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# FDA Perspective: "The Role of Basic Science in the Design of Clinical Trials for CNS Devices"

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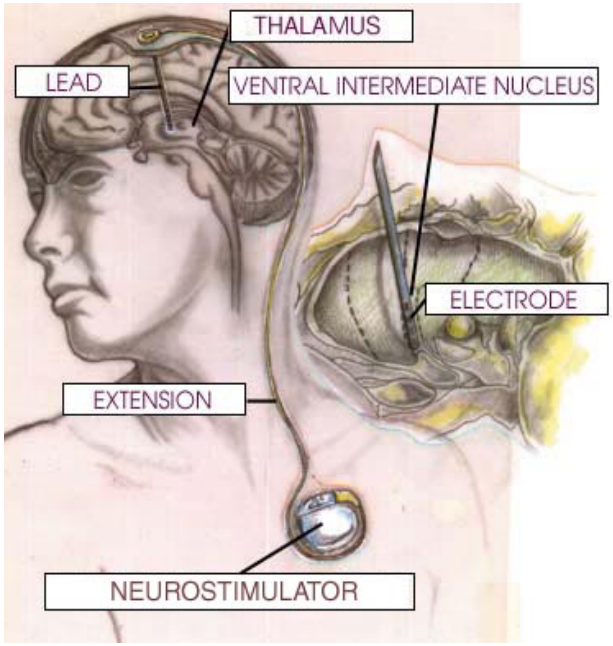
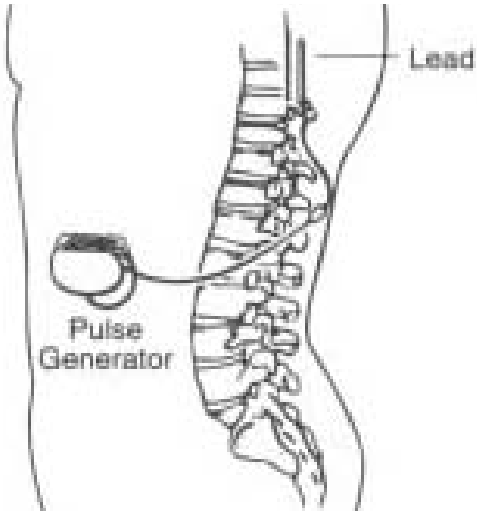
# Some CNS Devices

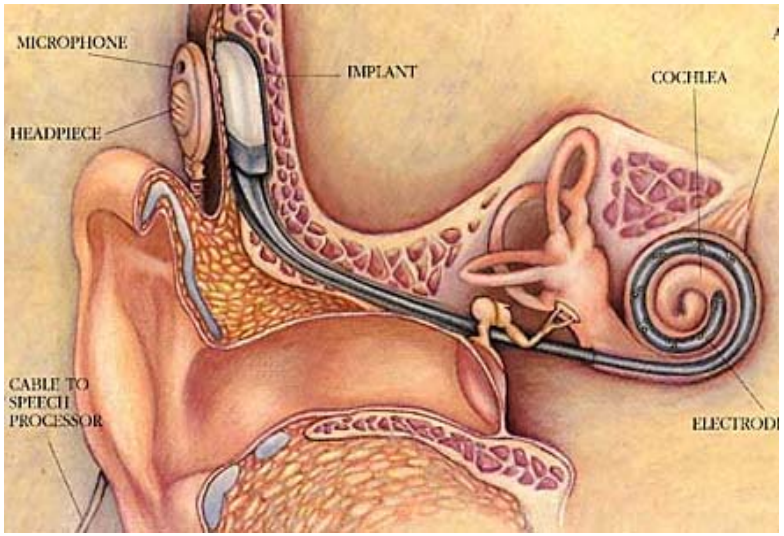
## Deep Brain Stimulator for Tremor




## Spinal Cord Stimulator for Pain




## Cochlear Implant for Hearing



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# Functions of Basic Science and Engineering in CNS Device Trials

- Is a clinical trial necessary? 85 - *90% of clearances for all devices do not need clinical trials*
- What type of clinical trial is necessary? *e.g.*, t*ype of control group*
- Does prior knowledge of mechanism provide confidence?
- What can be said about safety and efficacy before clinical trial?
- What are the clinical endpoints for safety and effectiveness? *Causal-path biomarkers → surrogate endpoints*
- Can trials be focused, and less burdensome?
- What can be predicted beyond the empirical trial? *side effects, interactions with drugs, help interpret results*

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# When Are Clinical Data Needed?

