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Neuromodulation as a Rehabilitation Tool in Aging, MCI, and Dementia

Benjamin M. Hampstead, PhD, ABPP/CN

Associate Professor

Neuropsychology Section

Department of Psychiatry

University of Michigan

Staff Psychologist

VA Ann Arbor Healthcare System

Clinical Core Leader

Michigan Alzheimer's Disease Core Center

MADCC

MICHIGAN ALZHEIMER'S DISEASE CORE CENTER

MICHIGAN MEDICINE

UNIVERSITY OF MICHIGAN

Conflict and Disclosures

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- While I may acknowledge commercial products/companies, I have no conflicts with them
- Content does not reflect the views of the US Government

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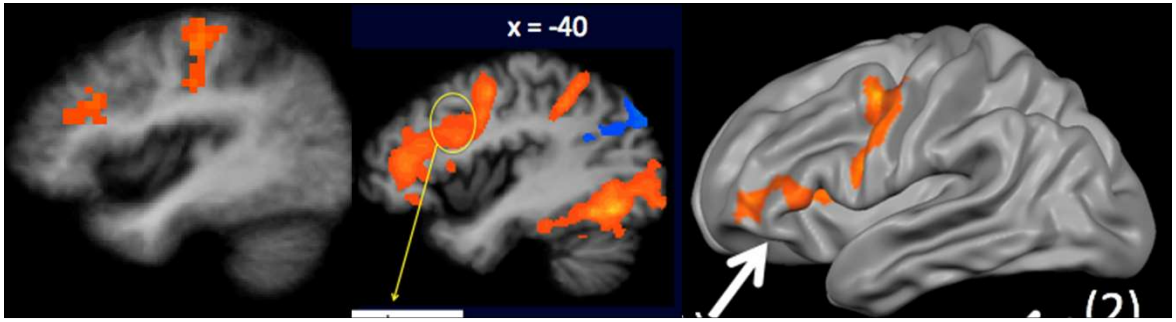
Enhancing Cognitively Oriented Treatments with tDCS

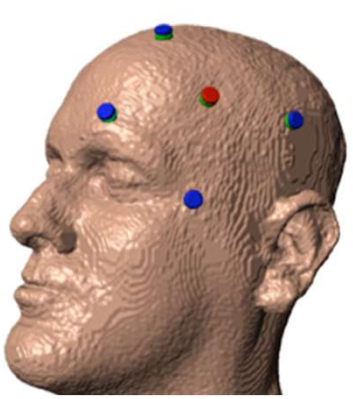
Combined mnemonic strategy training and high-definition transcranial direct current stimulation for memory deficits in mild cognitive impairment

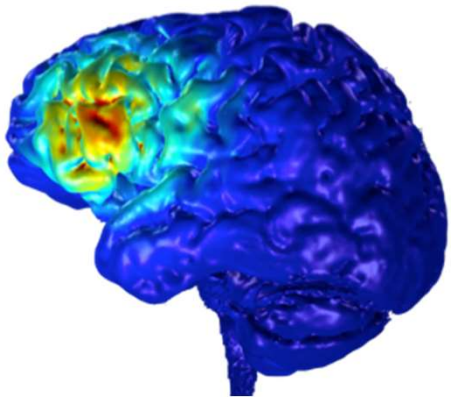
Benjamin M. Hampstead[a,b,c,d,*], Krishnankutty Sathian[d,e,f,g], Marom Bikson[h], Anthony Y. Stringer[d,g]

Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 459-470

- Double-blind RCT combining MST and HD-tDCS over left (ventro)lateral PFC
- Goal of 100 patients with MCI (~70% complete)







So what is tDCS and what are the effects/indications?

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Overview

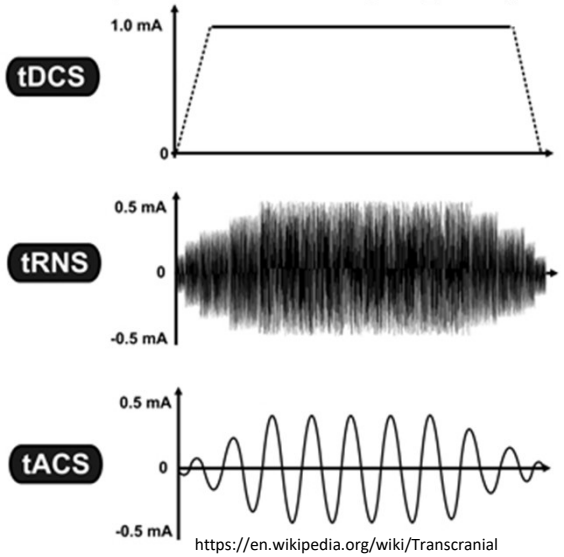
Caveat: I have 15 minutes!

