Combining Neuroimaging with Neurostimulation

Vincent P. Clark, PhD

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and Professor, Departments of Psychology and
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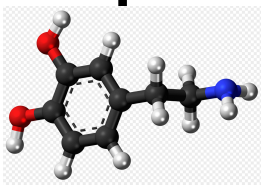
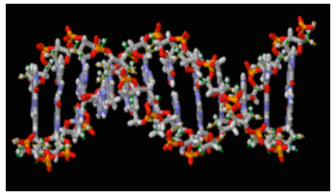
Professor of Translational Neuroscience,

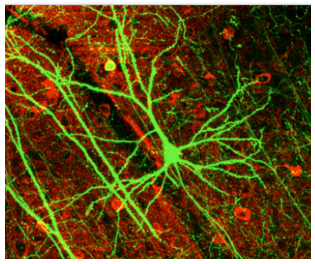
Mind Research Network (MRN)

The nervous system can be studied at multiple spatial and conceptual levels

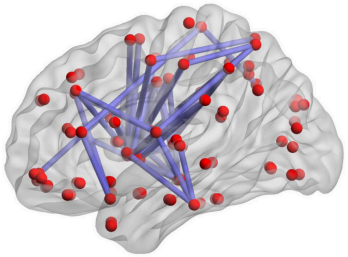




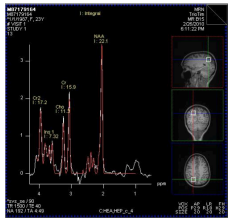
- **Molecular**
  - Molecular biology applied to the nervous system
  - Molecular neuroanatomy, mechanisms of molecular signaling, the effects of genetics and epigenetic, molecular basis of neuroplasticity

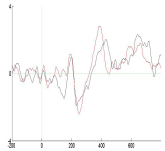


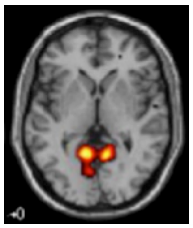
- **Cellular**
  - Morphological and physiological properties of neurons
- **Systems**
  - Mechanisms by which cells form networks and circuits
    - Brain neural networks (w/o feedback) and neural circuits (w/ feedback)
    - Reflexes, multisensory integration, motor coordination, circadian rhythms, emotional responses, attention, learning, and memory



  - Neuroethology, neuropsychology, neuroendocrinology, psychoneuroimmunology





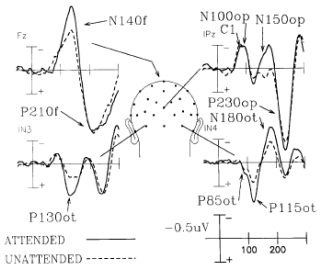


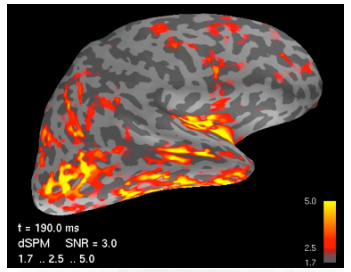
- **Cognitive**
  - How psychological functions and behavior are produced by brain systems

https://en.wikipedia.org/wiki/Dopamine#/media/File:Dopamine_3D_ball.png
https://en.wikipedia.org/wiki/DNA#/media/File:ADN_animation.gif
https://en.wikipedia.org/wiki/Biological_neural_network#/media/File:Brain_network.png

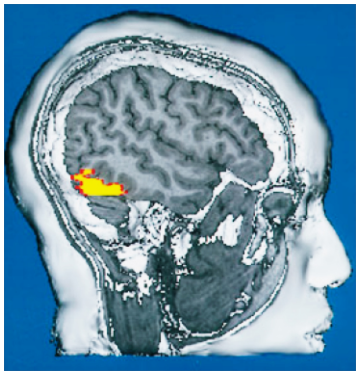
Commonly used neuroimaging technologies

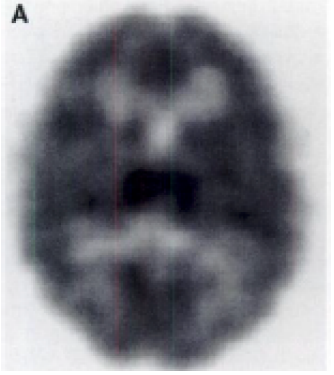
- Electromagnetic (EEG, MEG)
  - Data collection very fast – msecs or less per single sample
  - Excellent temporal resolution
  - Spatial resolution depends in part on source location (depth) and orientation relative to sensors



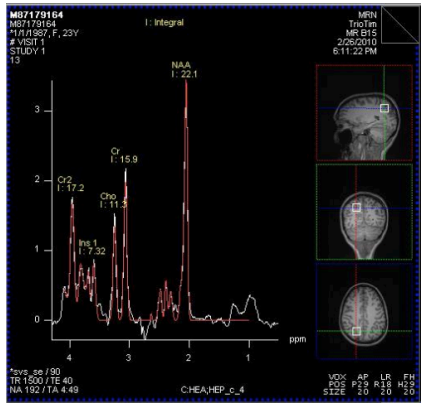


- Hemodynamic (fMRI, PET, SPECT, NIRS)
  - Data collection speed: NIRS msecs, fMRI and ASL secs
  - Sensitive to blood volume, oxygenation, and/or flow (slow processes)
  - Spatial resolution limited by methods, trade-off between time and volume



