Neuromodulation for Neurological & Neuropsychiatric Disease

Aviva Abosch, M.D., Ph.D.
*University of Minnesota*
*Department of Neurosurgery*
How does your brain work?

• Brain cells communicate by electrical signals
• In certain diseases, these signals can be abnormal resulting in misinformation
• This misinformation can manifest as tremor, difficulty moving, seizures, etc.
Neuromodulation defined...

- vs. Traditional Neurosurgery
  = *direct application of technologies to NS, for amelioration of function*

- Virtues:
  - Minimally invasive
  - No removal/severing connections
  - Can be turned on, off; modifiable
  - Window on nervous system
What is Deep Brain Stimulation?
Evidence:

• Randomized trial of STN DBS+meds vs. best medical therapy for PD
  ▪ (N=156) QOL & mUPDRS; 6m F/U
  ▪ DBS better
    • Deuschl, et al, German PSG; NEJM 355(9):896; 2006

• Randomized controlled trial of DBS vs. sham stimulation for primary dystonia
  ▪ (N=40) BFMDRS; 3m F/U
  ▪ DBS better
What’s New in DBS?

• Controlled studies of existing therapies
  ▪ Optimal target for each disorder?
    • STN vs. GPi for PD

• Novel technologies
  ▪ “Closed-loop” feedback systems
    • Sensing Electrode + Stimulation or Drug Delivery

• Novel applications of existing technologies
  • Epilepsy, depression, Tourette, OCD
  • PPN for gait & akinesia in PD

• Modifications of existing technologies
Novel Technologies

- “Smart” Systems for On-Demand Pacing
  - Neuropace™
    - Medically-refractory epilepsy
    - Implantation of depth & cortical electrodes
    - Detects abnormal brain activity
    - Responds by delivering stimulation prior to sz-onset
    - Multi-center, FDA-approved, industry-sponsored

- Such a closed-loop stimulation may
  - Improve results by delivering therapy only when needed
  - Decrease demands on stimulation systems
    - Q: Development of seizure prediction algorithms?
    - Q: Intervene with stimulation or drug → seizure aborted?
Epilepsy:

- Abnormal synchronization of brain cells’ electrical signals $\rightarrow$ Seizure
- Recurrent Seizures = Epilepsy
- 3 Million people in U.S.
  - 200,000 new cases/yr. in U.S.
**Basal Ganglia Function**

**Parallel Pathways Hypothesis:**

- **Segregated**
  - Fronto-striato-Pallido-thalamic-Frontal loop

- **Dysfunction of this circuit** → behavioral abn’s

---

**Limbic Loop:**
- TS & OCD
- TRD?

---

*Albin, Young, Penney, TINS 12: 366; ’89*
*Delong, TINS 13: 281; ‘90*
Importance of Mechanistic Approach:

- Neural correlates of neuropsychiatric disorders not yet well understood
- This understanding is critical for refining therapies & determining patient populations who will benefit
Converging Lines of Evidence:

- Disease characteristics
- Lesion data: surgical (historical)
- Behavioral changes from DBS for PD
- Current DBS trials—CNS “switch”
- Imaging: anat, fMRI, PET, SPECT, dtMRI
- Animal Models
  → Implicates C-BG-Thal-C circuitry
Neuropsychiatric Disorders Currently Treated:

- Tx-refractory Major Depression (TRD)
  - Depression: 121 million people worldwide
  - 20% TRD

- OCD
  - 3.3 million in U.S.
  - Up to 40% treatment-refractory

- Tourette Syndrome
  - 2-3% of U.S. population
Anat/Physiol Basis for TRD:

- Unlikely to be a single gene, neurotransmitter, or brain region problem
- Believed to be a “network” problem, driven by genetics & environment
- Functional Imaging:
  - Cg25 involved in acute sadness & anti-depressant therapy effect (SSRI; ECT, etc)
- Anatomic Connections of Cg25:
  - To BS, hypothalamus, & insula
    - Areas involved in circadian rhythm (sleep, appetite, libido)
  - Reciprocal connections to OFC, MPF, ACC
    - Areas involved in motivation, reward, learning & memory
Rationale: Cg25-Frontal Interactions in Negative mood regulation

Transient Sadness
CBF PET

Healthy Volunteers

Depressed Patients

Dep Recovery
FDG PET

F9  Cg25

Cg25  Cg31

Cg25  Cg31

R

Am J Psych
156:675-82 1999
Basis for DBS for TRD:

• Sx of severe depression can be reversibly induced by STN DBS in PD
  ▪ (Bejjani et al, NEJM 340:1476; ’99)

• focal brain stim can alter limbic system function:
  ▪ Infer. Thalamic Peduncle DBS (Jiminez et al, ’05)
  ▪ BA25/Cg-WM DBS (Mayberg et al, ‘05)
  ▪ N. Accumbens DBS (Schlaepfer et al, ‘)
  ▪ ALIC-VC/VS DBS for OCD (Brown; CCF; U Fla)
Cg25 DBS: Time Course of PET Changes:

Baseline
CBF PET
All Pts vs NC
Ham17 = 27+2

3m DBS
CBF Change
Responders
Ham17 = 9+6

6m DBS
CBF Change
Responders
Ham17 = 7.8+3

Mayberg et al.
Neuron, 45: 651-660, 2005
Conc: Treatment-Refractory Depression

- Cg25 DBS results in sx remission w/normalization of CBF
- Given that TRD is a network and not a single target, intervention at other sites on the “network” should result in sx improvement.