Non-Invasive Brain Stimulation (NIBS) overview

- **Emphasis on transcranial direct current stimulation (tDCS)**
  - **General parameters (how much & how long)**
  - **Current literature**
  - **Task-based fMRI changes using spatial navigation as a model**
  - **Future directions**

Non-Invasive Brain Stimulation (NIBS)

- General term for methods that use magnetic fields, electrical current, ultrasound, light (etc) to modulate brain functioning without incision or implantation
- Several types of NIBS exist
  - Transcranial magnetic stimulation (TMS)
  - **Transcranial direct current stimulation (tDCS)**
  - **Transcranial alternating current stimulation (tACS)**
  - **Transcranial random noise stimulation (tRNS)**
  - Pulsed ultrasound
  - Laser / blue light



https://en.wikipedia.org/wiki/Transcranial_random_noise_stimulation#/media/File:Fnhum-07-00435-g001.jpg

- Transcranial electrical stimulation (TES) includes electroconvulsive therapy (ECT) but is NOT defined by it!
  - E.g., ECT uses 700-900mA vs. 1-3mA for transcranial direct current stimulation (tDCS)
  - ECT induces a seizure; NIBS aims to modulate functioning (we do NOT want a seizure)

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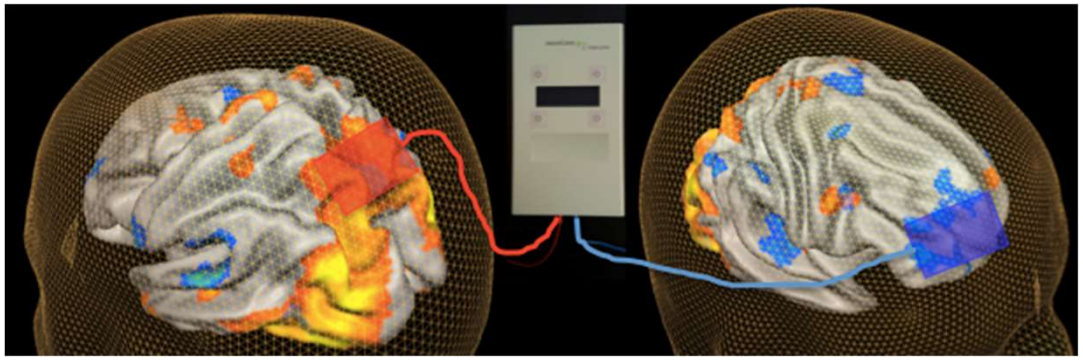
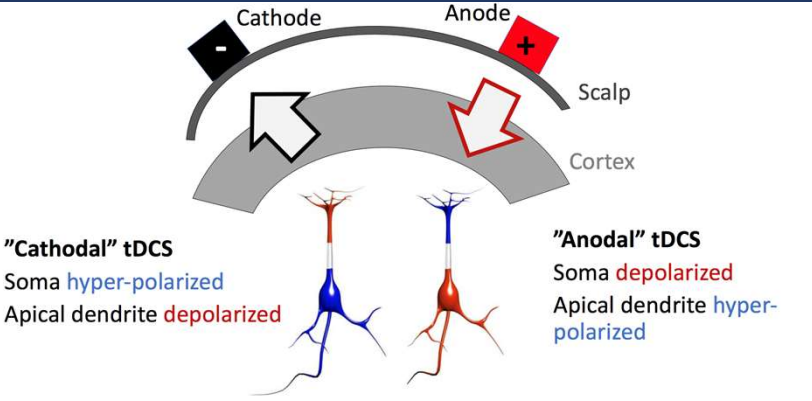
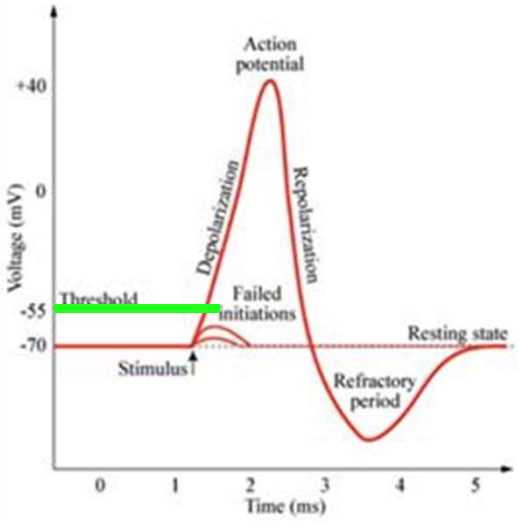
The Basics of tDCS





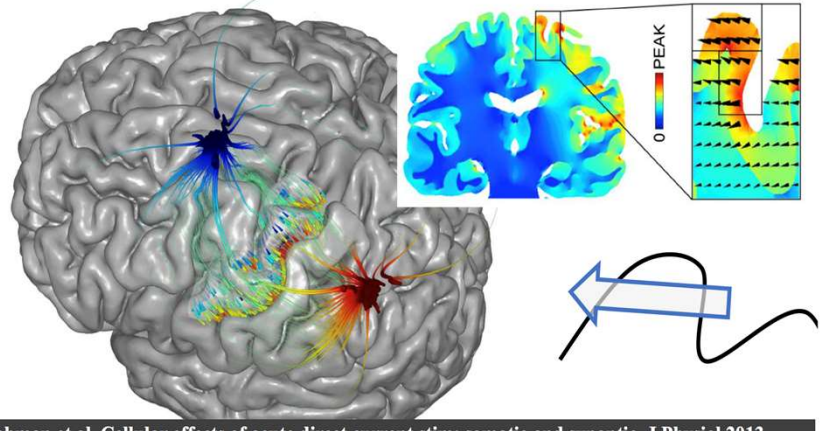
- Modulates neuronal excitability using weak electric currents (~1-2mA)
- Current flows between 2(+) electrodes
  - Anode (+) = <u>excitatory</u>*
  - Cathode (-) = inhibitory*