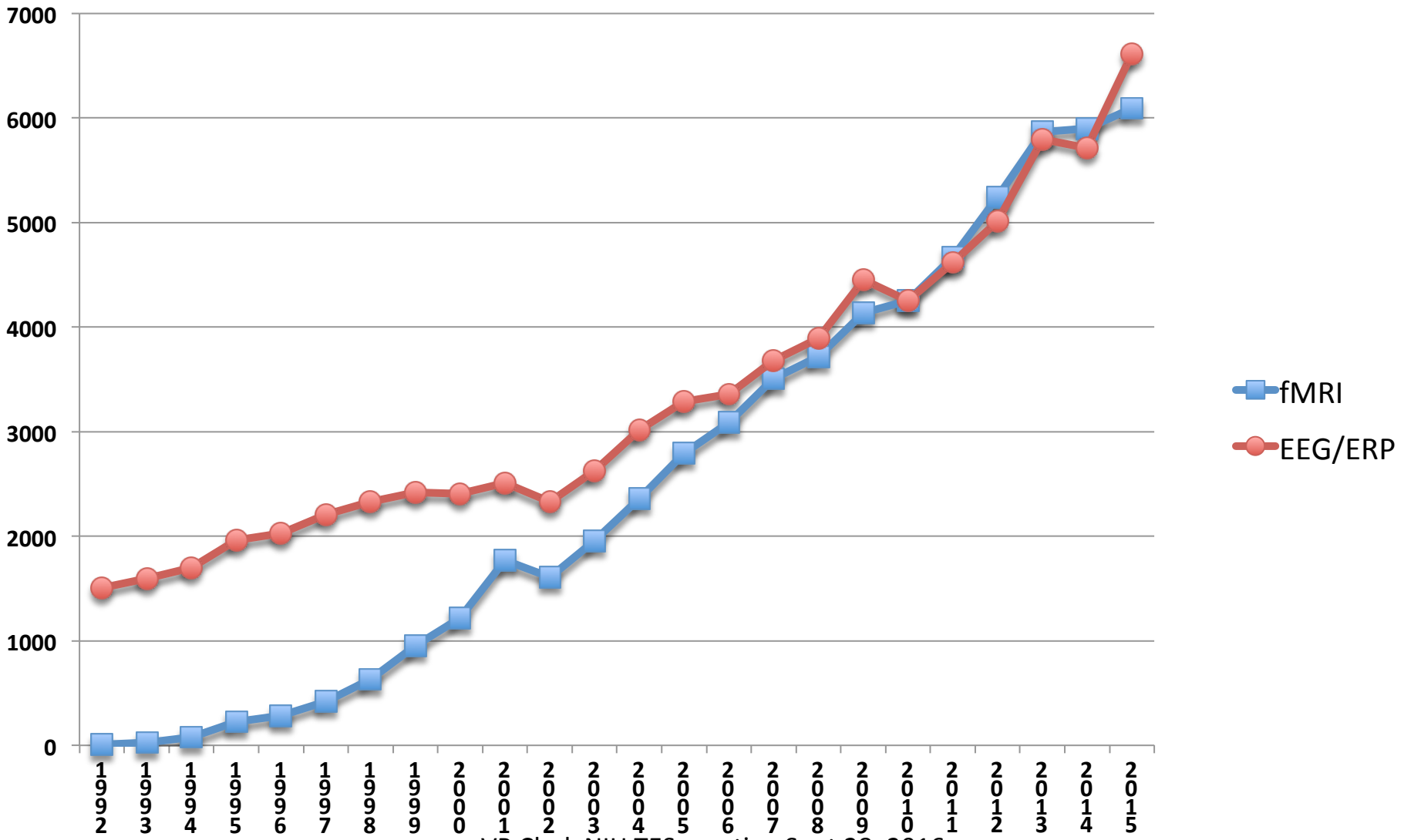


- Chemo (PET, SPECT, MRS)
  - Data collection takes minutes/hours per sample
  - Spatial resolution limited by methods, trade-offs between time and resolution, and depends on what isotope is used(PET, SPECT)

