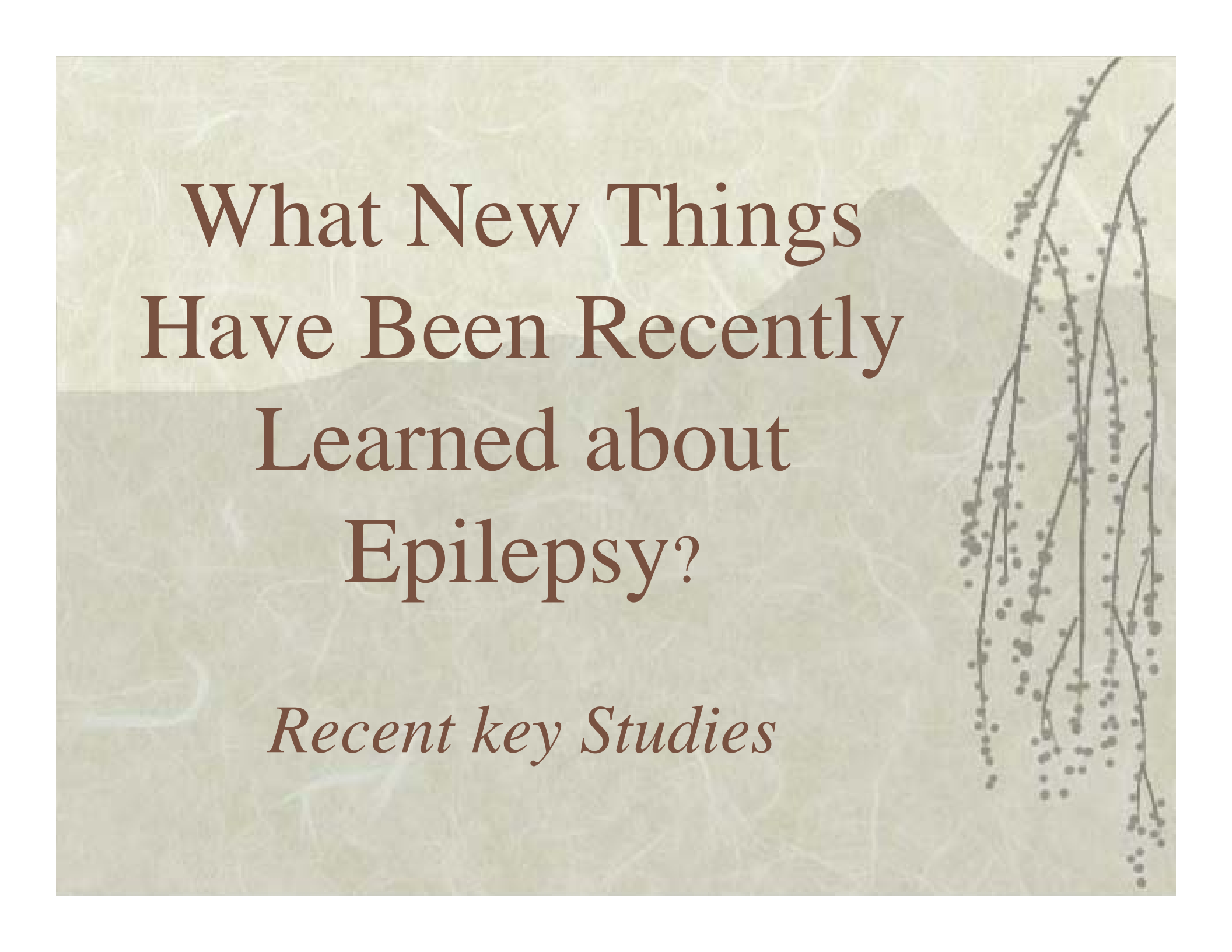


The background of the slide features a soft-focus landscape. In the upper portion, a range of mountains is visible under a pale sky. In the lower right corner, the dark, drooping branches of a willow tree are silhouetted against the lighter background. The overall color palette is muted, consisting of earthy browns, greys, and off-whites.

# **Current Epilepsy Clinical Research**

**John W. Miller, MD, PhD  
UW Regional Epilepsy Center**

The background of the slide features a soft-focus landscape. In the upper portion, a range of mountains is visible under a pale sky. On the right side, a willow tree with its characteristic drooping branches and small, dark buds is partially visible. The overall color palette is muted, consisting of earthy greens, browns, and greys, creating a calm and naturalistic atmosphere.