To support:

- PMA, PDP or HDE (almost always)
- 510(k) (10 – 15%*, usually involving new technology that could affect safety of effectiveness or a new population)
- New indication for an *approved* device (e.g., new indications for DBS)
- Significant change to device, especially Class III devices

*for all devices

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# When is a randomized, double-blinded, placebo-control trial most necessary?

- When no prior information exists – e.g., no previous experiments, when causal path is not known
- When prior information cannot be trusted – e.g., underpowered or poorly controlled trials, especially when there is a high likelihood of a placebo effect or regression to the mean

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# When clinical trials may not be justified?

- When Causal Effects are Known
  - to evaluate a scalpel: cuts because it is sharp
  - to evaluate a sterilizer: temperature and pressure
  - mathematical models used to support safety of a cochlear implant in MR imaging in a PMA
- Codified use of prior information: section 510(k)

The better the prior information, the less justified the randomized placebo-control study.

- Ethical Reasons – Declaration of Helsinki limits placebo controls

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*Fundamental science is provides the necessary context outside of a clinical trial.*

# Is the empirical trial enough?

- Willingness to infer causality
- Willingness to accept uncertainty, $\alpha \leq 5\%$
- Trails are never perfect
  - Real practice is different from clinical trial
  - Demographic differences
  - Duration of study
  - Patient drop-out
  - Blinding issues
  - Unknown covariates

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concept from Terrence Blaschke, Stanford U.

**em·pir·i·cism**
Function: *noun*
Date: 1657
**1 a :** a former school of medical practice founded on experience without the aid of science or theory **b :** QUACKERY, CHARLATANRY
**2 a :** the practice of relying on observation and experiment especially in the natural sciences **b :** a tenet arrived at empirically
**3 :** a theory that all knowledge originates in experience

Merriam Webster Dictionary

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# Simpson's Paradox

| **Combined** | Recovered | Did not recover | N | Recovery Rate |
|---|---|---|---|---|
| drug | 20 | 20 | 40 | 50% |
| no-drug | 16 | 24 | 40 | 40% |

| **Males** | Recovered | Did not recover | N | Recovery Rate |
|---|---|---|---|---|
| drug | 18 | 12 | 30 | 60% |
| no-drug | 7 | 3 | 10 | 70% |

| **Females** | Recovered | Did not recover | N | Recovery Rate |
|---|---|---|---|---|
| drug | 2 | 8 | 10 | 20% |
| no-drug | 9 | 21 | 30 | 30% |

from J. Pearl, *Causality*, Cambridge, 2000

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# *Uses of Fundamental Science within the Clinical Trial*

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# Preclinical Science - Electrical Stimulation Safety in CNS

- Heating (Energy - Joules)
- Electrochemical Toxicity (Charge Density, Charge Balance)
- Dielectric Breakdown (tissue E-Field)
- Changes to ion channels (E- field)
- Excitotoxicity (Pulse Repetition Rate, Activation Function ~ Tissue E-field)
- Physiological Interference (E-field, Repetition Rate)

# Safety Endpoints

- Standard Ones
  - Neurotoxicity
  - Histopathology (typically staining of cell bodies, glia and myelin)
- Nonstandard
  - changes to dendrites and axon terminals
  - alteration or loss of normal function

