

Methodological Challenges Developing Treatment for Cognitive Impairments Associated with Epilepsy

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*Items with asterisk involve income > \$10,000 for the last year.

All industry related income goes to the university.

Similarities in LTP & Kindling

- Best induced by High Frequency Stimulation
- NMDA
- Receptor-induced calcium cascade
- Induced genetic mechanisms
- Protein synthesis
- Synaptic facilitation (more specific for LTP)
- Both most easily induced in the hippocampus which is critical to memory & has the lowest seizure threshold
- Seizure reduce ability to induce LTP

LTP = long term potentiation

Meador. Epilepsia 2007;48(Suppl 9):23-5.

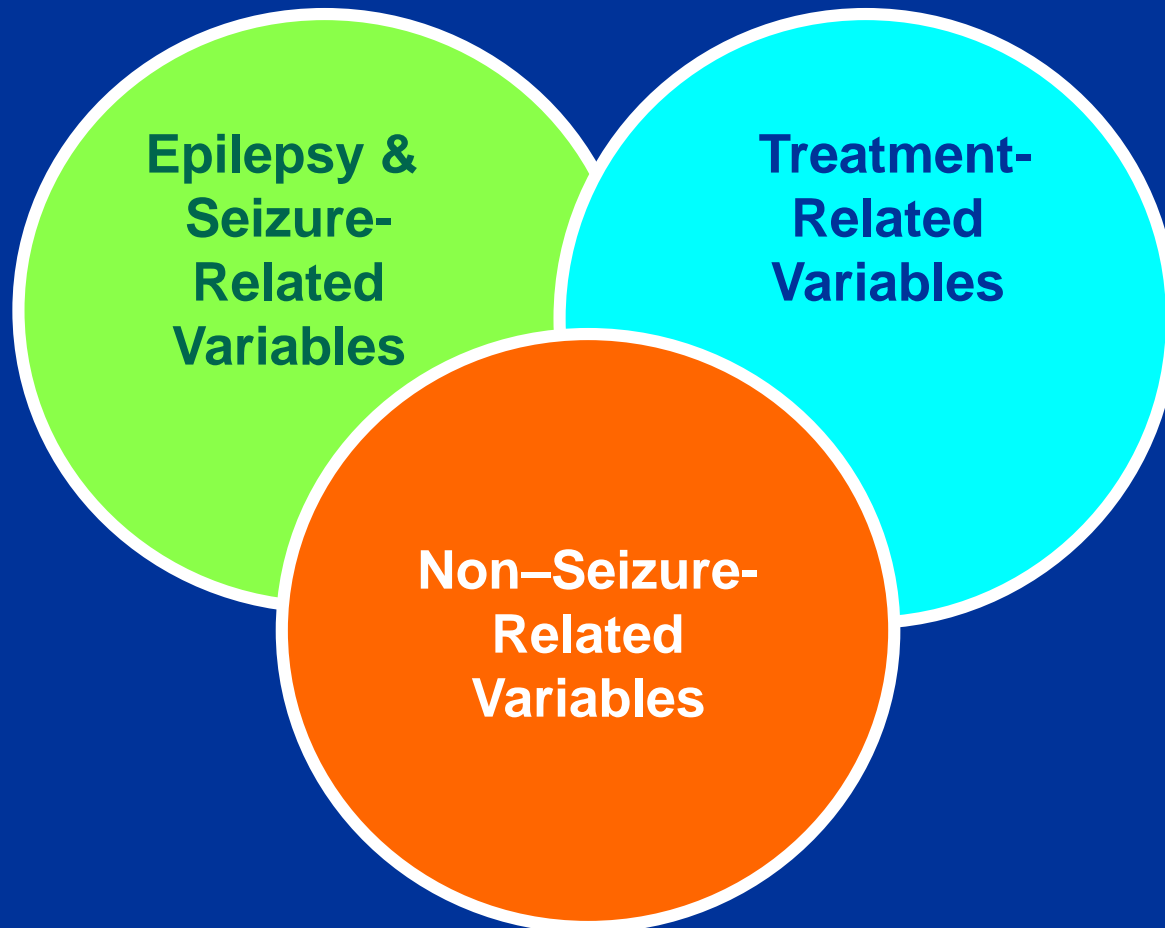
International Bureau for Epilepsy: 2004 Cognitive Function Survey

