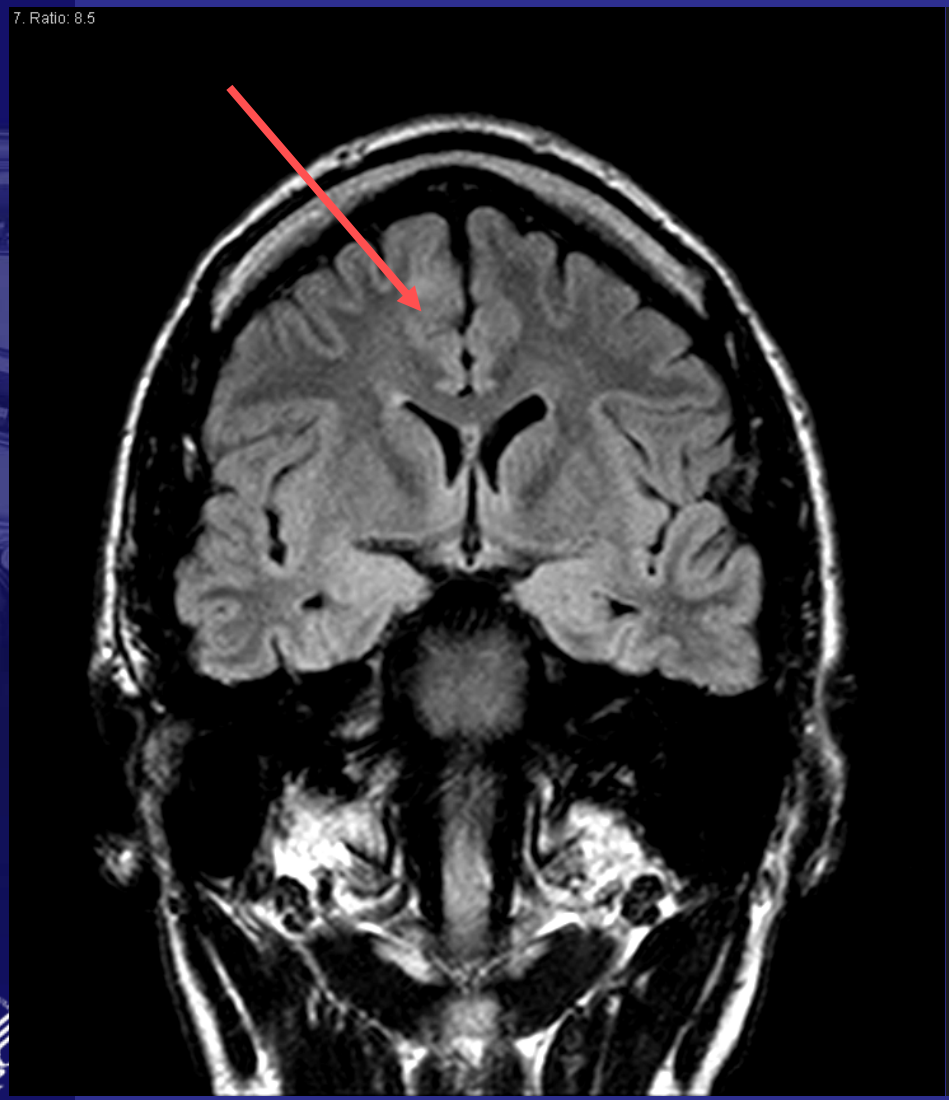
Dysplastic cortex – macrogyria as source of epilepsy