*effects appear to depend on cellular orientation relative to current flow



Radman, et al. Role of cortical morphology in uniform electric field stimulation. Brain Stim. 2013

Gyri level changes in outward/inward polarity



Rahman et al. Cellular effects of acute direct current stim: somatic and synaptic. J Physiol 2013

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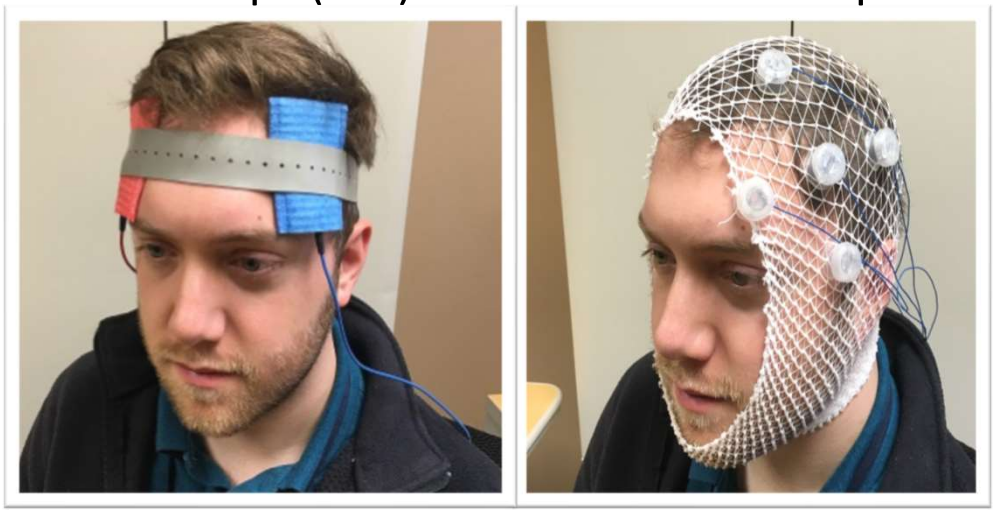
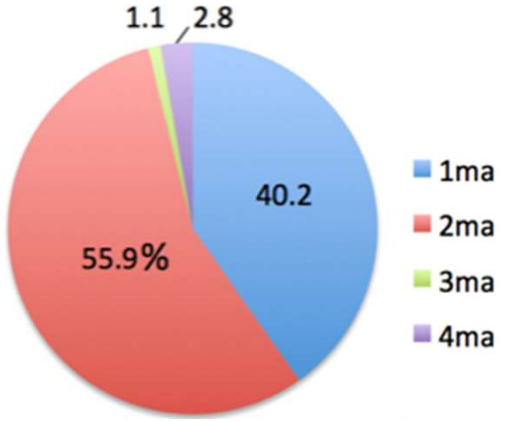
How Much and How Long?

How Much?

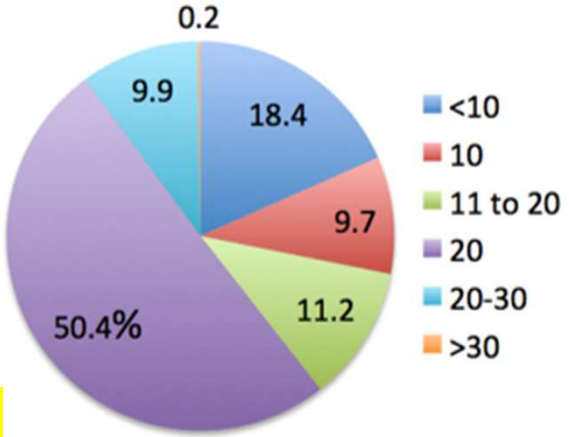
- Milliamps (mA) delivered at the scalp



96% of sessions have used ≤2mA (no clear rationale: 33,000+ sessions)



Data from Bikson et al., Brain Stimulation, 2016



How Long?

- 50% used 20-minute session - No clear rationale
- ~10% used > 20 minutes
- Limited ranges are unfortunate