- 44% Difficulty learning
- 45% Felt that they were slow thinkers
- 59% Felt sleepy or tired
- 63% AED effects prevented them from achieving activities or goals

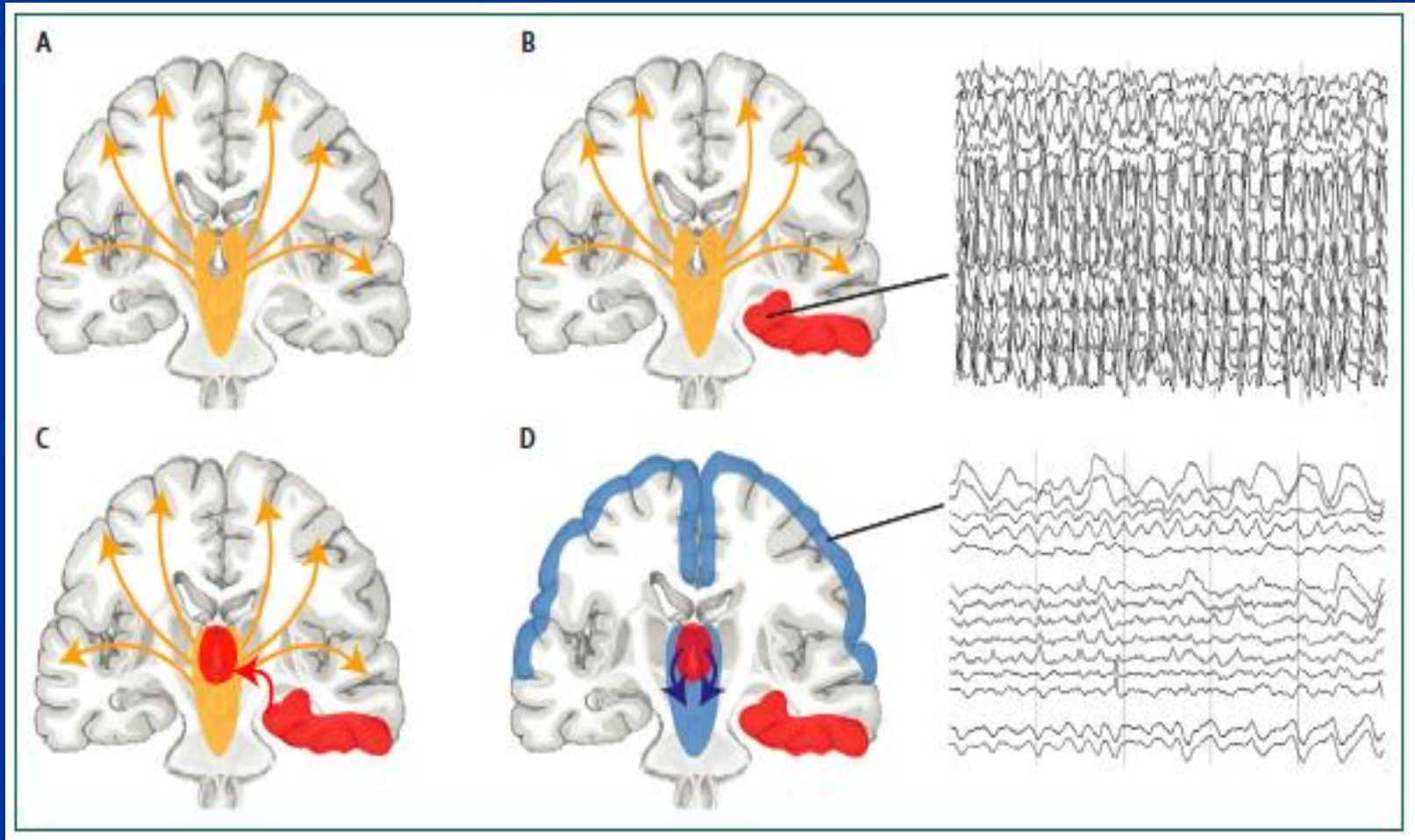
N = 425 Europeans with epilepsy

www.ibe-epilepsy.org/whatsnew_det.asp

Factors Affecting Cognition and Behavior in Epilepsy

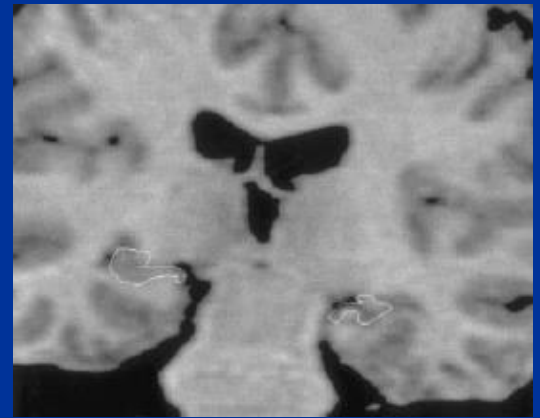


Temporal Lobe Seizures: Consciousness



Recent Review: Blumenfeld H. *Lancet Neurol.*
2012;11(9):814-26.

Longitudinal Study of Hippocampal Atrophy



- 12 unilateral TLE patients
- Repeat MRI: mean 3.4 yrs (2.5-5.2yrs)
- **Progressive hippocampal atrophy occurred only in patients with continuing seizures**
- Mean 10% loss of hippocampal volume in patients with continued seizures

