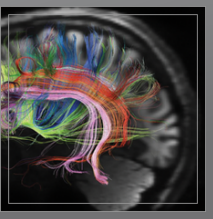


tES: Mechanisms, technologies and therapeutic applications

Organizers:

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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**

Experimental Medicine Approach 2012-

- **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)

Clinical Trial Pipeline - NIMH

DNBBS | **DTR** | **DSIR**

First in Human	Exploratory Experimental Therapeutics	Confirmatory Efficacy	Effectiveness (Prevention, Treatment, Services)
First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders (U01)*			Pilot Effectiveness Trials for Treatment, Preventive and Services Interventions (R34)
	Exploratory Clinical Trials of Novel Interventions for Mental Disorders (R61/R33)*		Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions (R01)
	Exploratory Clinical Trials of Novel Interventions for Mental Disorders (R33)*	Confirmatory Efficacy Trials of Non-Pharmacological Interventions (R01)	Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions (Collaborative R01)

Experimental Therapeutics Approach

- **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**

ClinicalTrials.gov

- ***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) X 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**

RDoC Research Domain Criteria Initiative

National Institute of Mental Health

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)**

RDoC
Research Domain Criteria Initiative

NIH National Institute of Mental Health

Introductions