# What New Things Have Been Recently Learned about Epilepsy?

*Recent key Studies*

# *How Dangerous is Epilepsy?*

- ❖ People with uncontrolled epilepsy are at risk for injuries and accidents
- ❖ Some have serious progressive underlying conditions, such as brain tumors
- ❖ People with uncontrolled epilepsy have a higher risk of sudden death (SUDEP)

## *The risk has been difficult to measure*

- ❖ It is different with different types of epilepsy, and with different degrees of seizure control.
- ❖ Many studies have underestimated risk because of lack of longterm and complete followup.

## *Long-term Followup of Childhood Epilepsy*

- ❖ All children (<16 years, 245) with epilepsy in Southwest Finland identified from 1961-1964.
- ❖ Followed for 40 years. Seizure control measured every 5 years; mortality determined from many sources, including national registry.
- ❖ Overall death rate 0.7%/year, most seizure related.
- ❖ Most common cause (30%) SUDEP.
- ❖ The only significant predictor of mortality was failure to control the seizures.
- ❖ Death rate for those with uncontrolled seizures: 1.6% per year.
- ❖ After successful surgery, mortality rate same as general population.

Sillanpää M, Shinnar S. N Engl J Med 2010; 363:2522-9.

# *Does Epilepsy Damage the Brain?*

- ❖ People with uncontrolled epilepsy, especially temporal lobe epilepsy, often have memory problems.
- ❖ They also sometimes have some signs of brain atrophy on MRI scans.
- ❖ Are these two things connected?
- ❖ Are seizures the cause of this brain atrophy and memory problems?

# *Part of an Answer:*

## *People with Uncontrolled Temporal Lobe Epilepsy Have Progressive Brain Atrophy*

- ❖ Repeated MRIs in people with temporal lobe epilepsy over 2.5 years show progressive, subtle thinning of the cortex (gray matter) in the frontal, temporal and parietal lobes.
- ❖ This progresses more rapidly in those with more frequent seizures.
- ❖ After epilepsy surgery, people who were seizure free had less atrophy than those who were not.

## *What Does This Mean?*

- ❖ The risk of epilepsy to life, and its effects on the brain are small over the short term.
- ❖ The long-term risks and consequences of epilepsy can be significant, and worse in those with uncontrolled, more frequent seizures.
- ❖ Even if seizures cannot be controlled, that efforts to reduce seizures as much as possible are important.
- ❖ New and better treatments are needed.

# *New Therapies: Ezogabine:*

## *The AED Formerly Known as Retigabine*

- ❖ Approved by FDA on June 13, 2011 under name Potiga as add-on treatment for adult focal epilepsy
- ❖ Unique mechanism: Neuronal potassium channel opener, opens KCNQ2 channel, activating M-current
- ❖ Effective in all animal seizure models tested
- ❖ Most common adverse effects in clinical trials: somnolence, dizziness, confusion, headache
- ❖ Effective adult dose 900-1200 mg/day
- ❖ Metabolism: half life, 8 hr

# *New Therapies: Other New Antiepileptic Medications*

- ❖ Ganaxolone: Neuroactive steroid, works on GABA receptor, tested for focal seizures and infantile spasms.
- ❖ Brivaracetam: Related to levetiracetam (Keppra)
- ❖ Perampanel: Selective antagonist for the AMPA glutamate receptor, tested for focal seizures and Parkinson's disease.
- ❖ Clobazam: Benzodiazepine, used in many other countries, licensed in U.S. on October 25, 2011, for the treatment of the Lennox-Gastaut Syndrome.

## *New Therapies: RNS*

- ❖ Responsive neural stimulation: recording electrodes implanted directly over seizure focus.
- ❖ Microchip programmed to detect seizures, and respond to give electrical shocks to interrupt seizures.
- ❖ Electrodes permanently implanted over brain.
- ❖ Submitted to FDA for approval.
- ❖ Most promising for seizures coming from brain areas that cannot be safely taken out.