TLE = temporal lobe epilepsy

Fuerst D et al. *Ann Neurol.* 2003;53:413-416

Cognitive Abilities Most Likely to be Affected by AEDs

- **Processing Speed** (e.g., reaction time)
- **Complex or Sustained Attention**
- **Dual Processing**
- **Verbal learning**
 - Paragraphs more sensitive than word lists for AEDs
- **Verbal fluency**
 - Rate at which words beginning with a specific letter can be generated

AEDs = antiepileptic drugs

Cognitive Effects of AEDs

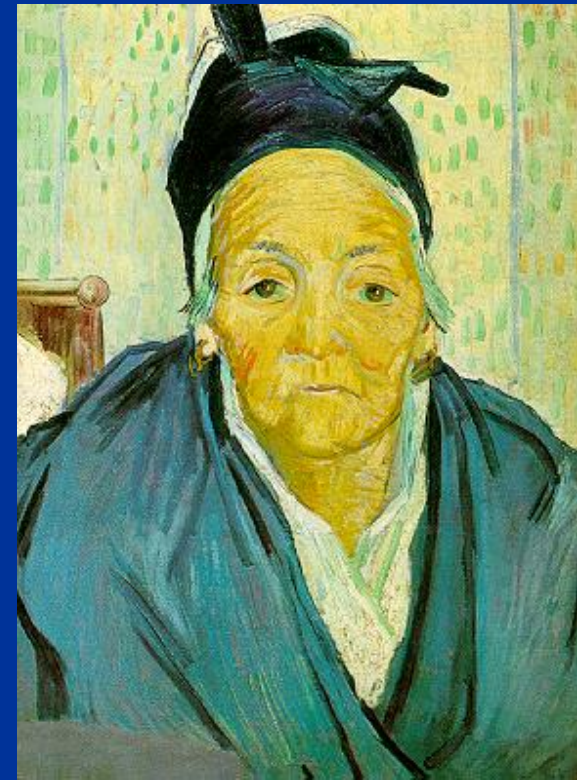
LEAST	Intermediate	MOST
Gabapentin	Carbamazepine	Barbituates
Lacosamide	Oxcarbazepine	Benzodiazepines
Lamotrigine	Phenytoin	Topiramate
Levetiracetam	Valproate	Zonisamide
Tiagabine		
Vigabatrin		

Data inadequate for other AEDs.