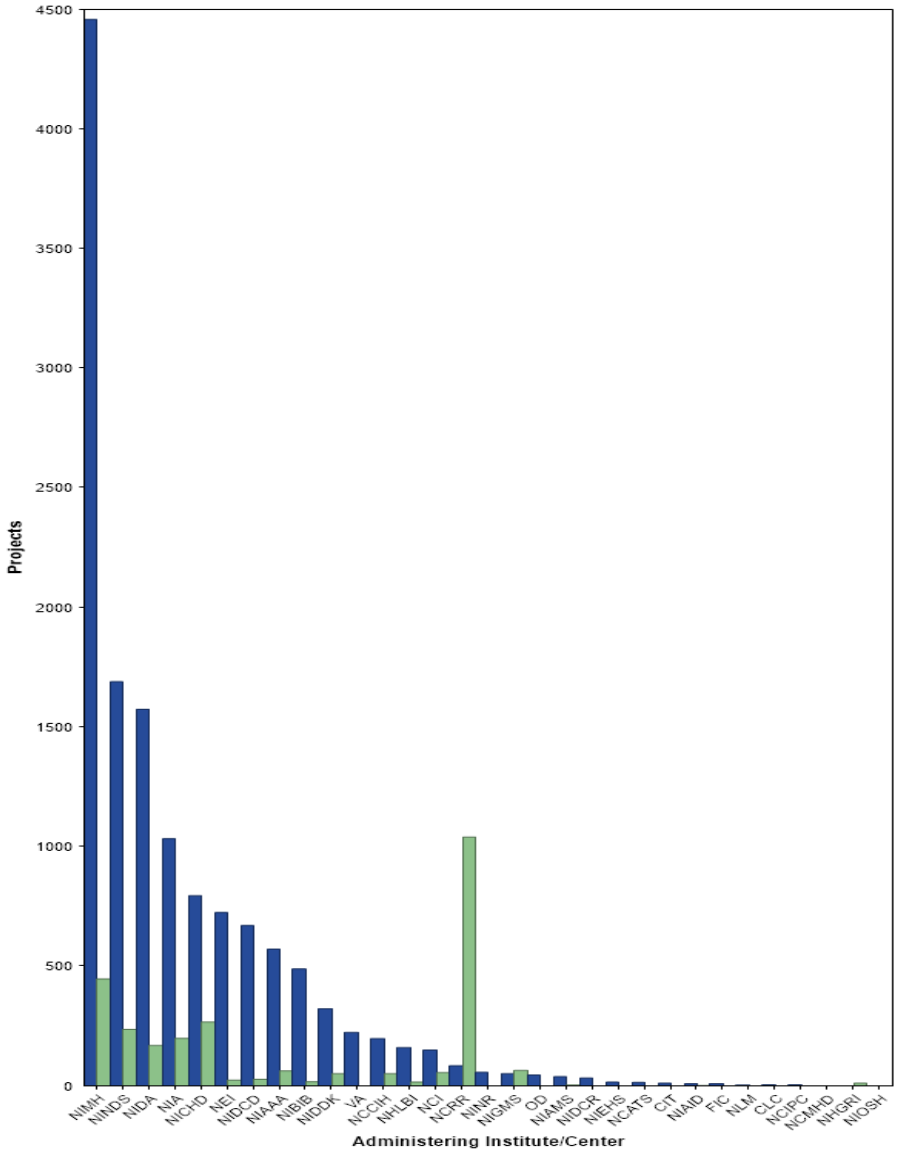


Neuroimaging has produced a tremendous volume of information…

Number of publications per year mentioning fMRI or EEG/ERP, 1992-2015, from Web of Science



… has been expensive …



Number and cost of funded proposals mentioning "fMRI" funded through NIH, 2005-2016 (from NIH RePORTER)

- 14,233 projects and subprojects
  - **Total $6,152,143,137**

Projects in blue, subprojects in green

… has produced many important advances…

The human brain is intrinsically organized into dynamic, anticorrelated functional

Michael D. Fox*†, Abraham Z. Snyder*‡, Justin L. Vincent*, Maurizio Corbett and Marcus E. Raichle*‡§¶

Departments of *Radiology, §Neurology, ¶Anatomy and Neurobiology, and ‖Biomedical Engineerin

Contributed by Marcus E. Raichle, May 19, 2005

During performance of attention-demanding cognitive tasks, certain regions of the brain routinely increase activity, whereas others routinely decrease activity. In this study, we investigate the extent to which this task-related dichotomy is represented intrinsically in the resting human brain through examination of spontaneous fluctuations in the functional MRI blood oxygen level-dependent signal. We identify two diametrically opposed, widely distributed brain networks on the basis of both spontaneous correlations within each network and anticorrelations between networks. One network consists of regions routinely exhibiting task-related activations and the other of regions routinely exhibiting task-related deactivations. This intrinsic organization, featuring the presence of anticorrelated networks in the absence of overt task performance, provides a critical context in which to understand brain function. We suggest that both task-driven neuronal responses and behavior are reflections of this dynamic, ongoing, functional organization of the brain.

functional MRI | functional connectivity | spontaneous activity

CONTROL OF GOAL-DIRECTED AND STIMULUS-DRIVEN ATTENTION IN THE BRAIN

Maurizio Corbetta and Gordon L. Shulman

We review evidence for partially segregated networks of brain areas that carry out different attentional functions. One system, which includes parts of the intraparietal cortex and superior frontal cortex, is involved in preparing and applying goal-directed (top-down) selection for stimuli and responses. This system is also modulated by the detection of stimuli. The other system, which includes the temporoparietal cortex and inferior frontal cortex, and is largely lateralized to the right hemisphere, is not involved in top-down selection. Instead, this system is specialized for the detection of behaviourally relevant stimuli, particularly when they are salient or unexpected. This ventral frontoparietal network works as a 'circuit breaker' for the dorsal system, directing attention to salient events. Both attentional systems interact during normal vision, and both are disrupted in unilateral spatial neglect.

individually for each subject, within which several new tests of face specificity were run. In each of five subjects tested, the predefined candidate "face area" also responded significantly more strongly to passive viewing of (1) intact than scrambled two-tone faces, (2) full front-view face photos than front-view photos of houses, and (in a different set of five subjects) (3) three-quarter-view face photos (with hair concealed) than photos of human hands; it also responded more strongly during (4) a consecutive matching task performed on three-quarter-view

interpretation of any study in which only two or three conditions are compared. Our data allow us to reject alternative accounts of the function of the fusiform face area (area "FF") that appeal to visual attention, subordinate-level classification, or general processing of any animate or human forms, demonstrating that this region is *selectively* involved in the perception of faces.