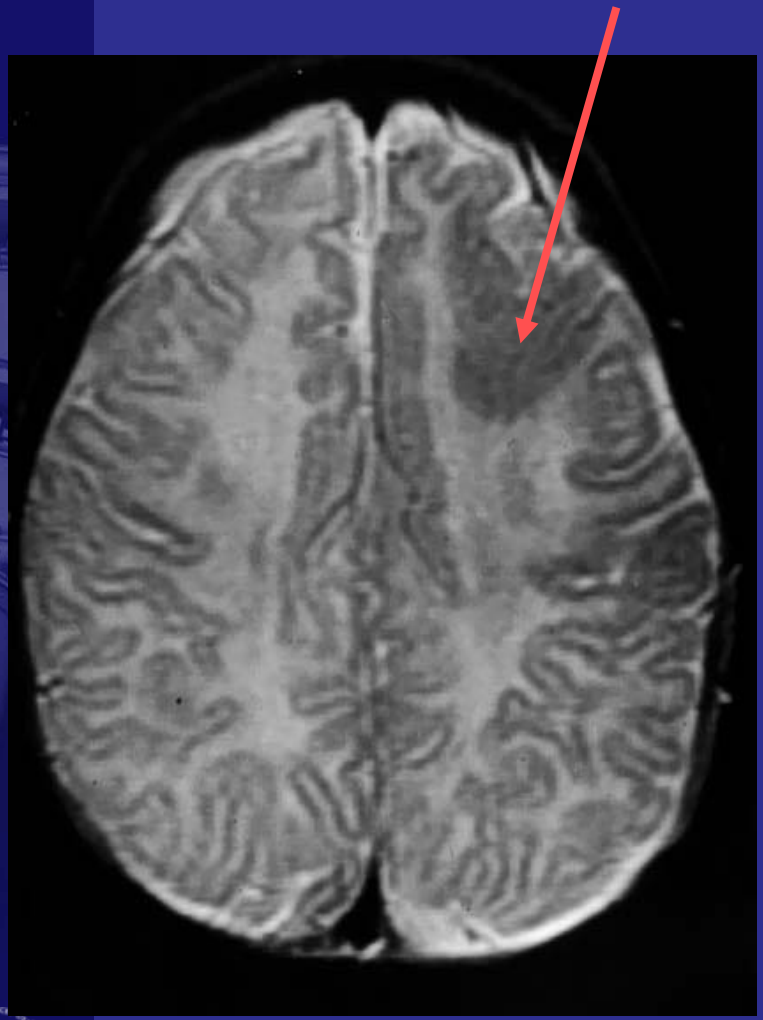
Mass Gen Hosp: Cole/Cash

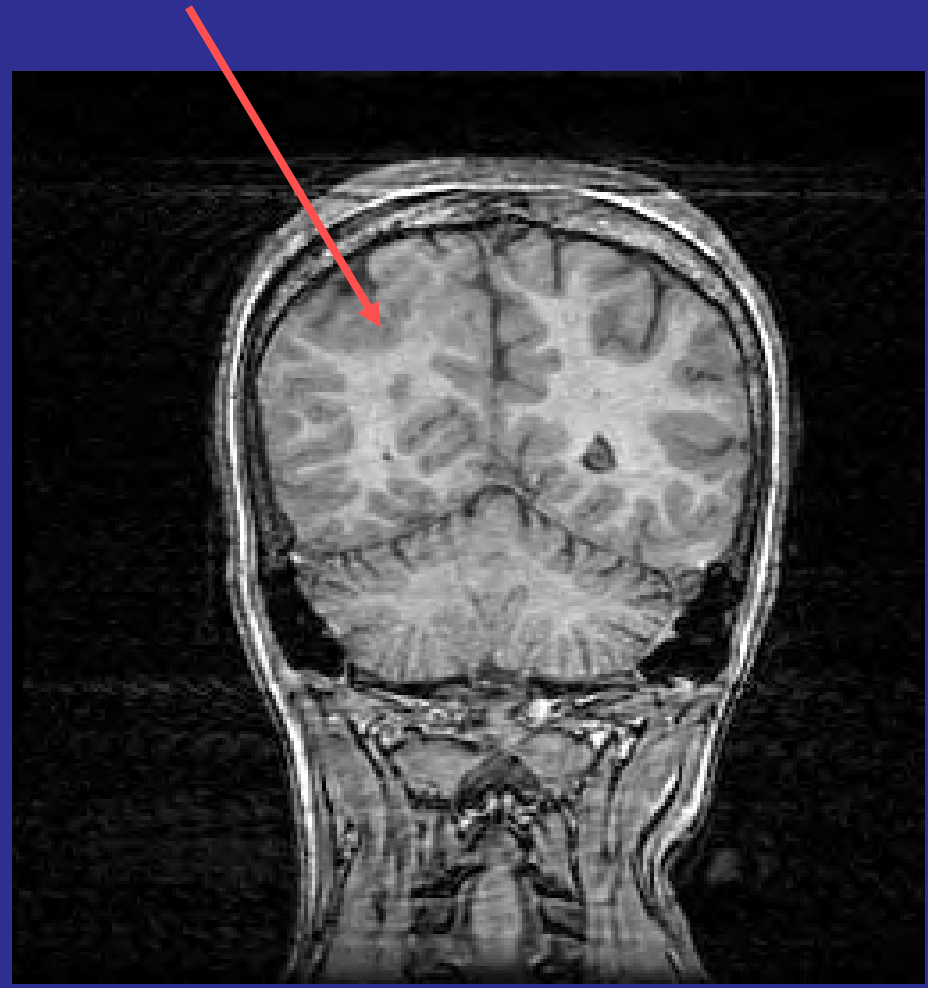
Subtle cortical dysplasia as source of focal epilepsy. Surgically curable?