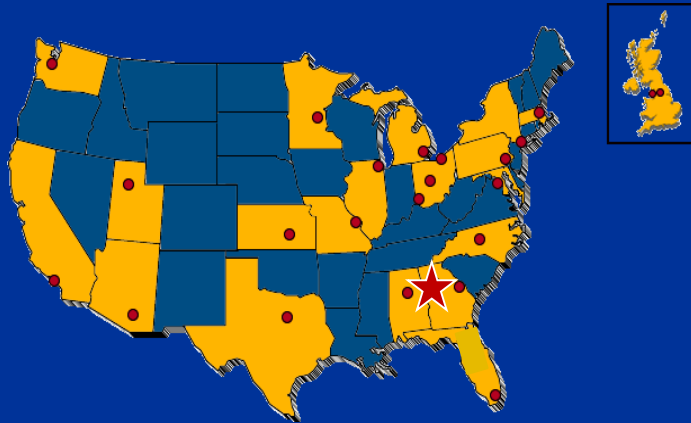
AED susceptibility can vary across patient groups & individual patients. Effects affected by titration, dose, & other factors.

Cognitive Effects of AEDs at Age Extremes

Very young & elderly more sensitive to cognitive effects of AEDs



Neurodevelopmental Effects of Antiepileptic Drugs



309 mother/child pairs from
25 centers in US & UK



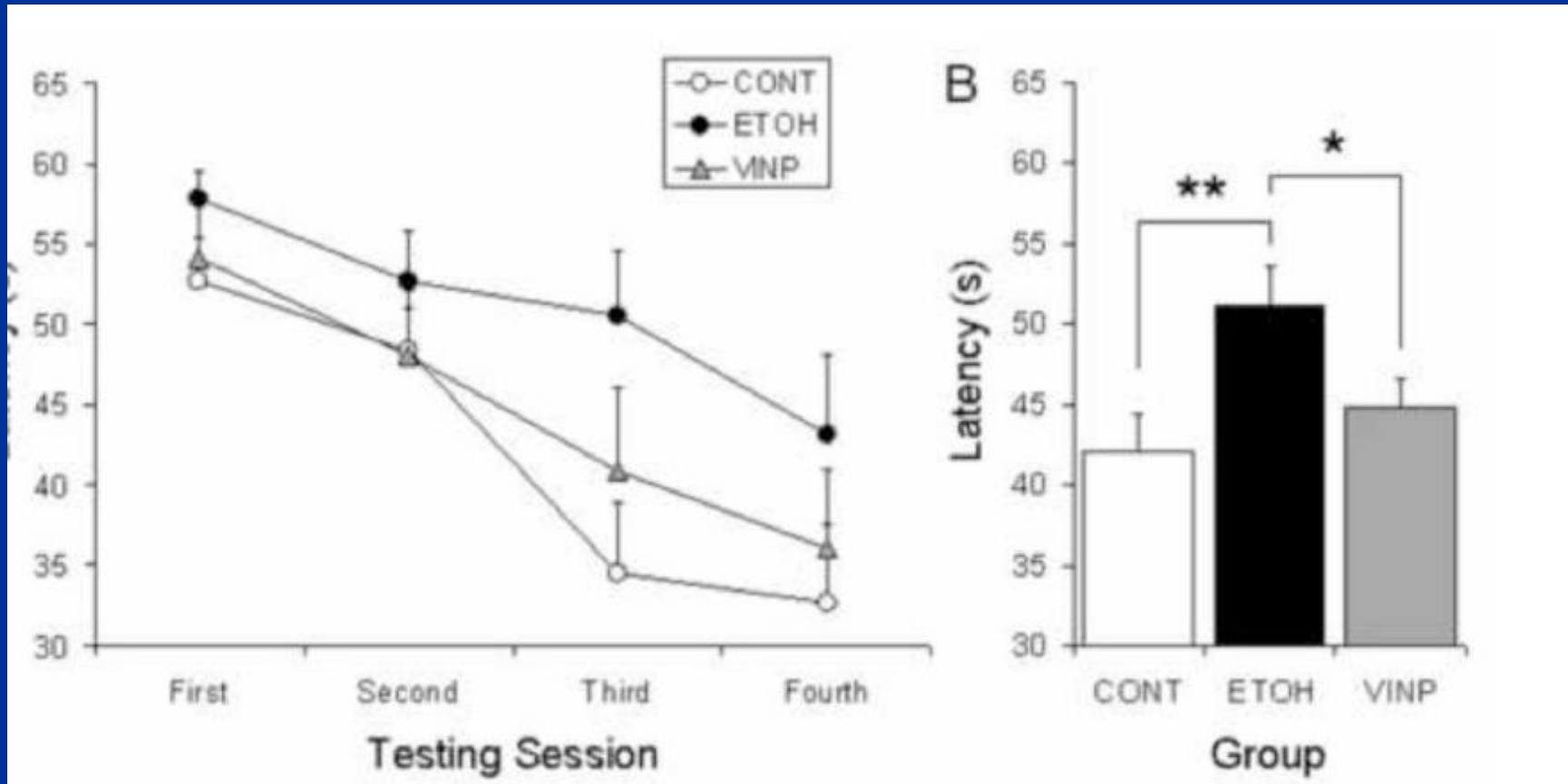
Meador et al. NEJM 2009;360:1597-605