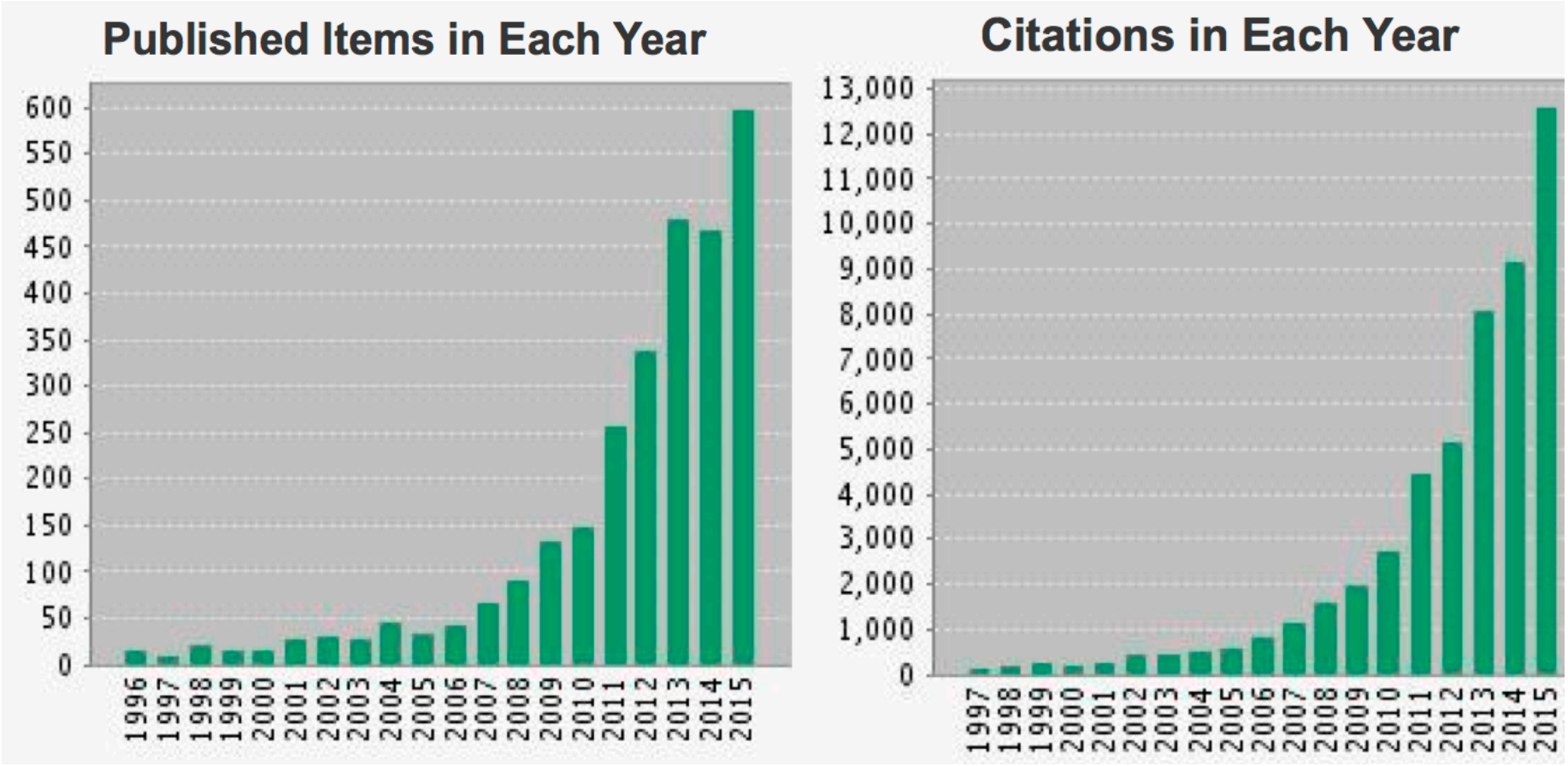
Key words: extrastriate cortex; face perception; functional MRI; fusiform gyrus; ventral visual pathway; object recognition

… but when used alone, is limited in its usefulness.

- Correlations found in neuroimaging can only be used to make inferences about causality
- Imaging has not provided much in the way of treatment benefits for community medicine, especially for mental health
- Stimulation provides new ways to apply information gained by neuroimaging