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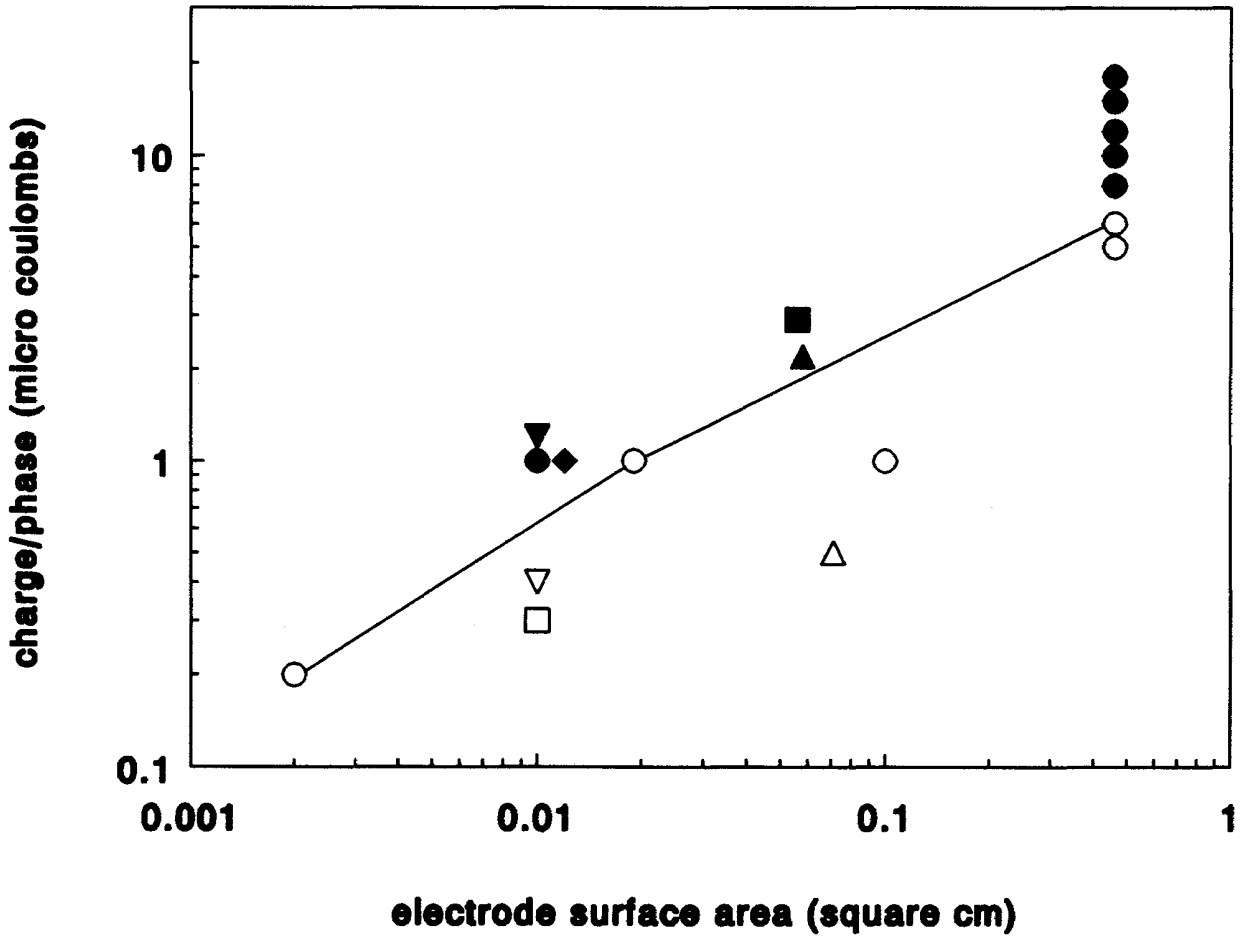
# Histology and Brain Stimulation, Nissl Stain