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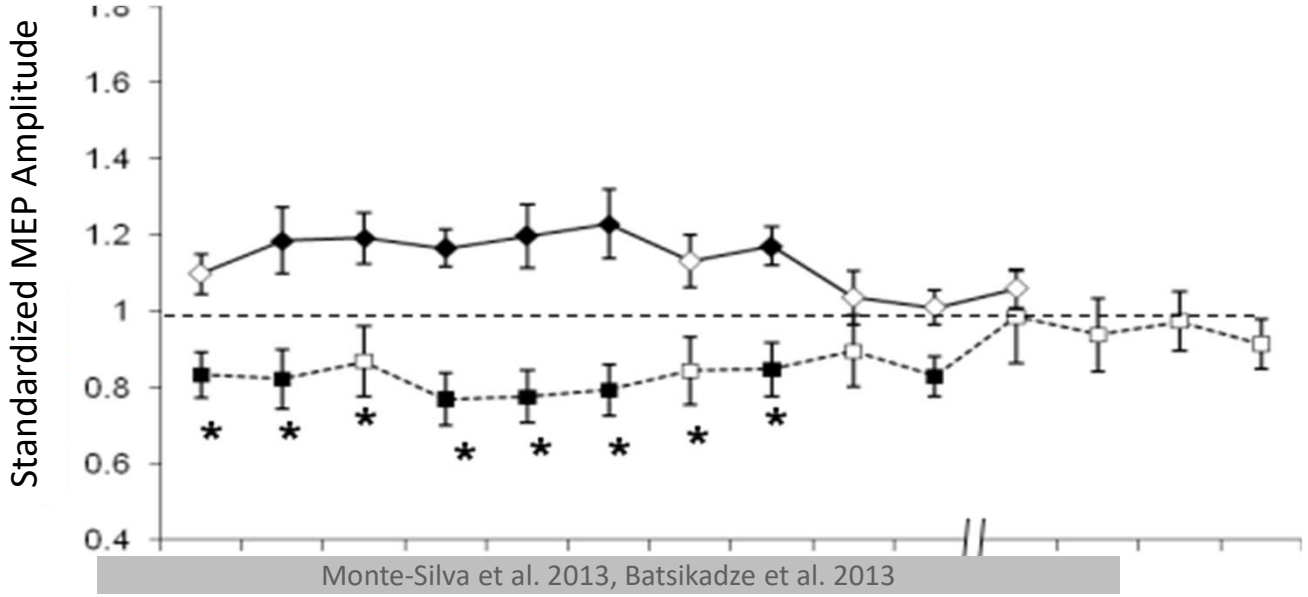
Neurophysiological Effects

- Most of our knowledge comes from the motor system

TMS pulse --> MEP → tDCS ("X" amplitude, "Y" duration, "Z" montage) → TMS pulse --> MEP

Time



Monte-Silva et al. 2013, Batsikadze et al. 2013

So anode = "excitatory" (depolarization) – generally true
And cathode = "inhibitory" (hyperpolarization) – however…

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How Much and How Long Depends…

Thanks to Dr. Nitsche: Mohsayebi et al., *under review*

1mA = “inhibitory”

- We need dose response data for non-motor abilities, regions, and/or networks!

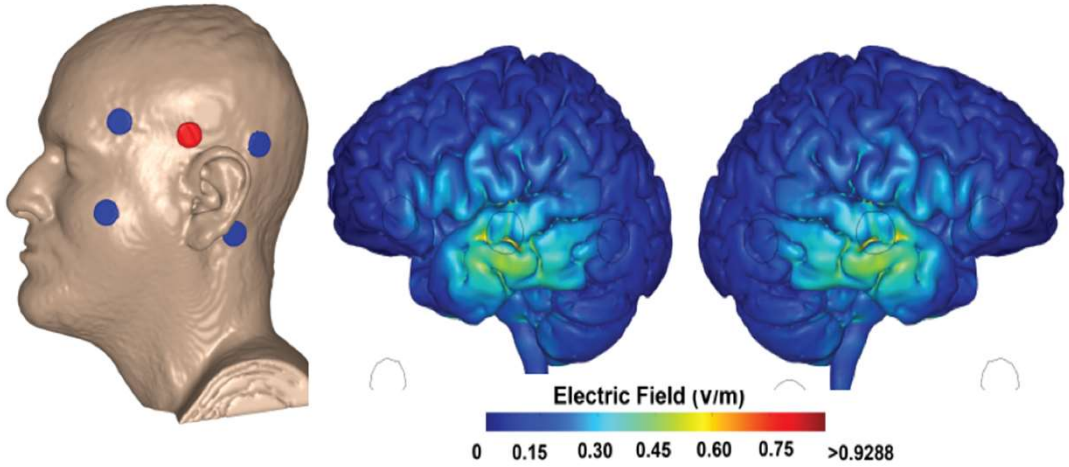
Ongoing Work

Treating mild cognitive impairment with High Definition transcranial direct current stimulation
Hampstead (PI) – NIA R01 AG058724

STUD: **S**timulation **T**o **U**ndermine **D**ementia

Double blind RCT comparing sham, 1mA, 2mA, 3mA HD-tDCS for 5 sessions

- 140 patients with MCI
- Pre & post rsfMRI, Neuropsychological testing
- Amyloid and tau PET



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Neuromodulation Appears Promising