Brain stimulation today

tDCS, tES & brain polarization



http://apps.webofknowledge.com

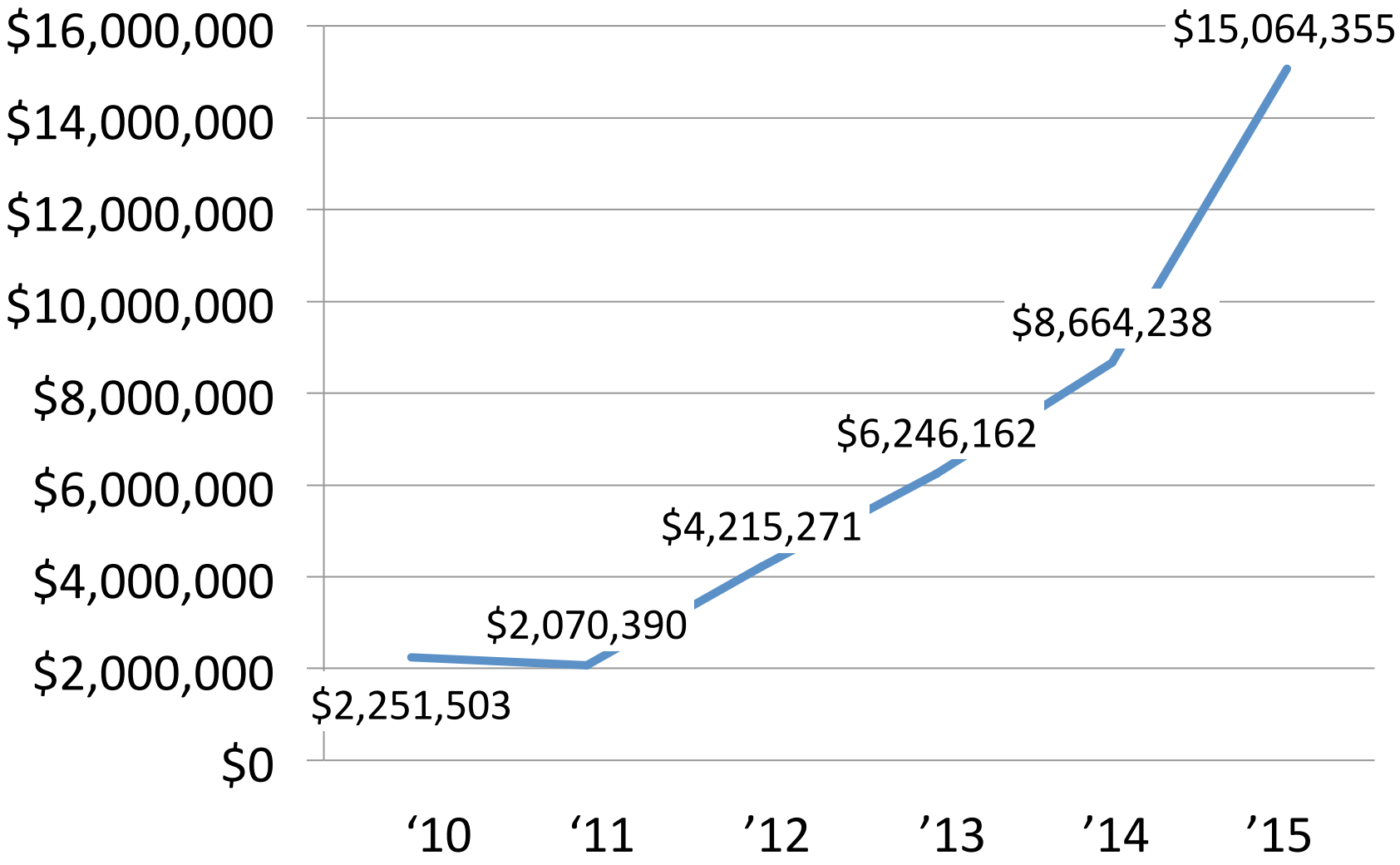
VP Clark NIH TES meeting Sept 28, 2016

Effect sizes for tDCS enhancement across studies + Increase, - Decrease (Avg. [Max])

- Working memory
  - d(+)=0.72 [+1.3], d(-)=-0.43 [-0.9]
- Explicit memory
  - d(+)=0.96 [+1.3] d(-)=-0.3 [-0.5]
- Implicit memory
  - d(+)=0.97 [+1.7] d(-)=-0.2 [-0.7]
- Perception
  - d(+)=1.28 [+1.6], d(-)=-0.84 [-2.0]
- Attention
  - d(+)=1.3 [+2.5], d(-)=-1.2 [-2.2]

Coffman, B.A., Clark, V.P., Parasuraman R. (2014). Battery powered thought: A review of methods for cognitive enhancement using transcranial direct current stimulation. *NeuroImage*, 85(3):895–908. doi:pii: S1053-8119(13)00855-0. 10.1016/j.neuroimage.2013.07.083.

NIH tDCS grant funding per year



From http://grantome.com

VP Clark NIH TES meeting Sept 28, 2016

There are two major questions regarding neurostimulation :

- Theory and mechanisms: **How does stimulation work?**
  - How does stimulation alter brain processes?
  - What does this tell us about natural brain function?
- Stimulation as a tool: **What are the most effective ways to apply stimulation …**
  - to verify hypotheses generated through neuroimaging?
  - to enhance cognition?
  - to suppress symptoms of brain and mental illness?
  - to delay, prevent or cure brain and mental illness?
- **Imaging can help answer both types of questions**
  - Need imaging to perfect stimulation techniques
    - Both to optimize effects and to understand mechanisms (to better optimize effects)
  - Identify physiological mechanisms that underlie the effects of tES
  - Identify short- and long-term effects at the molecular- and circuit-levels
  - Identify differences in brain effects of different protocols
    - Intensity, duration, electrode position, polarity etc.
  - Inform treatment development

Examples

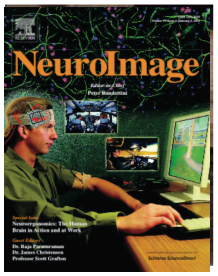
- Testing causal hypotheses derived from imaging data and optimizing stimulation parameters
  - fMRI: Clark et al. 2012
  - EEG: Elbert et al. 1981
- Developing individualized protocols
  - Ulm et al. 2015
  - Datta et al. 2012
- Mapping E-fields *in-vivo*
  - Antal et al. 2012
- Identify brain effects of tDCS protocols
  - Thoma pilot replication of Brunelin et al. 2012

NeuroImage 59 (2012) 117–128

Contents lists available at ScienceDirect

NeuroImage

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



TDCS guided using fMRI significantly accelerates learning to identify concealed objects

Vincent P. Clark [a,b,*], Brian A. Coffman [a,b], Andy R. Mayer [a], Michael P. Weisend [a], Terran D.R. Lane [c], Vince D. Calhoun [a,c,d], Elaine M. Raybourn [e], Christopher M. Garcia [a,b], Eric M. Wassermann [f]