Mass Gen Hosp: Cole/Cash

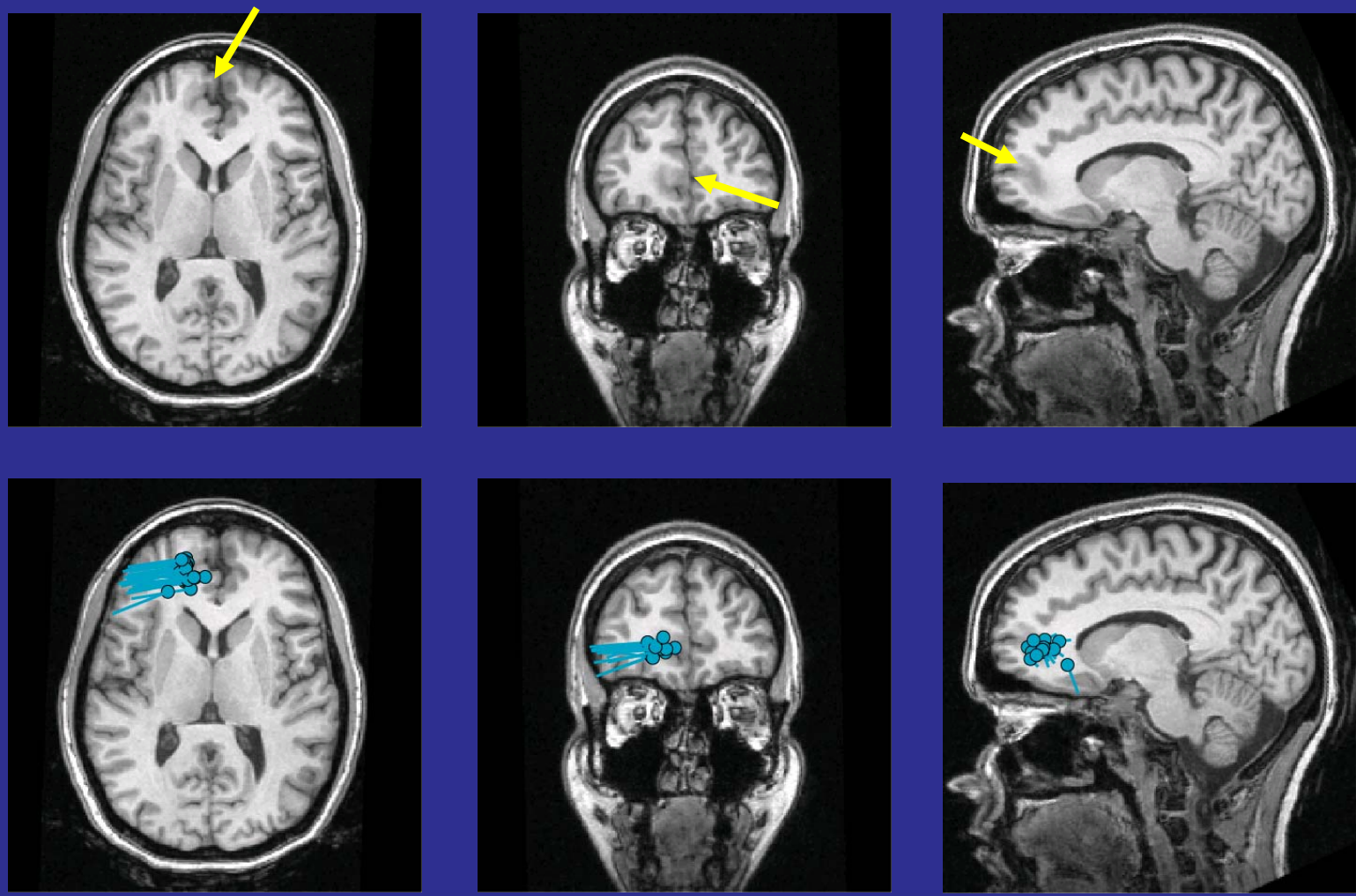
2 different patients with sizable dysplastic lesions seen on MRI





