Investigating the Neurophysiological Effects of Direct Current Stimulation

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1. Define area of interest
   * Interface of Cognitive Neurology and Functional Neurosurgery
   * Neuromodulation – DBS, tDCS,

2. Basic Science Research or Clinical Research?

3. Funding

   * SEARCH THE LITERATURE TO FIND A NICHE

   * GOOD MENTORSHIP IS ESSENTIAL
Goals

1. To acquire knowledge and learn certain skills and techniques, otherwise not explored in the medical school curriculum, that will be useful in my career.
   - Grant allocation
   - Animal surgeries
   - EEG
   - Data analysis (MatLab, STATA, excel)
   - Deep exploration of a topic
   - Publishing: abstracts, articles

2. To create an animal model for direct current stimulation
Goal of Brain Stimulation: Enhancing the brain’s natural plasticity

- **TMS and tDCS**
  - Brain injury
  - Cognitive impairment
  - Stroke
  - Movement disorders
  - Depression (overcoming “learned helplessness”)
  - ADHD

- **DBS and Epidural Cortical Stimulation**
  - Movement disorders (e.g. Parkinson’s)
  - Psychiatric disorders Depression (e.g. overcoming “learned helplessness”)

Could neuromodulation be use to enhance cognitive processes in normal people?
Gap in Current Treatment
“finding a niche”

* No tDCS animal models to allow assessment of approach for specific brain regions and deficits
* tDCS poor isolation of specific brain regions due to spread.
* Effects of direct current DBS has not been examined
  * in humans or animals.
* Previous studies have focused on behavioral changes of tDCS but lack specific biomarker for effect
  [Jacobson, 2011 #23]
There is evidence for efficacy of tDCS (direct current)

There is evidence for efficacy of intracranial DBS (alternating current)

However, little is known about the effects of intracranial direct current stimulation.

Furthermore molecular, anatomic, and physiological mechanisms by which these stimulation paradigms cause long term adaptation are not well understood.

With a flexible animal model, we could measure both physiologic and molecular changes

- We can look at effects of genes and drugs
- We can look at functional and behavioral changes

We propose a simple rodent model of tDCS which can be used in the future to better understand how brain stimulation alters brain function
Anodal stimulation will lead to a facilitation of auditory response [because it should lead to facilitation of any cognitive response!] in primary auditory cortex

- *Via an overall reduction in low frequency power especially in the frequency ranges [Keeser et al., 2011; Jacobson et al., 2011]*
- *Effect should be somewhat durable across time*
- *Cathodal stimulation will lead to opposite effect.*
Anodal, Cathodal, Sham

Sham
Anodal
Cathodal

+ - + -

Somatosensory Cortex
L. Aud Cortex

Anterior
Inferior
Posterior
Why the auditory cortex?

* Most straightforward link to employed auditory task
  * Although PFC and other regions would have worked
* Auditory cortex has a causal link to a specific EEG biomarker: the N40
  * “If the N40 response is intact, the auditory cortex is intact”
* Experimental surgeries were successful
Groups and Order

1. WEEK 0: Record → Stimulate → Record
   - 24 c7/Bi6 mice
     - Anodal
       - Pre Stim
       - Post Stim
     - Cathodal
       - Pre Stim
       - Post Stim
     - Sham
       - Pre Stim
       - Post Stim

2. WEEKs 1 and 2: Record - Record
   - 24 c7/Bi6 mice
     - Anodal
     - Cathodal
     - Sham
Weeks 4 and 5

* Week 4: Record → Stimulate at LOWER DOSE (5 microAmps) → Record
* Week 5 → Record
“How do I record EEG responses to Auditory Evoked Potentials?”

- Equipment from Translational Neuroscience Lab.
  - Hardware
  - Software
    - SPIKE
    - MatLab/EEG Lab for analysis
“How do I Stimulate?”