Funded by NIH/NINDS #2RO1 NS 38455 and #1 R01050659

Fetal valproate exposure related with lower IQ.

	<u>Carbamazepine</u>	<u>Lamotrigine</u>	<u>Phenytoin</u>	<u>Valproate</u>
Mean IQ	98	101	99	92
Difference	6	9	7	
(CIs)	(0.6:12.0)	(3.1:14.6)	(0.2:14.0)	

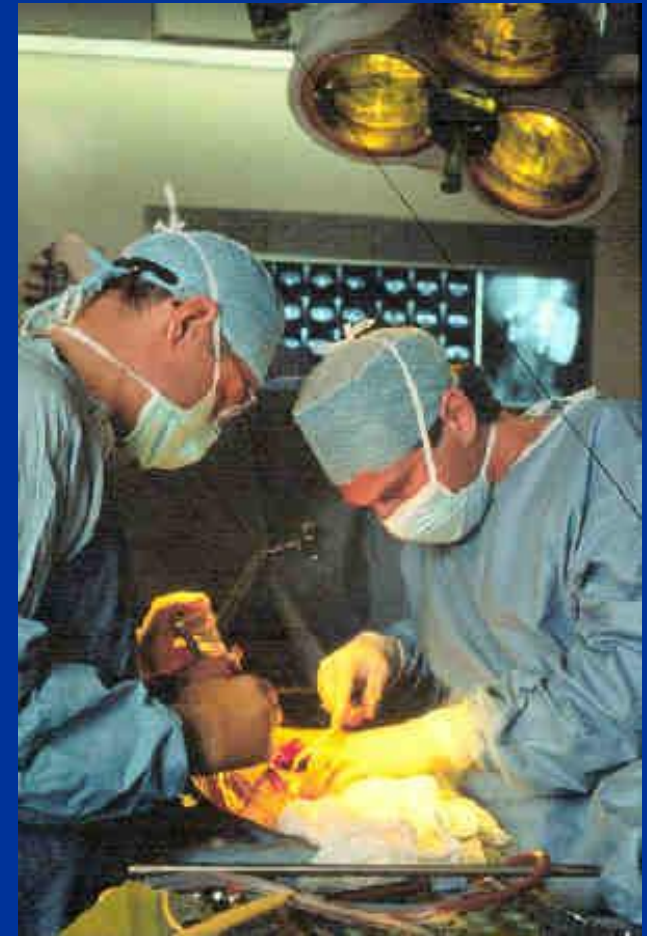
Vinpocentine Reduces Effects of Neonatal-Alcohol Exposure in Rats



Phosphodiesterase type 1 inhibitor reverses alcohol-induced memory deficits.