# *New Therapies: Thalamic Stimulation*

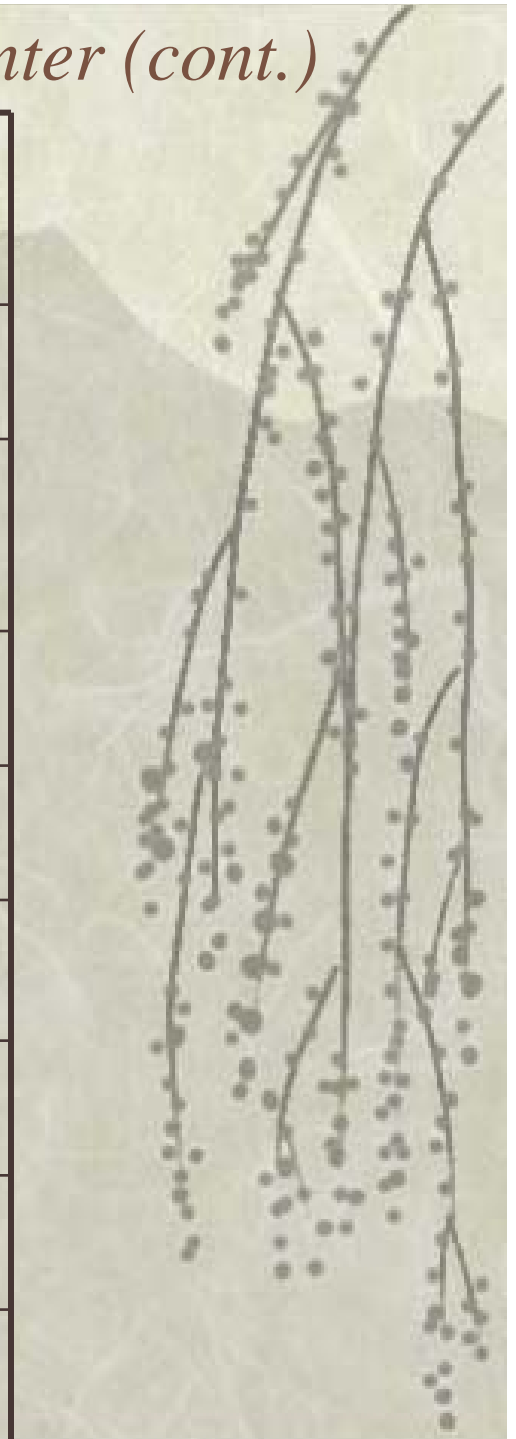
- ❖ Deep brain stimulation: Electrodes implanted in the anterior thalamus to give periodic electrical pulses.
- ❖ Submitted to FDA for review.
- ❖ Improvement in seizure control in clinical trials compared to control group was modest.

## *Some Clinical Studies at UW Regional Epilepsy Center*

ROSE	Radiosurgery or open surgery for epilepsy	NIH
Vanquix	Diazepam autoinjector for acute repetitive seizures	King
Eslicarbazepine	Controlled double blind add on study for refractory partial seizures	Easi
Brivaracetam	Controlled double blind add on study for refractory partial seizures	UCB
Focal Cooling	Focal cooling as prophylactic treatment for epilepsy	CURE/DOD
MONEAD	Maternal outcomes and neurodevelopmental effects of antiepileptic drugs	NIH pending
EPGP	Epilepsy phenome genome project	NIH
	Reorganization of language prior to anterior temporal lobe surgery: Can deficits be mitigated?	NIH
MEW	Epilepsy self-management intervention research	CDC

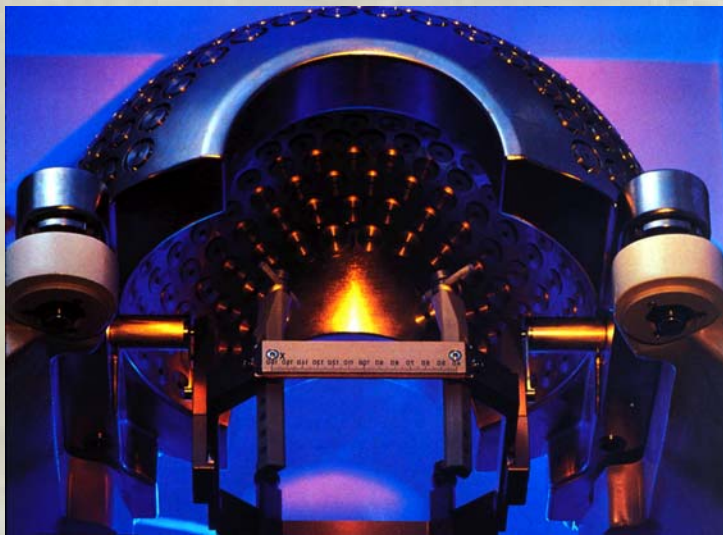
## *Epilepsy Studies at UW Regional Epilepsy Center (cont.)*