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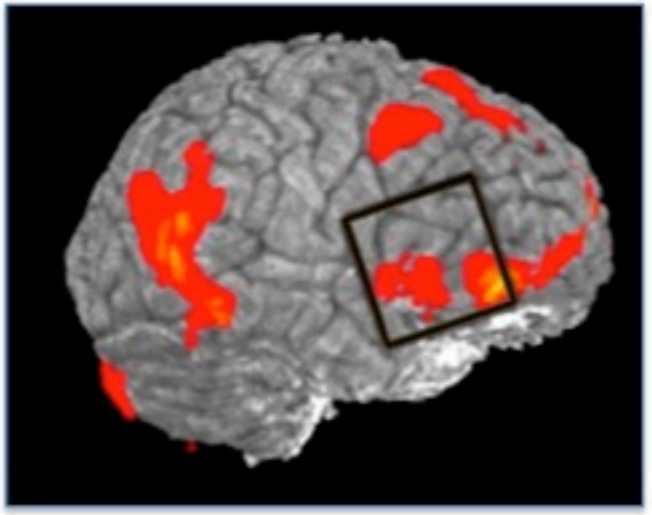
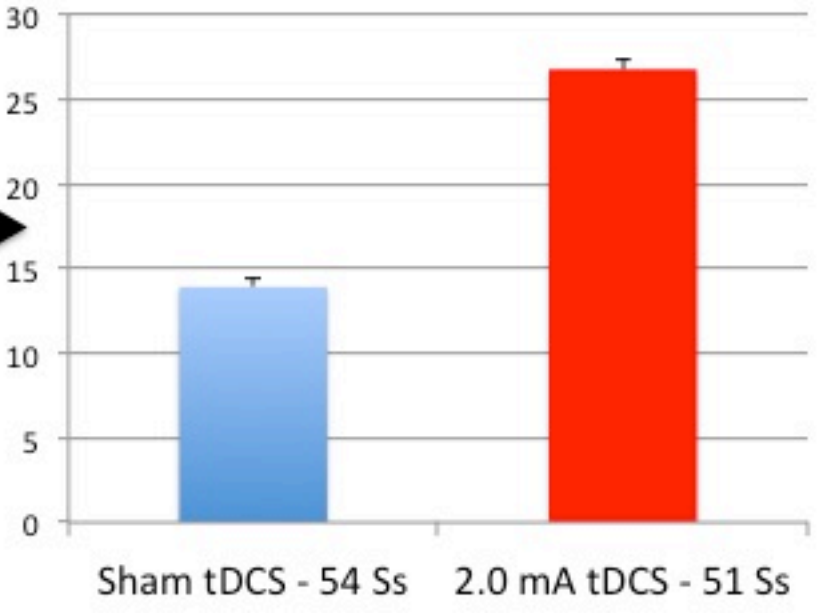
[b] Department of Psychology, University of New Mexico, Albuquerque, NM 87131, USA
[c] Department of Computer Science, University of New Mexico, Albuquerque, NM 87131, USA
[d] Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM 87131, USA
[e] Sandia National Laboratories, Albuquerque, NM 87123, USA
[f] National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA

Summary



Clark et al. *NeuroImage* 2012



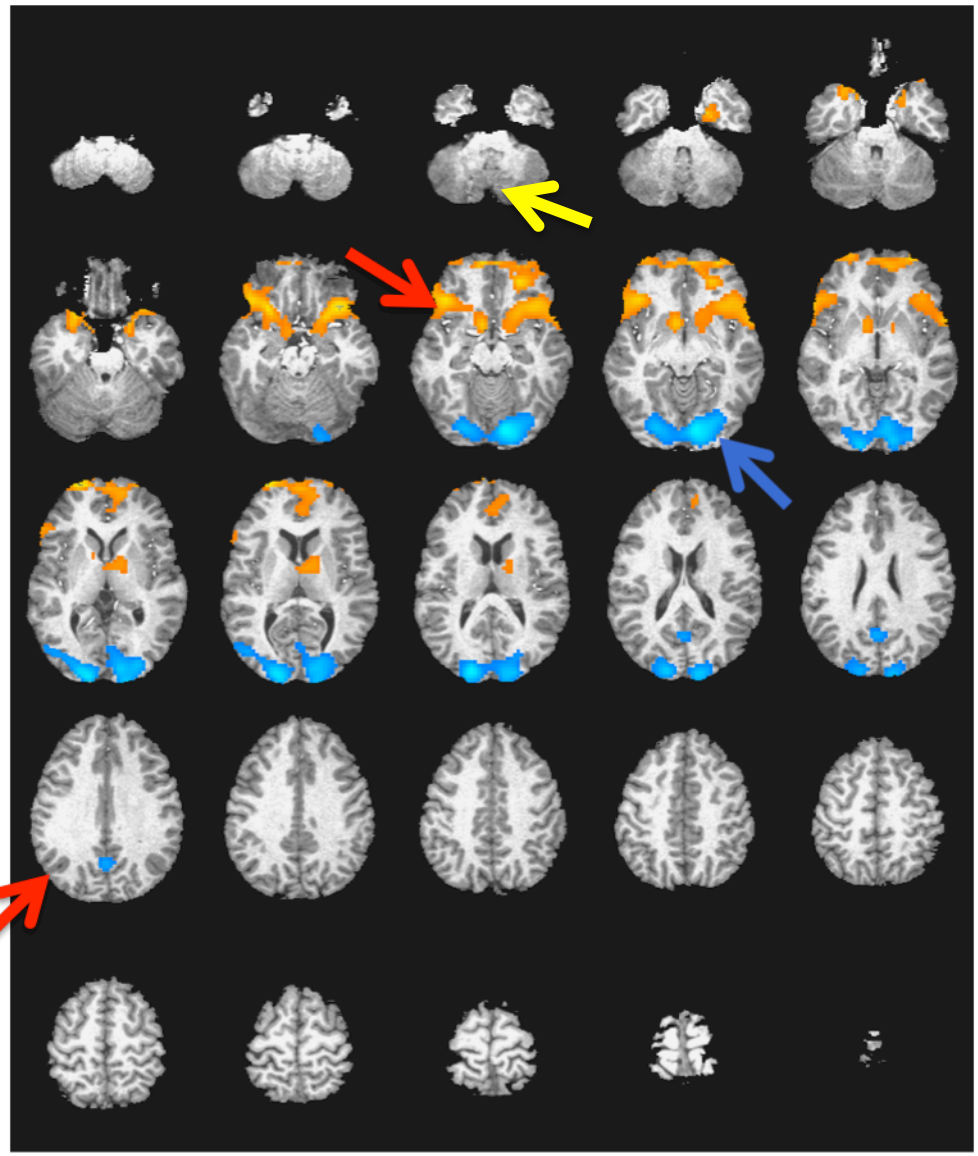
Clark, VP et al. (2012) TDCS guided using fMRI significantly accelerates learning to identify concealed objects. *NeuroImage* 59:117-128.

fMRI data predicts tDCS placements that enhance learning

Neither

Anode

Cathode



Clark, VP et al. (2012) TDCS guided using fMRI significantly accelerates learning to identify concealed objects. *NeuroImage* 59:117-128.

