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

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

- Epilepsy & Seizure-Related Variables
- Treatment-Related Variables
- Non-Seizure-Related Variables
Temporal Lobe Seizures: Consciousness

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

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

<table>
<thead>
<tr>
<th>LEAST</th>
<th>Intermediate</th>
<th>MOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Carbamazepine</td>
<td>Barbituates</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Oxcarbazepine</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Phenytoin</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Valproate</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Tiagabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

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

Fetal valproate exposure related with lower IQ.

<table>
<thead>
<tr>
<th></th>
<th>Carbamazepine</th>
<th>Lamotrigine</th>
<th>Phenytoin</th>
<th>Valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IQ</td>
<td>98</td>
<td>101</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>Difference</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>(CIs)</td>
<td>(0.6:12.0)</td>
<td>(3.1:14.6)</td>
<td>(0.2:14.0)</td>
<td></td>
</tr>
</tbody>
</table>
Vinpocentine Reduces Effects of Neonatal-Alcohol Exposure in Rats

Phosphodiesterase type 1 inhibitor reverses alcohol-induced memory deficits.

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 predictable to large extent
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
• Choice of appropriate stat analysis
• Balance of Type I & II errors
• Stat control of confounding factors
• Statistical vs. Clinical Significance
<table>
<thead>
<tr>
<th>Perception of Cognition vs. Performance</th>
<th>All studies combined</th>
<th>Healthy volunteers</th>
<th>Patients with epilepsy</th>
<th>Patients with Parkinson’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perception of Cognition vs. Mood</td>
<td>59% (36/61)</td>
<td>48% (20/42)</td>
<td>81% (13/16)</td>
<td>100% (3/3)</td>
</tr>
<tr>
<td>Perception of Cognition vs. Performance</td>
<td>2% (4/171)</td>
<td>1% (2/138)</td>
<td>8% (1/12)</td>
<td>5% (1/21)</td>
</tr>
<tr>
<td>Mood vs. Cognitive Performance</td>
<td>2% (9/425)</td>
<td>2% (8/322)</td>
<td>1% (1/96)</td>
<td>0% (0/7)</td>
</tr>
</tbody>
</table>

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