data from on McCreery et al., 1991

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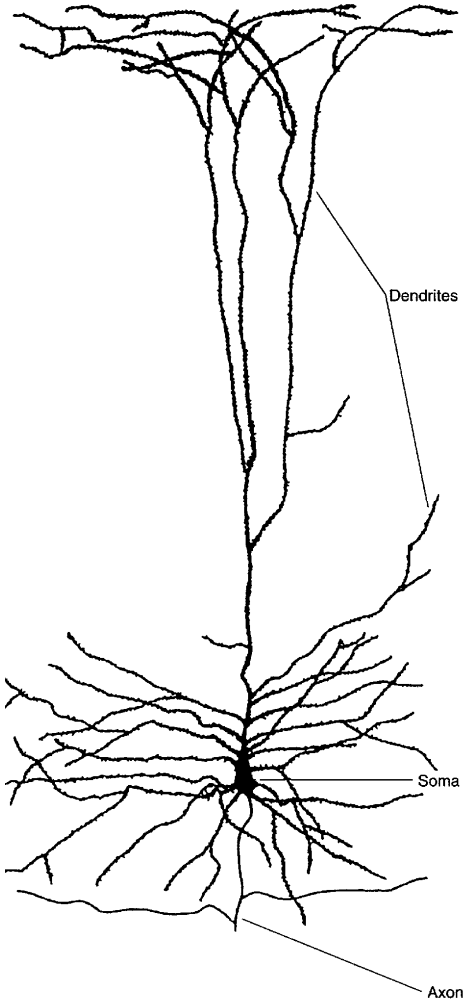
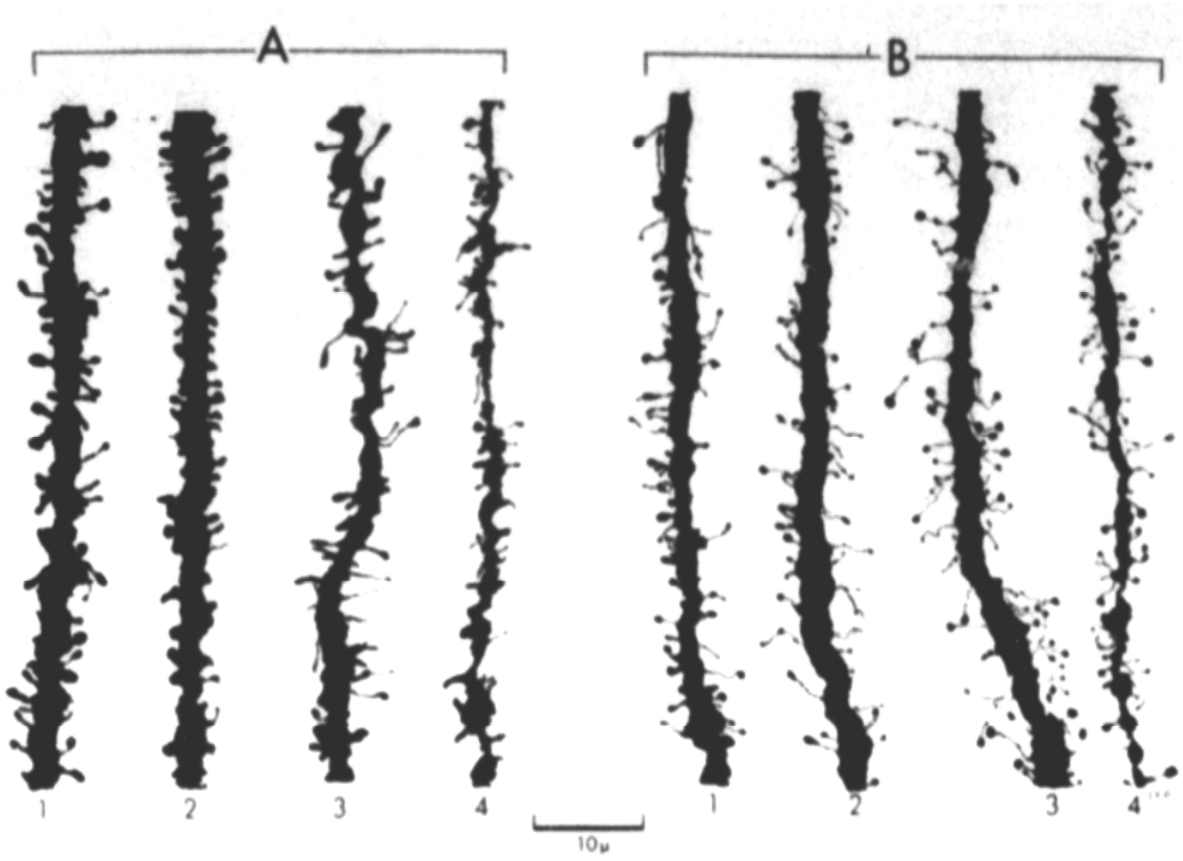
# Limits of Standard Histology