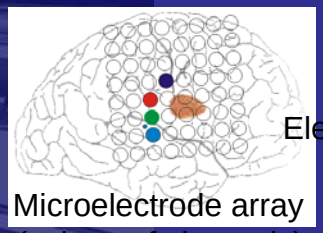
Mass Gen Hosp: Cole/Cash

Magneto Encephalography (MEG) based localization of Equivalent Current Dipoles of Interictal Spikes



Yellow arrows show region of dysplastic cortex.
Blue circles and bars show location and orientation of ECDs.

Seizure activity recorded on an intracortical grid and laminar microelectrode array showing changing pattern of cortical layers involved in the generation of ictal discharges



Microelectrode array
(subset of channels)

Potential gradient +
Multi-unit activity

Grid Electrodes

upper

middle

lower cortex

Interictal Spike

60 uv

Cortical Layer

Upper

Lower

sink

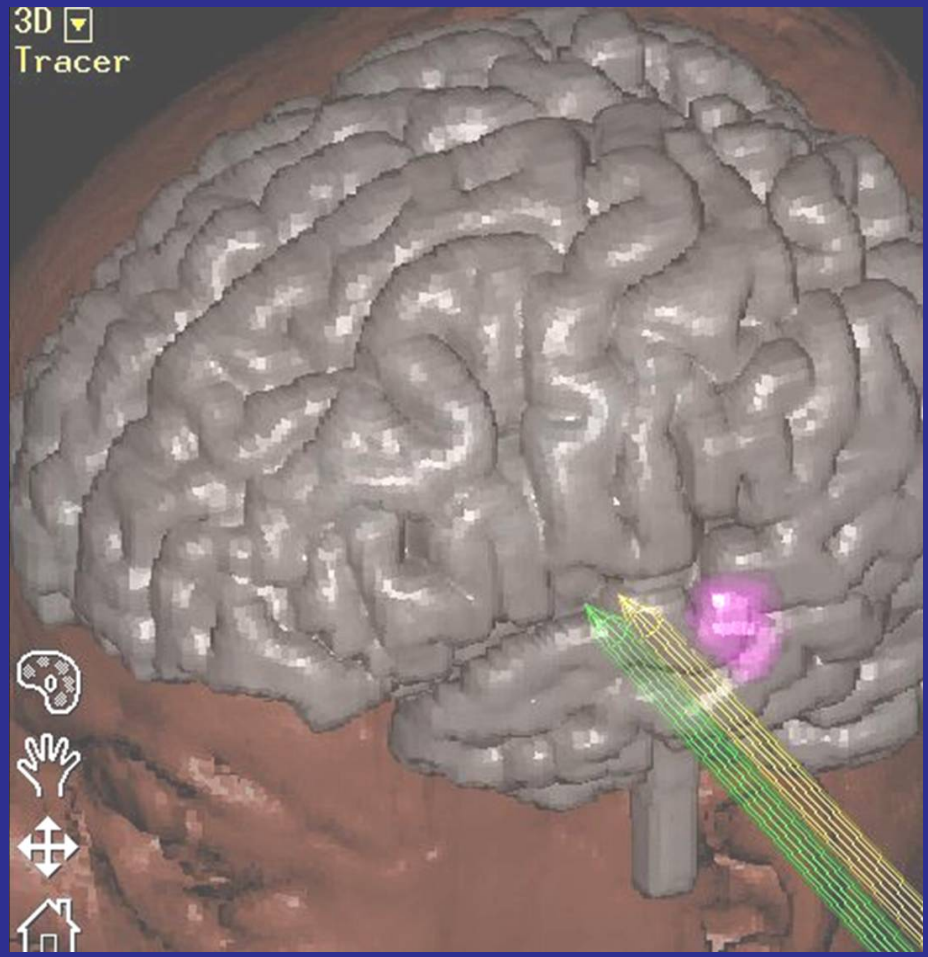
source

-1

0

1

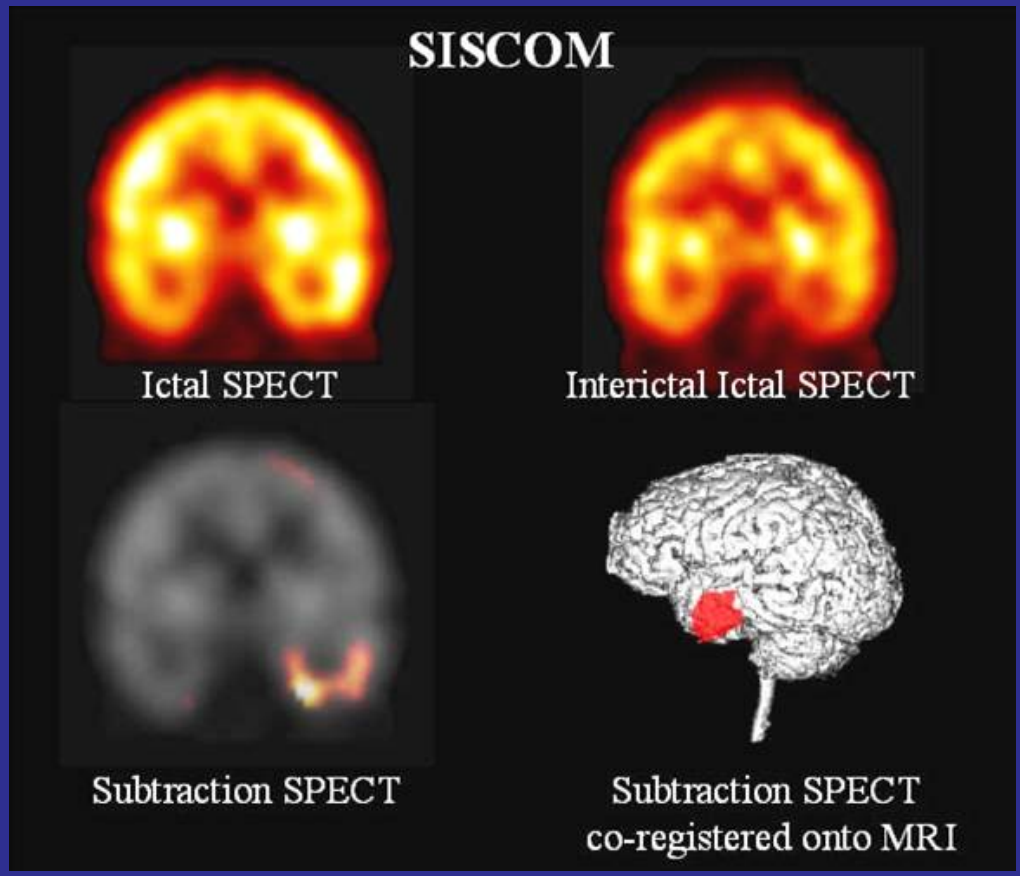
sec



Brain with focus of epileptiform activity from SPECT mapped onto MRI

From Greg Cascino Mayo Clinic Rochester

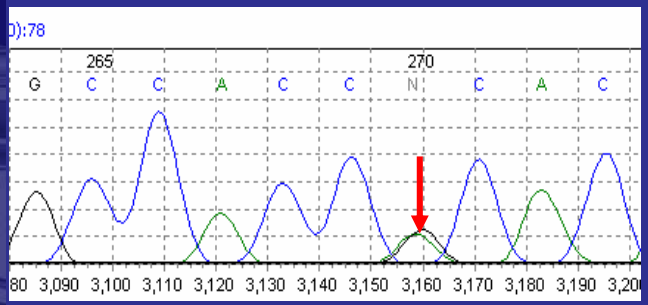
SPECT overlay on MRI scan of a left temporal lobe focus



From Greg Cascino Mayo Clinic Rochester

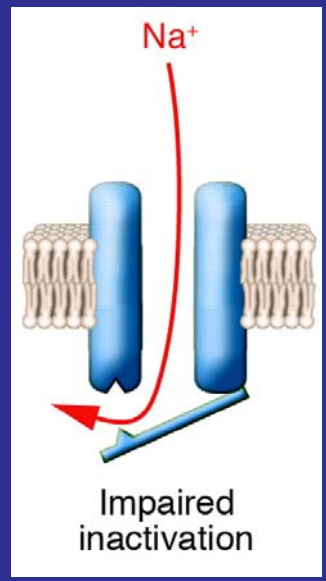
Ion Channel Genes & Epilepsy

Patient



Amino Acid Change

Channel



Gene-specific therapy

Novel AED