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Review

Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis

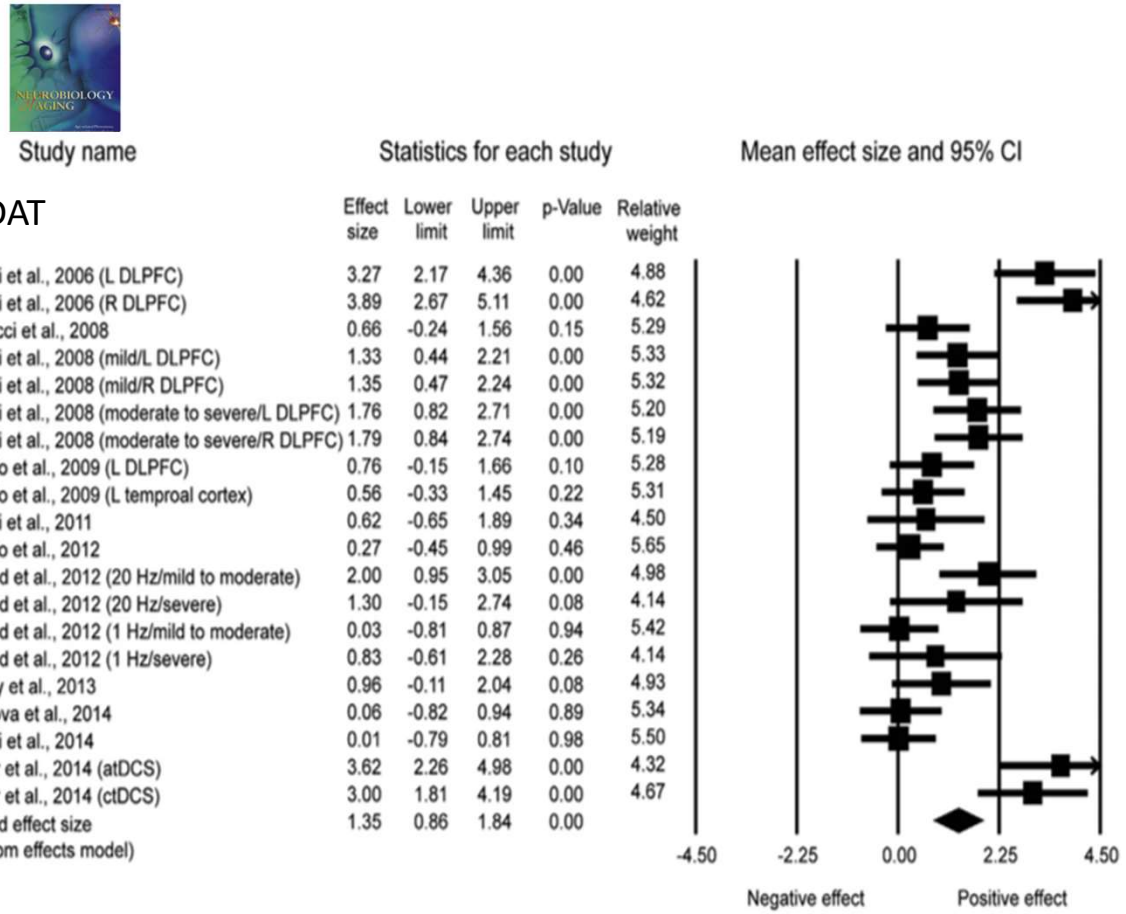
Wan-Yu Hsu [a], Yixuan Ku [a,b], Theodore P. Zanto [a], Adam Gazzaley [a,c,*]

TMS & tDCS

DAT: 11 studies, n=200

ES = 1.35

Adjusted ES = 0.78



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tDCS Specifically…

- How do we assess neurophysiological effect?
  - Ensure target engagement – fMRI as example

MCI

- Enhanced semantic word retrieval in MCI to HOC levels (Meinzer et al., 2015)
  - fMRI – based changes suggested tDCS may have "restorative" effect

DAT:

- Global functioning – Yes (Khedr et al., 2014) and No (Suemoto et al., 2014; Boggio et al., 2012)
- No change in attention or working memory (Ferrucci et al., 2008; Boggio et al., 2009)
- No change in neuropsychiatric symptoms (Suemoto et al., 2014)

Memory is consistently improved with stimulation over the temporal cortex (e.g., T3 &/or T4)

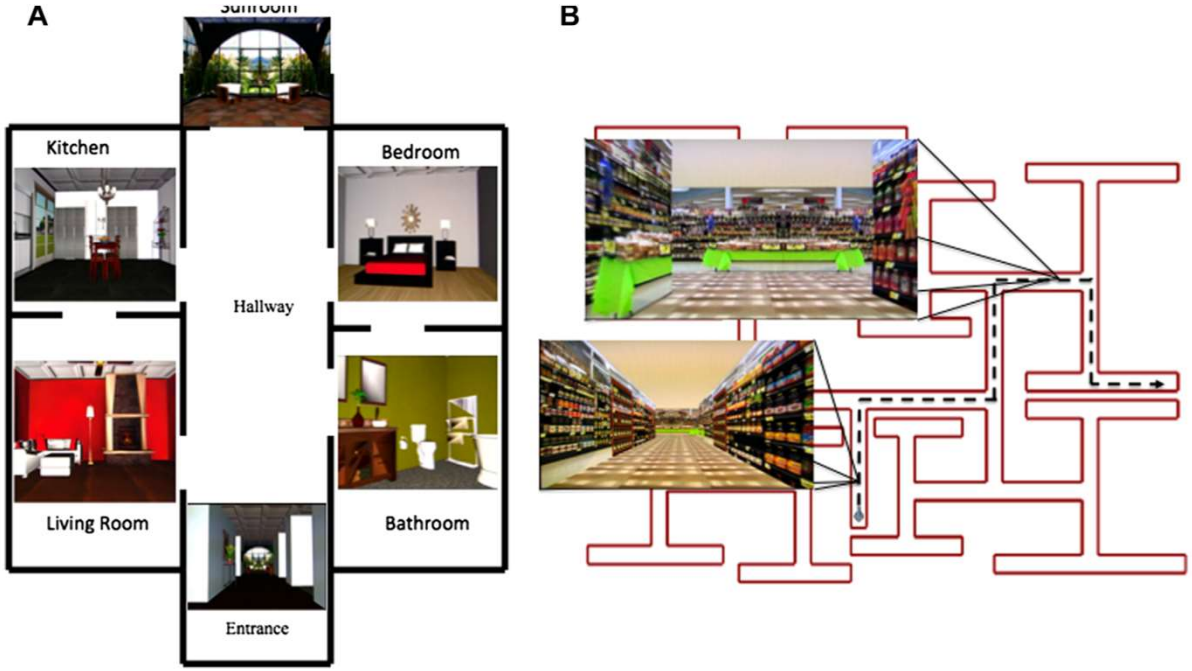
- Visual recognition memory improved with single session (Boggio et al., 2009) & persisted for 1-month after 5 sessions (Boggio et al., 2012)
- Verbal recognition memory improved after single session (Ferrucci et al., 2008; Marceglia et al., 2016)
  - Enhanced high-frequency alpha and beta oscillations in TPJ (Marceglia et al., 2016)