from D. Purpura, 1973

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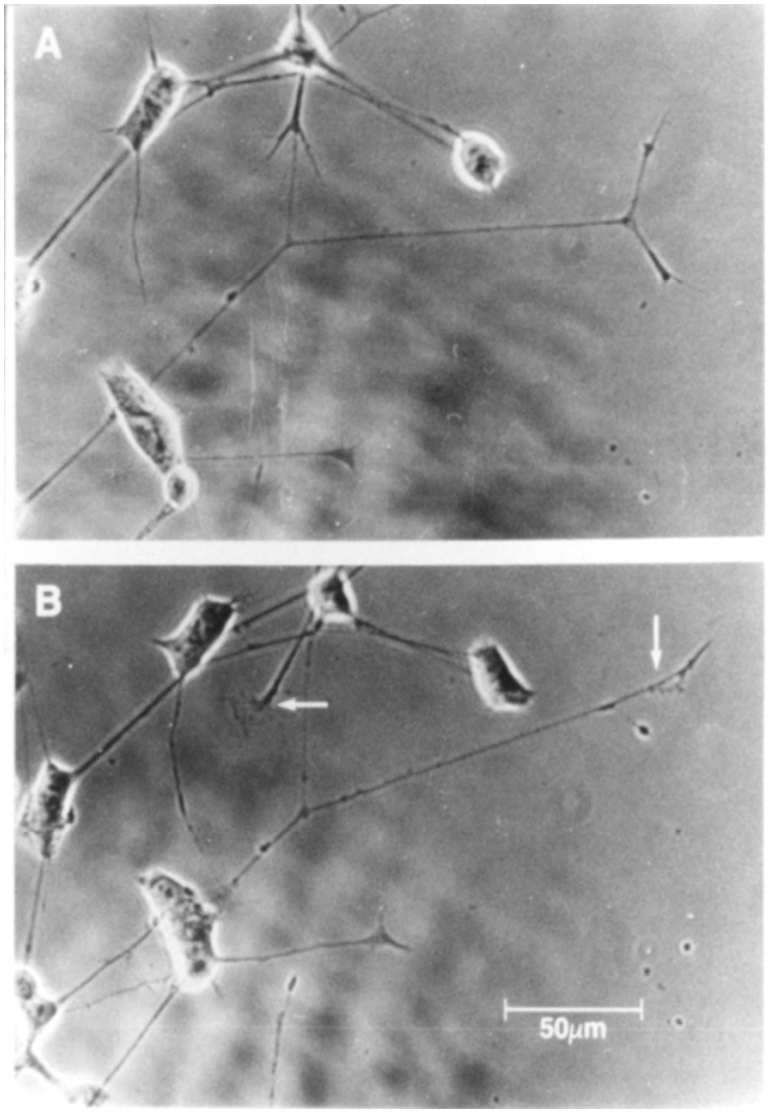
# In vitro study of stimulation: Human Neuroblastoma Cells Stimulated for 1 Hour



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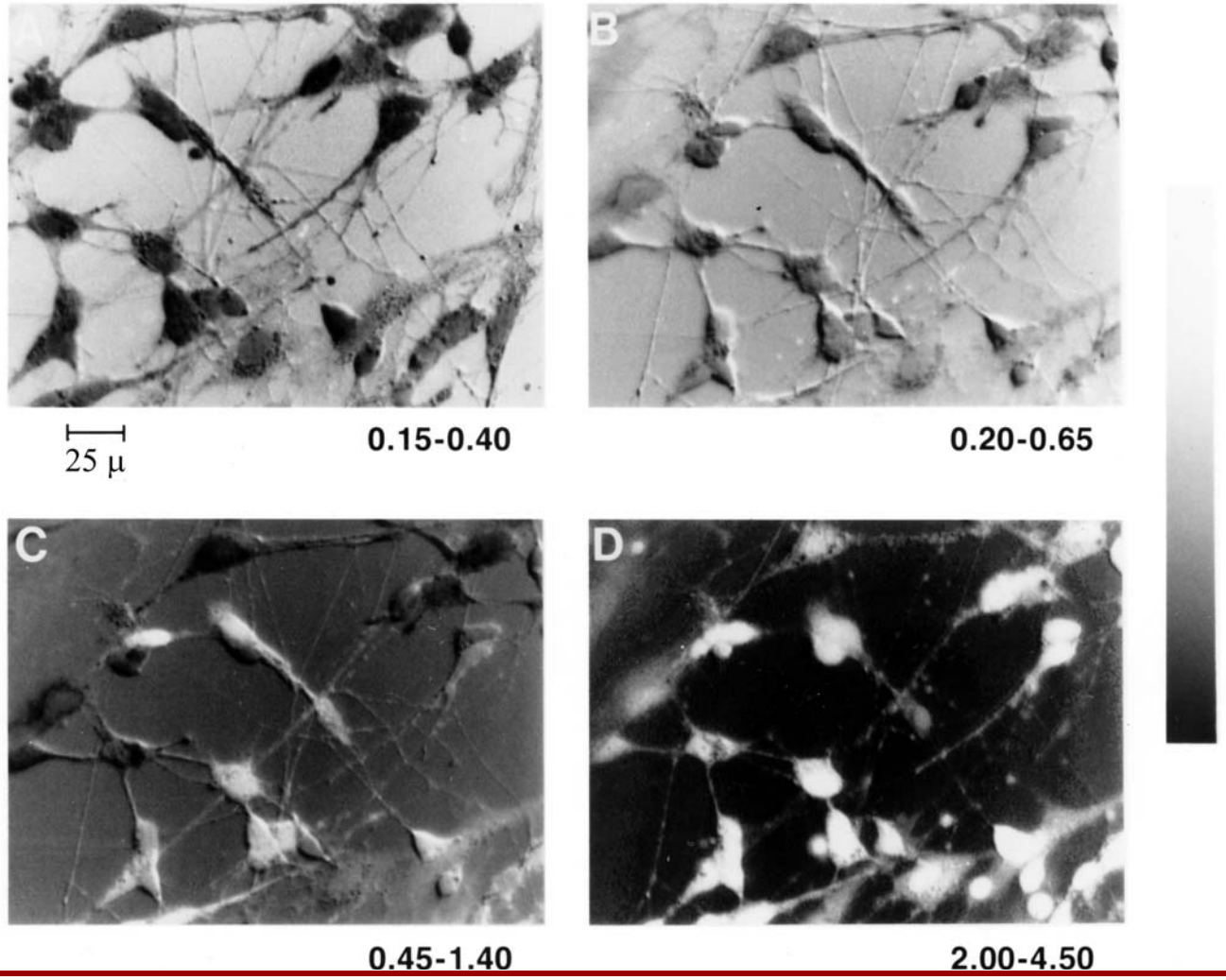
# $Ca^{2+}$ Elevation - Metabolic Overload, 3hrs