Role of hyperpolarization-activated ion channels (HCN channels) in development of epilepsy	NIH
Antiepileptic efficacy study: Retrospective analysis of drug combinations at Fircrest	Royalty
Use of fMRI, language, memory, and IQ tests to identify brain structures and networks causing cognitive problems in epilepsy.	NIH
Use of noninvasive, dense array, 256 channel EEG to localize seizures and brain function	
Signal analysis of the sleep EEG to lateralize and localize seizures.	
Sodium currents in a mouse model of severe myoclonic epilepsy of infancy	NIH
Optimizing the efficiency of long-term video EEG monitoring	
Ecological validity of neuropsychological assessment in an epilepsy surgery sample	
Fluid percussion injury model of post-traumatic epilepsy in the rat	NIH



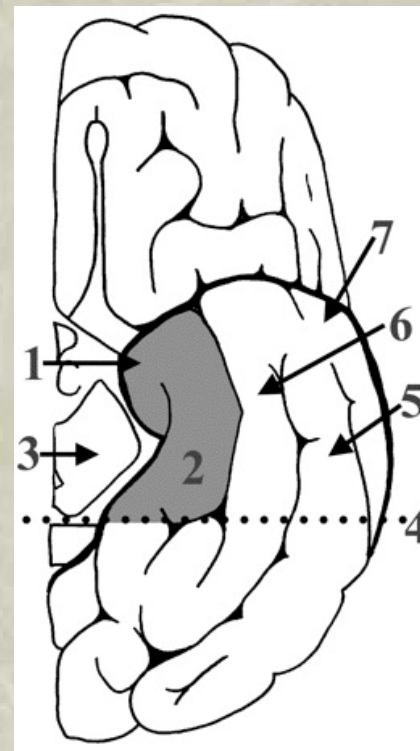
# ROSE

*radiosurgery or Open Surgery for Epilepsy*



**RS**

**VS**



**ATL**

# Background: Radiosurgery for Mesial Temporal Epilepsy

- ❖ Régis et al, *Epilepsia*. 2004; 45(5):504-15
  - 21 patients with mesial temporal epilepsy, treated with 24 Gy radiosurgery
  - At 2 years, 65% seizure free
  - 5 had short term adverse effects of depression, headache, nausea, vomiting, or imbalance
  - No permanent neurological adverse effects except visual field changes
- ❖ 8 year Followup: Bartolomei et al, *Neurology*. 2008; 6;70(19):1658-63
  - 9 of 15 patients (60%) were seizure free
  - Seizures stop after 12 months on average, often preceded by increase aura or seizures (6 patients)

# Background: Radiosurgery for Mesial Temporal Epilepsy

- ❖ Multicenter trial comparing 20 and 24 Gy radiosurgery targeting hippocampus, amygdala and parahippocampal gyrus.
- ❖ 24 Gy patients had higher risk of transient headaches and steroid use.
- ❖ Seizure freedom for prior year at 36 months: 24 Gy 10/13 (77%); 20 Gy 10/17 (59%).
- ❖ In this uncontrolled study, the risk of verbal memory decline with dominant side radiosurgery less than half of what is reported for anterior temporal lobectomy.

## *ROSE: Hypotheses*

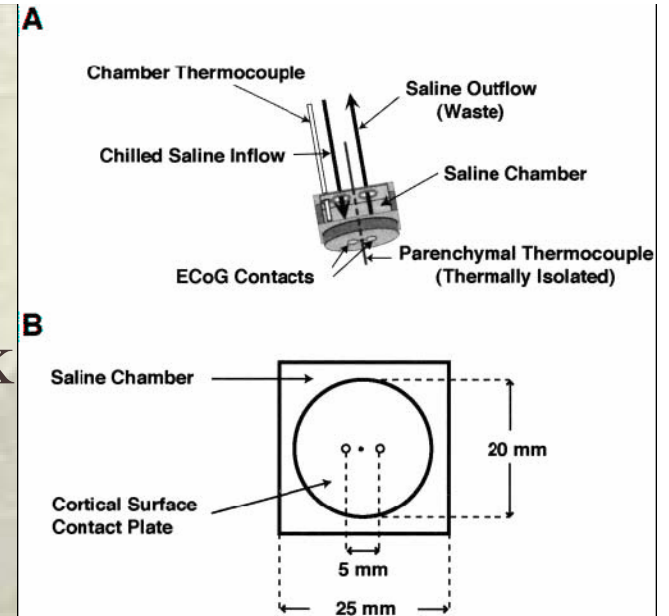
- ❖ Radiosurgery seizure freedom at 25-36 months no worse than temporal lobectomy
- ❖ With speech dominant procedures, risk of verbal memory decline greater with temporal lobectomy than radiosurgery
- ❖ Similar quality of life improvements with both methods
- ❖ Radiosurgery cost effective compared to temporal lobectomy