Measuring Neurophysiology – Spatial Navigation

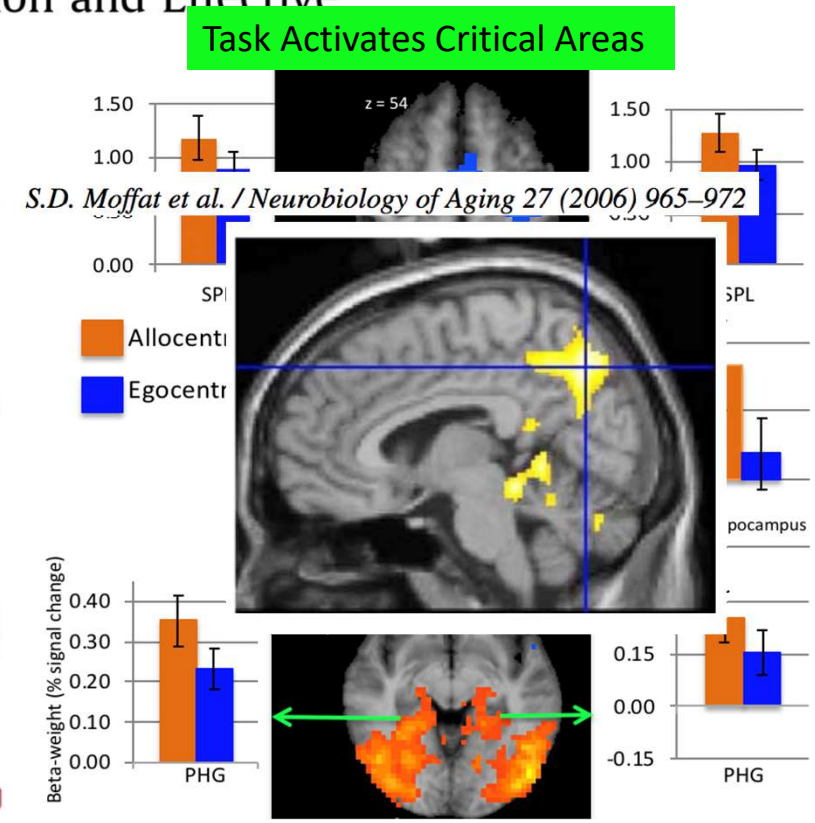
Transcranial Direct Current Stimulation Modulates Activation and Effective Connectivity During Spatial Navigation

Benjamin M. Hampstead [a,b,*], Gregory S. Brown [b], Justin F. Hartley [a]

Block Design (60” active blocks; 20” rest blocks)



