tES: Mechanisms, technologies and therapeutic applications

Organizers:

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September 28-29, 2016
Definition: transcranial Electrical Stimulation (tES)

- Transcranial electrical stimulation encompasses all methods of non-invasive current application to the brain used in research and clinical practice, including ECT.

- Primary focus of this workshop is on contemporary forms of low current electrical stimulation used in research and clinical applications (last decade), employing basic, well-defined waveforms
  - 5-20 min stimulation, peak current 1-2mA
  - Conventionally 2 electrodes – target region + elsewhere on scalp or body
  - Saline soaked sponges wrapped around a conductive rubber electrode (though gel may be used) or array of smaller electrodes for more focal stimulation (High Definition-tDCS)

(Guleyupoglu..Bikson (2013) Classification of methods in tES and evolving strategy from historical approaches to contemporary innovations. J Neurosci Methods 297-311)
tES Techniques

- Transcranial direct current stimulation (tDCS) 2000-
  - Constant unidirectional low current stimulation delivered via scalp electrodes, modulates resting membrane potential

- Transcranial alternating current stimulation (tACS) 2008-
  - Alternating currents (sinusoidal waveform at 10-40 Hz) delivered via scalp electrodes to entrain in a frequency-specific fashion the neural oscillations

- Transcranial random noise stimulation (tRNS) 2006-
  - Alternating current applied at random frequencies from 0.1 to 640 Hz, adding neural 'noise' to targeted regions and potentiating task-related neural activity.

*(Filmer et al (2014) TINS 37(12), 742-753)*
Motivation for tES Workshop

- Increase in applications using tDCS/tACS for therapeutics
- Neuromodulation less well represented than pharmacologic and psychosocial/cognitive-behavioral interventions in NIMH portfolio
- Good safety and tolerability profile
- Low cost, portability
- Potential for stand-alone or multimodal, learning-based interventions (cognitive, motor)
- Advances in understanding mechanisms, biomarkers of responsiveness, and technology (electronics, montages supported by computational models) may help inform stimulation protocols

(Guleyupoglu..Bikson (2013) Classification of methods in tES and evolving strategy from historical approaches to contemporary innovations. J Neurosci Methods 297-311)
Goals for Workshop

• To critically assess the use and potential of tES and identify research needs for optimizing protocols and further developing therapeutic applications of these modalities
  ▪ Examine the *physiological mechanisms* underlying tES effects
  ▪ Examine the *technologies* and technical strategies for optimizing treatment protocols
  ▪ Examine the state of the science with respect to *therapeutic applications and trial designs*
  ▪ Identify *research gaps, obstacles, strategies for overcoming these, and opportunities* for further developing these modalities for therapeutic applications
• Progress in treatment development lagging due to insufficient understanding of pathophysiology and an absence of new targets

• Goal is to identify or verify new targets for treatment development or identify therapies that directly influence disease outcome or knowledge of disease

• Studies can be small, but include biomarkers and neurocognitive outcomes that can help determine mechanisms of action

• Negative results can be informative in ruling out a target, e.g., if target is engaged without therapeutic results, target may be ruled out as worthy of further study

(T. Insel, blog, June 12, 2012 nimh.nih.gov)
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<td><strong>First in Human</strong>&lt;br&gt;Exploratory Experimental Therapeutics</td>
<td>First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders (U01)*</td>
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<td>DTR</td>
<td><strong>Confirmatory Efficacy</strong>&lt;br&gt;Trials of Non-Pharmacological Interventions</td>
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<td>DSIR</td>
<td><strong>Effectiveness (Prevention, Treatment, Services)</strong>&lt;br&gt;Pilot Effectiveness Trials for Treatment, Preventive and Services Interventions (R34)</td>
<td>Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions (R01)</td>
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<td>Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions (Collaborative R01)</td>
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R61/R33 Phased mechanism for exploratory clinical trials of novel interventions – required elements

- Well-defined, objectively-measured intervention target (disease mechanism or mechanism of intervention effect)
- *Dose/parameter optimization* (R61)
- Demonstrate that the intervention *engages/alters* the target (R61)
- A priori *go/no-go criteria* for R61 to determine whether to *proceed to R33 phase*
- *Replicate* effect of intervention on target and examine clinical effects (R33 phase)
Increased Transparency and Data Sharing

- *Increased transparency* – prospective trial registration, monitoring, posting of results in public database

- *More comprehensive reporting* - to address concerns about failure to publish, publication bias or lack of access to raw data (patient-level data)
  - Individual-level data from clinical studies (raw and processed) archived and shared through the *NIMH Data Archive (NDA)*
Research Domain Criteria (RDoC) Initiative

Research framework for studying psychopathology based on dimensions of neurobiology and observable behavior, 2009-

- Matrix of biobehavioral domains & constructs (e.g., cognition/cognitive control, working memory, negative & positive valence/reward learning) \( \times \) levels of analysis

- Goal to understand brain disorders at multiple levels of analysis—genes - molecules - cells - circuits - behavioral dimensions – self report

- Integrative: Map constructs onto specific biological systems or circuits

- Foster targeted, individualized/precision medicine based on modern clinical neuroscience
Research Domain Criteria (RDoC) cont’d

• Transdiagnostic sampling, subtyping within or across DSM categories, dimensional measures

• Compatible with circuit-based approach to interventions and targeting specific symptoms or domains (e.g., hallucinations, cognitive control)
Introductions