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# Clinical Safety in Cochlear Implants

- Absence of pain
- Long-term changes
  - Electrical threshold
  - Comfort levels
  - Dynamic range (maximum comfort level minus threshold)
- Electrode impedance changes
- Neural Function

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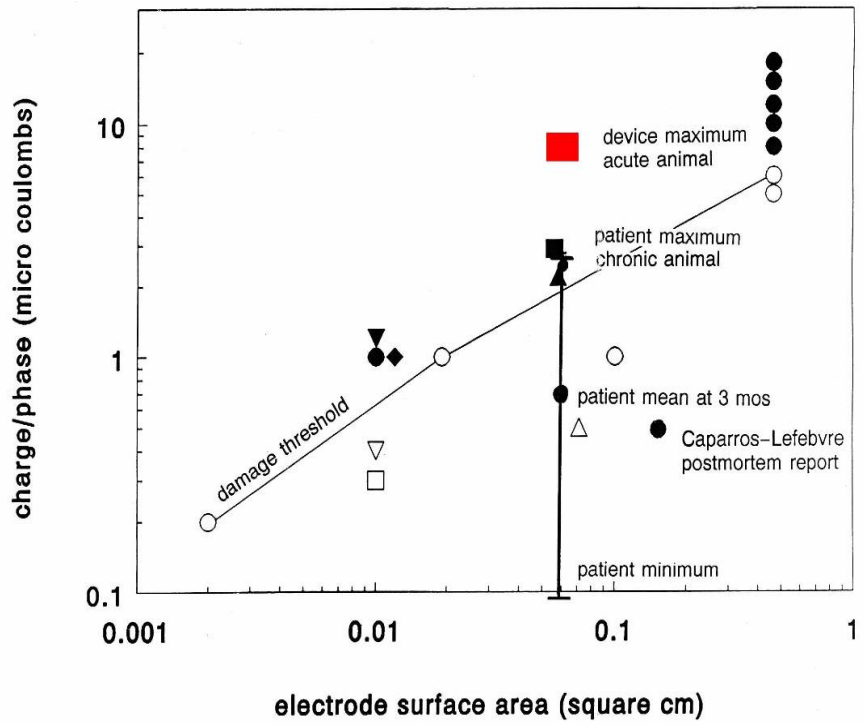
# Deep Brain Stimulation – 1997 Approval

| | |
|---|---|
| Electrode Surface Area | 0.06 $cm^2$ |
| Pulse Duration | 4500 microseconds |
| Amplitude | 10.5 V, or 21.0 mA into 500 Ω |
| Charge per Phase | 9.45 μCoulombs |
| Charge Density | 150 μCoulombs/$cm^2$ |
| Frequency | 185 Hz |




Problems

1. High charge density possible.
2. Small lesions seen in autopsy.
3. Progressive impairment in 10% of patients.

Solutions

1. The sponsor has agreed to provide programmer warning and labeling for parameters which result in charge densities greater than 30 μCoulombs/$cm^2$
2. Post-approval autopsy studies
3. Post-approval effectiveness study

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# Looking Forward

- CNS causal-path biomarkers needed – correlates are not good enough.
- Are biomarkers really needed for affective disorders when patients feelings and function are paramount?
- How can we compare between trials?
- Can “placebo” effects be used effectively by device treatments?