Task Activates Critical Areas



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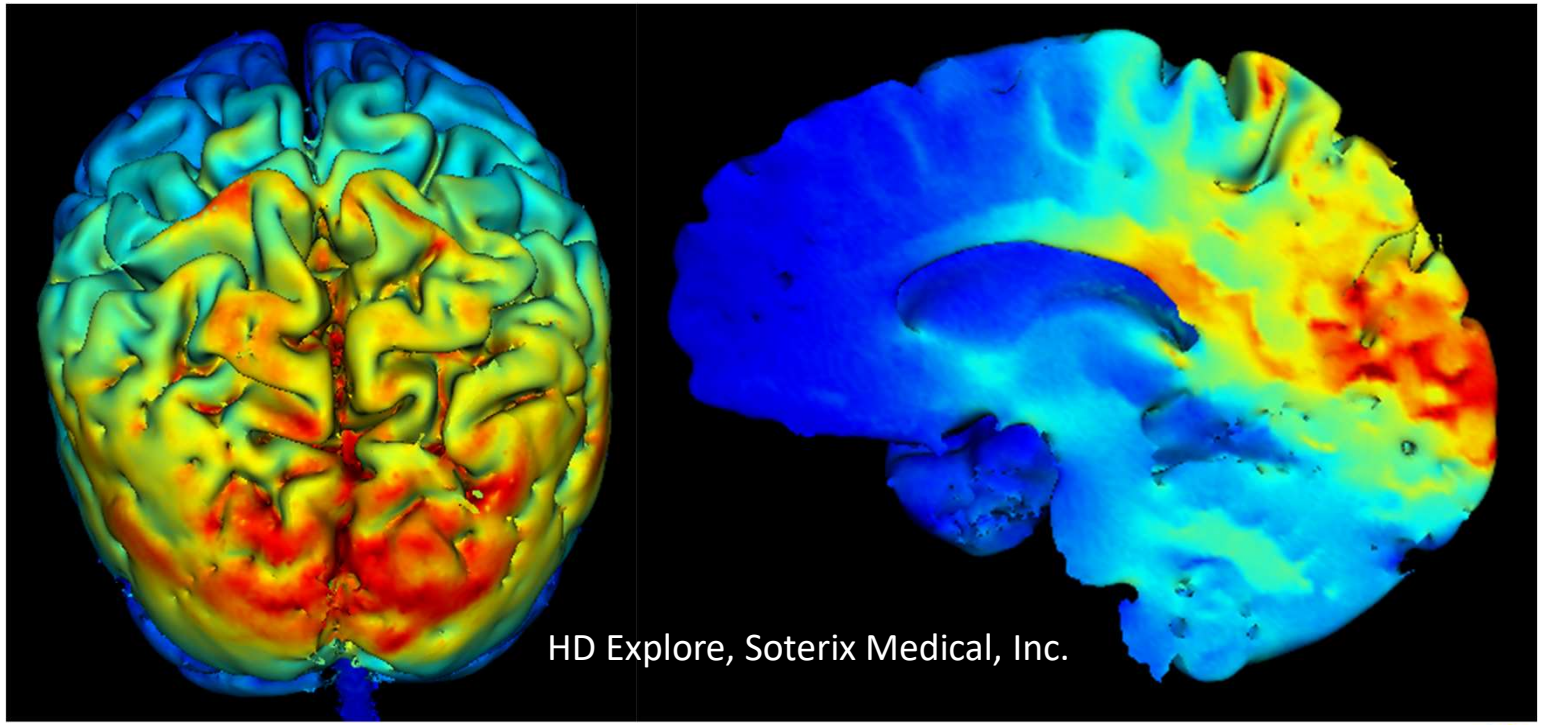
Measuring Neurophysiology – Spatial Navigation

Hampstead et al., *in preparation*

12 cognitively intact older adults
3 sessions each
Randomized order of central anode, cathode, and sham
Different stimulus sets each session – also randomized

Center electrode over Pz
Ring: Oz, Cz, P7, P8
2mA for 20 minutes
Memory encoding (offline ~20m)
Memory test after (~80m post)



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Measuring Neurophysiology – Spatial Navigation