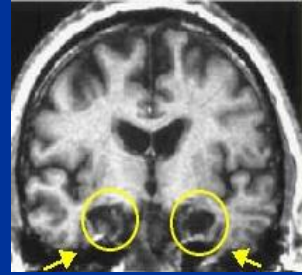
Filgueiras CC, Krahe TE, Medina AE. *Neurosci Lett.* 2010;473(3):202-7.

Epilepsy Surgery



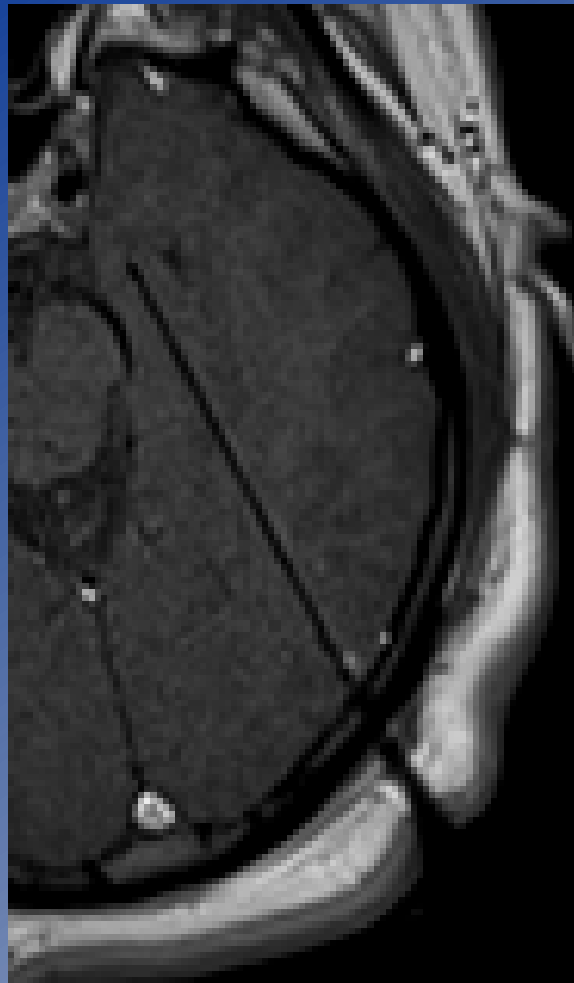


Neuropsychological Effects of Anterior Temporal Lobectomy

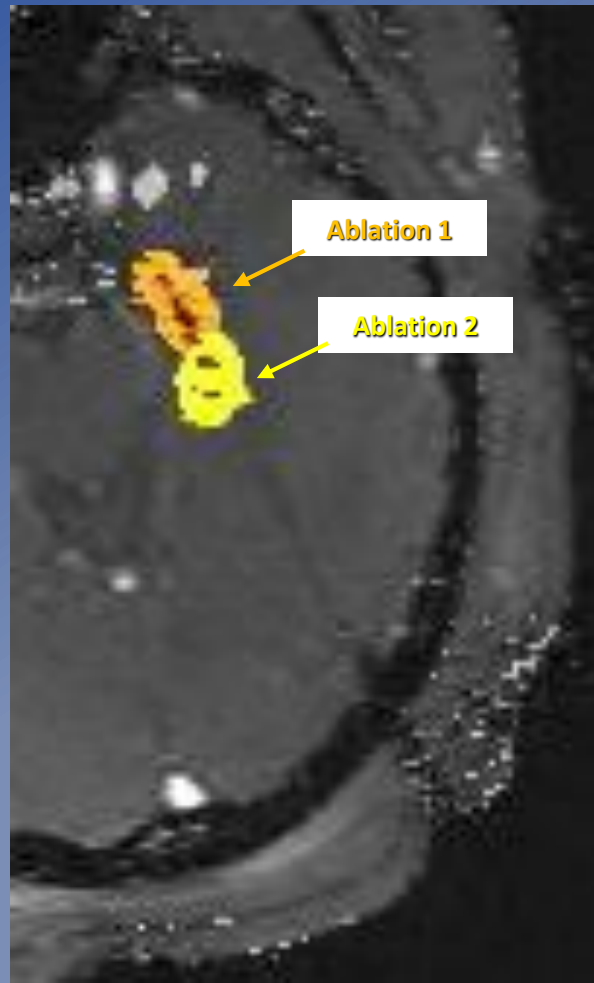


- **LEFT**
 - Naming Deficits
 - Worsening of Verbal Episodic Memory
- **RIGHT**
 - Non-Verbal Episodic Memory Deficits
(less consistent & less clinically significance)
- **Postop deficits are predicatable to large extend**