- Simplest approach: use same electrodes to stimulate as used for recording.
- Intracranial Self Stimulation Device and Software
  - PHM-152 hardware
  - Modified Med-PC IV software programs
CONCLUSIONS FROM TRIALS:
1. 100 microamps too much!
2. Stimulation: 20 microamps for 20 minutes
1. To create an effective mouse model of direct current stimulation
   * Intracranial electrode
   * ICSS device tweaked for direct current
   * Direct current used: **20 microAmps for 20 minutes**
     * Anodal, Cathodal, and Sham Stimulation Groups

2. To record Auditory Evoked Potentials before and after stimulation, analyze them, and **COMPARE BETWEEN GROUPS**.
   * Check for waveform differences between groups
     * P20, P40, P80 Amplitudes
     * P20, p40, p80 latencies
     * gPLF (inter-trial coherence).
   * ISI of 0.5 used (others being investigated)
EEG

P20: thalamo-cortical signaling
N40: auditory cortex signaling
P80: associative cortices signaling
1. To create an effective mouse model of direct current stimulation
   * *Intracranial* electrode
   * ICSS device tweaked for direct current
   * Direct current used: **20 microAmps**
     * Anodal, Cathodal, and Sham Stimulation Groups
2. To record Auditory Evoked Potentials before and after stimulation, analyze them, and **compare between groups**.
   * Compare total power, baseline power, evoked power, induced power, total power at different frequencies (delta, theta, alpha, beta, gamma(low and high)).
   * **Check for waveform differences between groups (0.5 ISI)**
     * P20, P40, P80 Amplitudes
     * P20, p40, p80 latencies
     * gPLF (inter-trial coherence).
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<th>Variable</th>
<th>Groups Compared to Sham</th>
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In week 2 we see less effects...
The current stimulation’s effects are blunting over time for most variables.
Theta Power

R1*Group; LS Means
Current effect: F(6, 33)=6.9055, p=.00008
Effective hypothesis decomposition
Vertical bars denote 0.95 confidence intervals

Decibels (dB)

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<thead>
<tr>
<th></th>
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<th>1 Post Theta</th>
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R1

0 Pre Theta 0 Post Theta 1 Post Theta 2 Post Theta
N40 Amplitude

R1*Group; LS Means
Current effect: F(6, 33)=.62468, p=.70922
Effective hypothesis decomposition
Vertical bars denote 0.95 confidence intervals
N40 amplitudes and latencies did not change across time for any group. There were no differences in any frequency range in the sham group across time and no differences in any frequency range prior to stimulation.

There was a reduction in delta power in anodal and cathodal groups (p=0.034) and a trend towards an interaction between group and time (p=0.118). Exploratory analyses revealed reduced delta power 1 wk (p=0.015) and 2wk (p=0.005) in the anodal and 1hr (p=0.021) and 1wk (p=0.039) in the cathodal conditions.

There was also a reduction in theta power in the anodal and cathodal groups (p<0.001) as well as a reduction over time (p=0.002). A time x group interaction (p<0.001) showed a reduction of theta power in the anodal group at 1hr (p=0.003), 1wk (p<0.001) and 2wk (p<0.001) as well as a reduction in the cathodal group at 1hr (p<0.001).

Finally, there was a reduction in alpha power in the stimulation groups (p<0.001), a reduction over time (p<0.05), and a significant time by group interaction (p<0.001) that showed a decrease in the anodal group at 1wk (p<0.001) and 2wk (p<0.001) and in the cathodal group at 1hr (p<0.01).
Issues

* Use of stainless steel electrodes
  * Associated with ion deposition
  * Platinum would be better
* EEG recording site = site of stimulation
  * Recordings from distant sites may be better for high frequency band analysis
* No major effect differences between Anodal and Cathodal stimulation
  * In my model, looks like a dose-response difference
  * Spacing of electrodes– not ideal for tDCS
* Future direction: introduce behavioral correlates
The purpose of this study was to develop a simple mouse model for intracranial direct current stimulation. This will serve to better understand mechanism of direct current brain stimulation and of FOCUSED brain stimulation in general. Current quality and quantity can be altered very easily with our model. Application is wide: functional neurosurgery and non-invasive brain stimulation.

Future: our approach can be combined with animal models of various pathologies. Future: add more electrodes to record from more areas.
Our experiment shows that auditory evoked potential low frequency power is reduced with current stimulation.

- Effect lasts 1 to 2 weeks in our model
- Effect is unlikely due to brain damage as seen with intact N40 values.

As evident in human studies decreases in low frequency wavelength power may be tied to improved processing [Keeser et al., 2011; Jacobson et al., 2011]

- Decreasing resting Theta power is target of biofeedback therapies
- Decreased power in low-freq bands associated with increased fMRI BOLD response
- Decreased power in low-freq band associated with improvement in n-Back working memory task
Thank You