Clark, VP et al. (2013). An evolutionary perspective on attentional processes. pp. 207–215. In: G.R. Mangun (Ed.) Cognitive Electrophysiology of Attention. Elsevier.

Falcone, B et al. (2012). Transcranial direct current stimulation augments perceptual sensitivity and 24-hour retention in a complex threat detection task. PLoS ONE, 7(4): e34993.

Coffman, BA et al. Impact of tDCS on performance and learning of target detection: Interaction with stimulus characteristics and experimental design. Neuropsychologia, 50(7):1594-1602.

Coffman, BA et al. (2012). Enhancement of object detection with transcranial direct current stimulation is associated with increased attention. BMC Neuroscience, 13:108.

A replication of this tDCS effect at another institution

Transcranial Direct Current Stimulation Augments Perceptual Sensitivity and 24-Hour Retention in a Complex Threat Detection Task

Brian Falcone[1], Brian A. Coffman[2], Vincent P. Clark[2], Raja Parasuraman[1]*

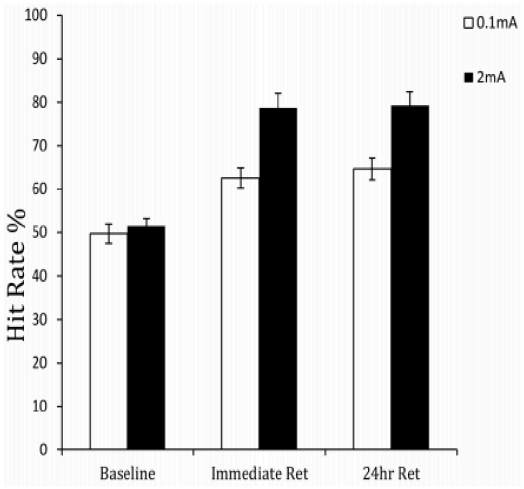
1 Center of Excellence in Neuroergonomics, Technology, and Cognition (CENTEC), George Mason University, Fairfax, Virginia, United States of America, **2** The Mind Research Network and Lovelace Biomedical and Environmental Research Institute, University of New Mexico, Albuquerque, New Mexico, United States of America

Abstract

We have previously shown that transcranial direct current stimulation (tDCS) improved performance of a complex visual perceptual learning task (Clark et al. 2012). However, it is not known whether tDCS can enhance perceptual sensitivity independently of non-specific, arousal-linked changes in response bias, nor whether any such sensitivity benefit can be retained over time. We examined the influence of stimulation of the right inferior frontal cortex using tDCS on perceptual learning and retention in 37 healthy participants, using signal detection theory to distinguish effects on perceptual sensitivity (d') from response bias ($ß$). Anodal stimulation with 2 mA increased d', compared to a 0.1 mA sham stimulation control, with no effect on $ß$. On completion of training, participants in the active stimulation group had more than double the perceptual sensitivity of the control group. Furthermore, the performance enhancement was maintained for 24 hours. The results show that tDCS augments both skill acquisition and retention in a complex detection task and that the benefits are rooted in an improvement in sensitivity (d'), rather than changes in response bias ($ß$). Stimulation-driven acceleration of learning and its retention over 24 hours may result from increased activation of prefrontal cortical regions that provide top-down attentional control signals to object recognition areas.

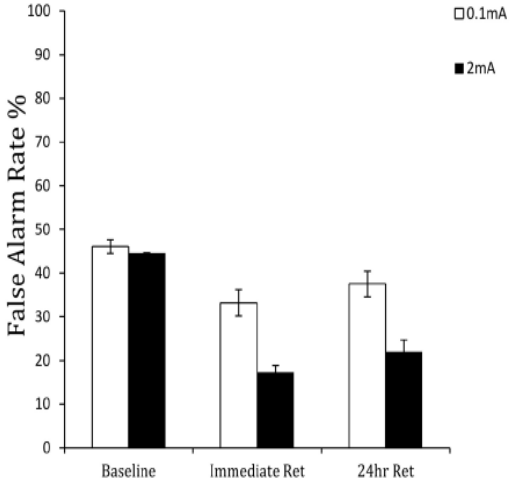
Citation: Falcone B, Coffman BA, Clark VP, Parasuraman R (2012) Transcranial Direct Current Stimulation Augments Perceptual Sensitivity and 24-Hour Retention in a Complex Threat Detection Task. PLoS ONE 7(4): e34993. doi:10.1371/journal.pone.0034993