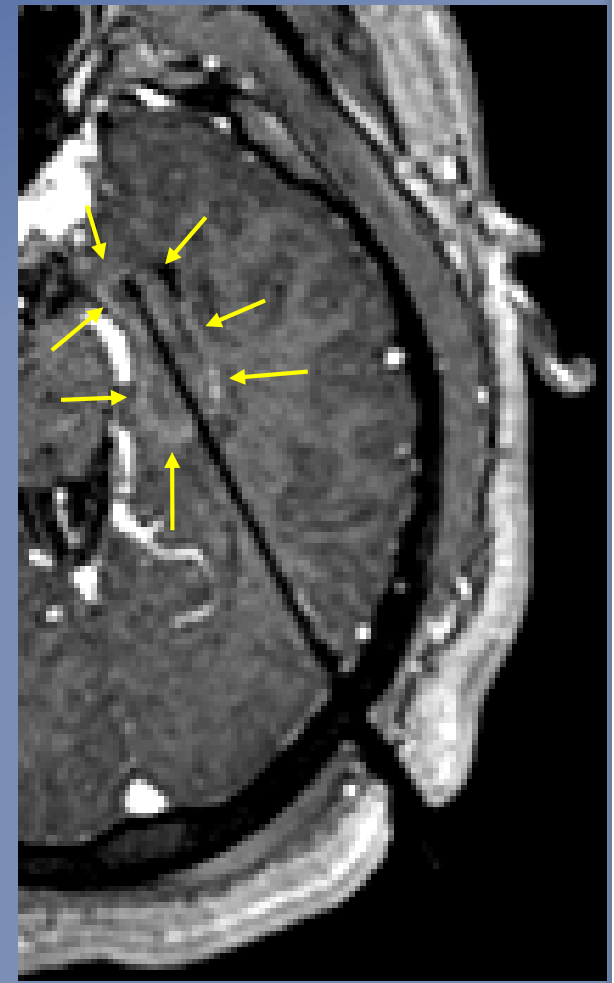
Stereotactic Epilepsy Surgery: Reduced Cognitive Deficits