No significant change in memory as a function of polarity

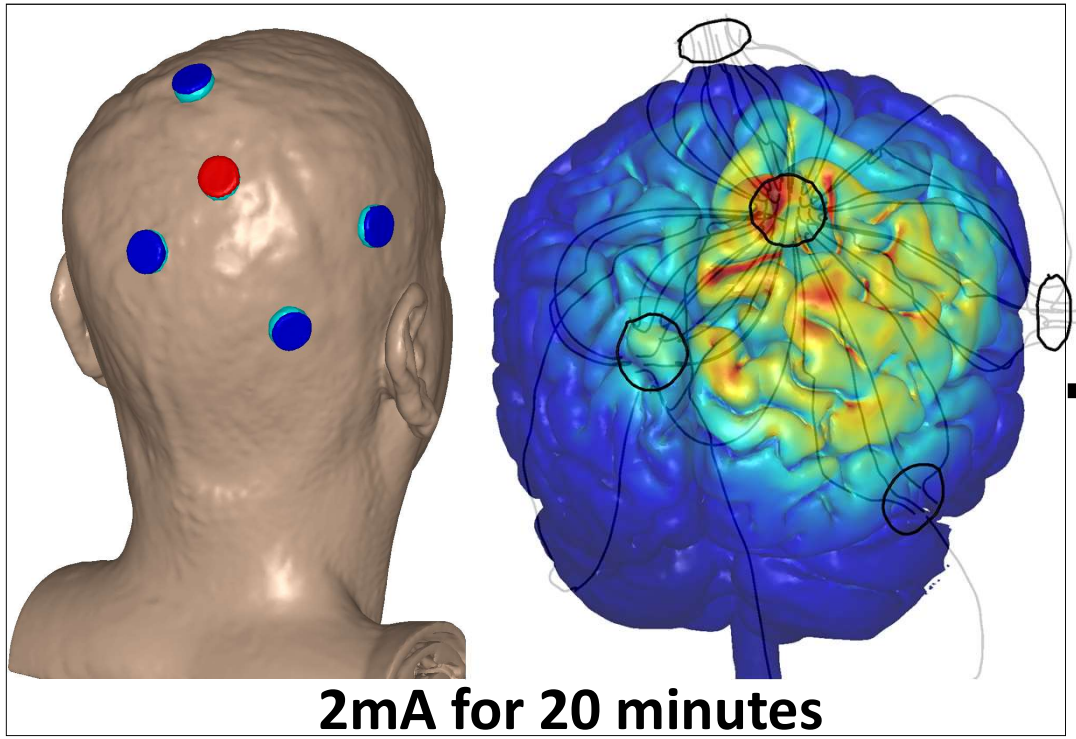
Hampstead et al., *in preparation*

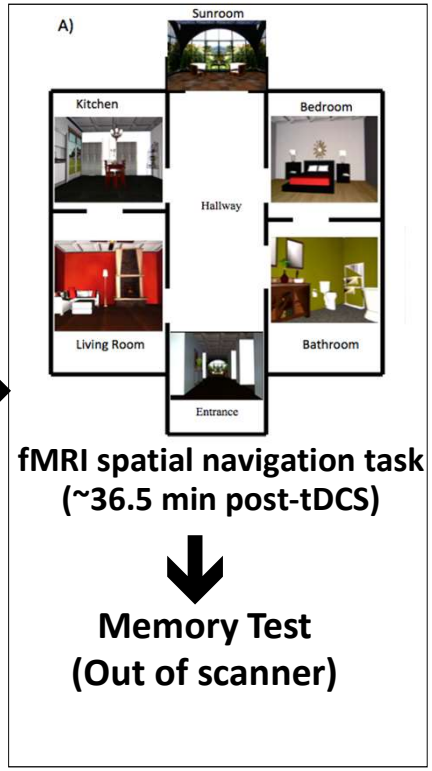
A Follow-Up in Controls and MCI

Hampstead et al., *in preparation*

22 Cognitively intact older adults (CIOA) & 20 MCI.

1 Active, 1 Sham session (randomized, counterbalanced) – Different stimuli





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Increased Hippocampal BOLD but Reduced Connectivity

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Single Sessions may NOT be Representative

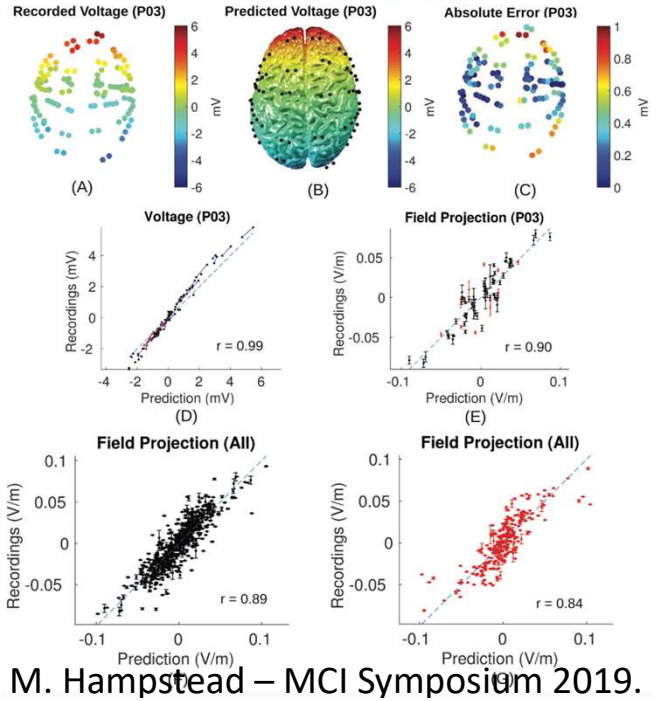
What Really Matters – How Much in the Brain?

Models allow us to relate dose at the scalp (mA) to the electric field/current intensity in the brain (V/m)

- A linear relationship is generally accepted
- BUT what is the brain's response? Is it also linear?

Measurements and models of electric fields in the *in vivo* human brain during transcranial electric stimulation

Yu Huang[1†], Anli A Liu[2*†], Belen Lafon[1], Daniel Friedman[2], Michael Dayan[3], Xiuyuan Wang[2], Marom Bikson[1], Werner K Doyle[2], Orrin Devinsky[2], Lucas C Parra[1*]
eLife 2017;6:e18834. DOI: 10.7554/eLife.18834



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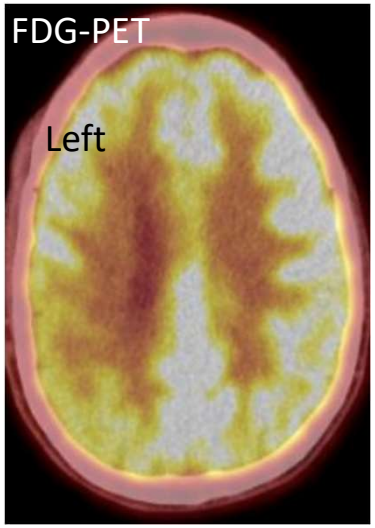
Translation: Individualized Montages

57 year old, right handed, female
Presents with

- **Progressive language deficits (~ last 3-4 years) consistent with logopenic variant primary progressive aphasia**
- **Depression & anxiety**
- **History of severe motor vehicle accident (~25 years prior)**



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Summary

TDCS and other forms of NIBS may hold promise

- Memory seems to show some consistent effects
- tDCS can alter measures of neurophysiology
  - Integrate neuroimaging to select and verify targets?

We need:

- Dose-response curves for non-motor abilities
  - How much? (mA vs. V/m)
  - How long? (length per session; number/timing of sessions)
  - Where? (pad vs. HD, montage, individualized models)
  - When? (Functional targeting?)

Monte-Silva et al. 2010, 2013

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