# *ROSE: Criteria for Enrollment*

- ❖ Refractory epilepsy with mesial temporal sclerosis, with concordant EEG and MRI who would otherwise be offered surgery.
- ❖  $\geq 3$  complex partial seizures in 3 months on stable AEDs.
- ❖ Age  $\geq 18$ ; IQ  $\geq 70$ ; no visual field deficits; no other MRI abnormalities; no severe medical or progressive neurological condition.
- ❖ No severe psychiatric or substance abuse condition or active nonepileptic seizures.

# *Focal Cooling*

- ❖ Preliminary evidence in experimental animals that cortical cooling can block seizures in a model of chronic focal epilepsy
- ❖ Purpose of subproject to determine the degree of intraoperative surface cooling necessary to achieve  $\sim 1.2^{\circ}\text{C}$  cooling 5 to 10 mm into human neocortex.
- ❖ Joint project with Washington University in St. Louis.
- ❖ UW: 4-5 patients where planned resections include the entire region cooled.



# *Managing Epilepsy Well*

- ❖ Purpose is to develop an epilepsy self-management intervention and test it on patients
- ❖ 1. Needs assessment to tailor a self-management program specific to the medical and psychosocial needs of patients with epilepsy.
- ❖ 2. Randomized, controlled trial of effectiveness of epilepsy self-management intervention.
- ❖ 3. Determine variables predicting the effectiveness of this intervention.
- ❖ 4. Disseminate the epilepsy self-management program.

# *NEAD*

## *Neurodevelopmental Effects of AEDs*

- ❖ Identify pregnant women on monotherapy with phenytoin, carbamazepine, valproate, lamotrigine.
- ❖ Assess and follow offspring prospectively.
- ❖ Main findings:
  - Serious adverse fetal outcomes: carbamazepine 8.2%, lamotrigine 1.0%, phenytoin 10.7%, and valproate 20.3%
  - IQ at age 3 compared to children exposed lamotrigine:
    - Valproate 9 points lower (P=0.009)
    - Phenytoin 2 points lower
    - Carbamazepine 3 points lower

# ***MONHEAD proposal:***

## *Maternal Outcomes and Neurodevelopmental Effects of AEDs*

### ❖ Candidate women:

- Pregnant with epilepsy on levetiracetam, lamotrigine, or carbamazepine
- Pregnant with epilepsy on polytherapy, or any monotherapy
- Pregnant with epilepsy on no AED
- Not pregnant with epilepsy on any therapy
- Pregnant without epilepsy on no AEDs

### ❖ Studied in women during pregnancy:

- seizures, AED levels, OB complications, depression

### ❖ Studied in the offspring:

- VIQ and other neurodevelopmental effects
- adverse neonatal outcomes, especially small for gestational age
- % AED transfer via placenta, in breast milk and to nursing child
- additional effects of nursing on IQ of offspring

# *Epilepsy Phenome Genome Project*

- ❖ To create a database of phenotype and genotype data from patients with epilepsy and to investigate the genetics of common and rare forms of epilepsy and pharmacoresistance.
- ❖ Recruitment:
  - Sibling pairs with generalized or focal epilepsy
  - Triads (pt + both parents)
    - infantile spasms or LGS that is cryptogenic or due to FCD
    - epilepsy due to polymicrogyria or bilateral periventricular nodular heterotopia
- ❖ Data:
  - Clinical history, EEG/LTM samples, MRI images and blood
- ❖ Childrens Hospital leads study

The background features a textured, light beige surface. In the center, there are faint, layered mountain ranges. On the right side, a willow tree with long, thin branches and small, dark buds is depicted. The text is centered on the left side of the image.

*Your  
Help is  
Needed*