Pre-ablation T1

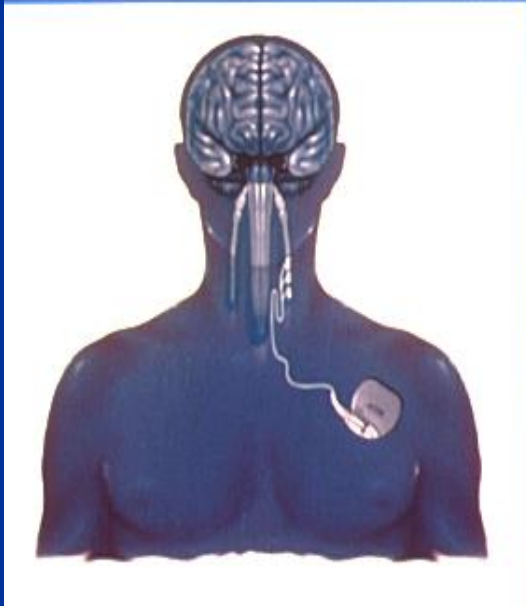


Combined Irreversible Damage Estimate

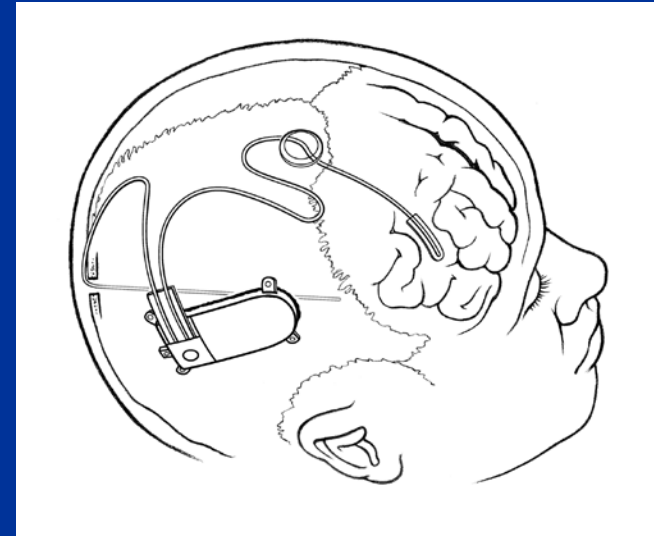


Post-ablation T1 with Contrast

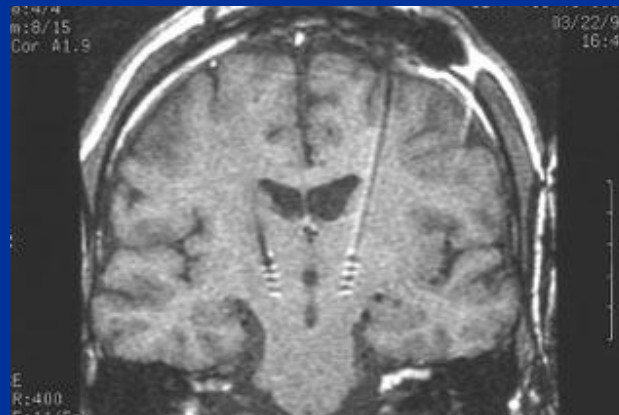
Brain Stimulation for Epilepsy: No Significant Cognitive Effects



VNS



RNS



SANTE

Challenges to Study Design

Methodological

- **Double-blind, Placebo-controlled Randomized Trial**
 - Subject selection bias
- **Choice of Epilepsy Group**
- **Cognitive Measures: choice & administration**
 - Appropriate measures administered by properly trained personnel
 - ? Role of computers
- **Dosing regimen**
 - Therapeutic window
 - Biomarkers (eg, blood levels)
 - Length of exposure
- **Confounding factors**
 - seizures, etiology, depression

- **Generalization**

To what extent will results with this sample generalize to others?

Statistical

- **Power analysis to determine sample size**
- **Choic of appropriate stat analysis**
- **Balance of Type I & II errors**
- **Stat control of confounding factors**
- **Statistical vs. Clinical Significance**

Perception of Cognitive Performance

% significant correlations

	All studies combined	Healthy volunteers	Patients with epilepsy	Patients with Parkinson's
Perception of Cognition vs. Mood	59% (36/61)	48% (20/42)	81% (13/16)	100% (3/3)
Perception of Cognition vs. Performance	2% (4/171)	1% (2/138)	8% (1/12)	5% (1/21)
Mood vs. Cognitive Performance	2% (9/425)	2% (8/322)	1% (1/96)	0% (0/7)

Neuropsychological Tests

Domain: test examples

- **Sustained Attention:** CPT
- **Processing Speed:** WISC Processing Speed (Coding & Symbol Search)
- **Memory:** word lists, paragraphs
- **Verbal Fluency:** animal or letter fluency
- **Motor:** Grooved Pegboard
- **Behavior:** BSID, BAI, C-SSRS, POMS
- **Fetal-Neonatal Exposure:** Above plus IQ, full language, cerebral lateralization, executive & school performance
- **Role of Computerized Tests ?**

Potential Approaches to Treatment of Cognitive Deficits in Epilepsy

- Pharmacological agents
- Genetic manipulations
- Stem cells
- Electrical stimulation

- Preliminary trials conducted with anticholinesterases, memantine, & stimulants.
- Vinpocetine: a phosphodiesterase type 1 inhibitor which enhances LTP and has anticonvulsant activity.
- Restoring Glutamate/GABA balance