Hit Rate



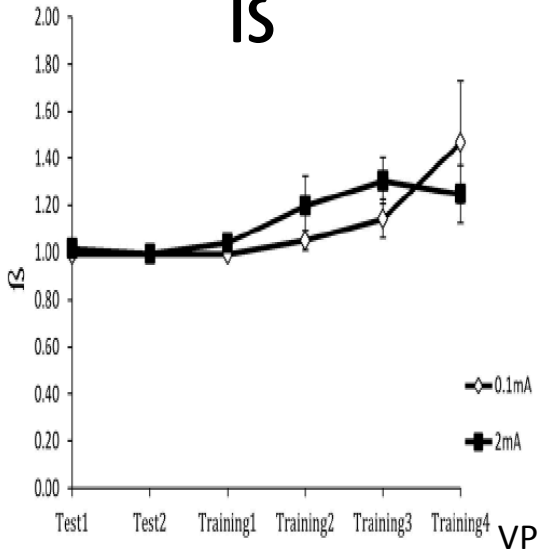
F(1,35) = 14.584, p < 0.001

False Alarms



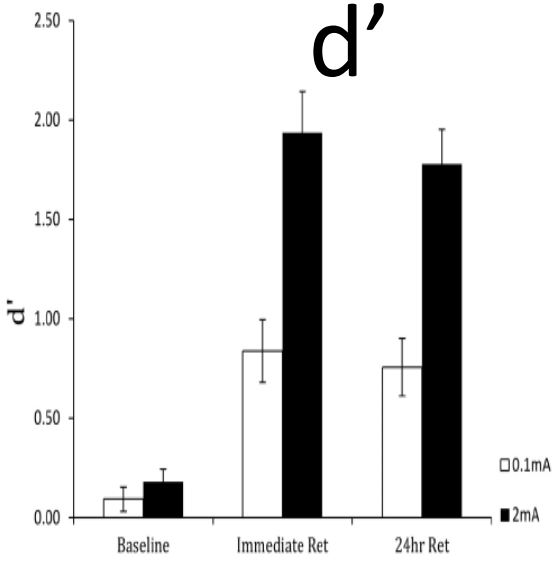
F(1,35) = 7.050, p < 0.05

ß



F(1,35) = 0.133, n.s.

d’



F(1,35)=12.676, p < 0.001

By contrast to Horvath et al. (2015), tDCS **DOES** generate a reliable effect on cognition

Brain Stimulation 8 (2015) 535–550

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS)

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Keywords:
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Quantitative review
Executive function
Language
Memory
Working memory

ABSTRACT

Background: Over the last 15-years, transcranial direct current stimulation (tDCS), a relatively novel form of neuromodulation, has seen a surge of popularity in both clinical and academic settings. Despite numerous claims suggesting that a single session of tDCS can modulate cognition in healthy adult populations (especially working memory and language production), the paradigms utilized and results reported in the literature are extremely variable. To address this, we conduct the largest quantitative review of the cognitive data to date.

Methods: Single-session tDCS data in healthy adults (18–50) from every cognitive outcome measure reported by at least two different research groups in the literature was collected. Outcome measures were divided into 4 broad categories: executive function, language, memory, and miscellaneous. To account for the paradigmatic variability in the literature, we undertook a three-tier analysis system; each with less-stringent inclusion criteria than the prior. Standard mean difference values with 95% CIs were generated for included studies and pooled for each analysis.

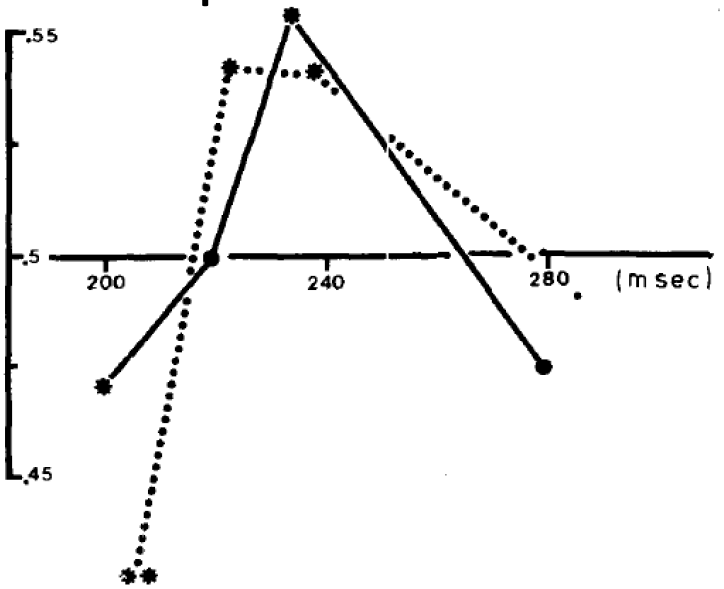
Results: Of the 59 analyses conducted, tDCS was found to not have a significant effect on any – regardless of inclusion laxity. This includes no effect on any working memory outcome or language production task.

Conclusion: Our quantitative review does not support the idea that tDCS generates a reliable effect on cognition in healthy adults. Reasons for and limitations of this finding are discussed. This work raises important questions regarding the efficacy of tDCS, state-dependency effects, and future directions for this tool in cognitive research.

One of the first modern tDCS experiments was based on ERPs

Thomas Elbert with Niels Birbaumer, 1981

- Applied 0.3 mA (Cz vs. ear)
- Speeded reaction times in a simple RT task



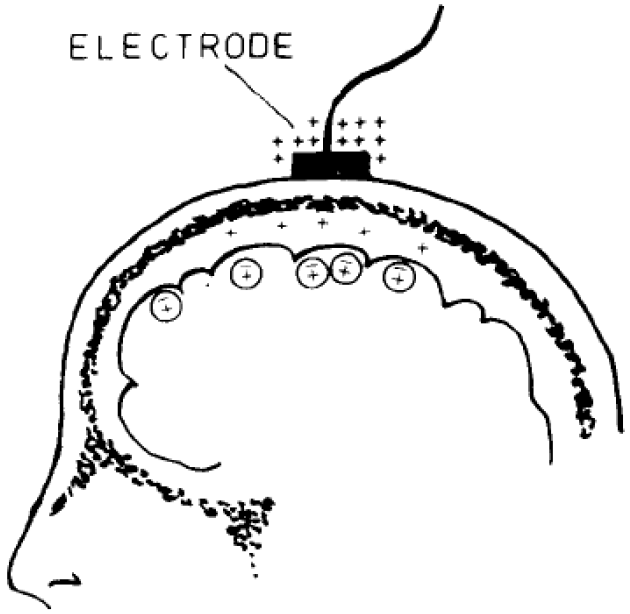
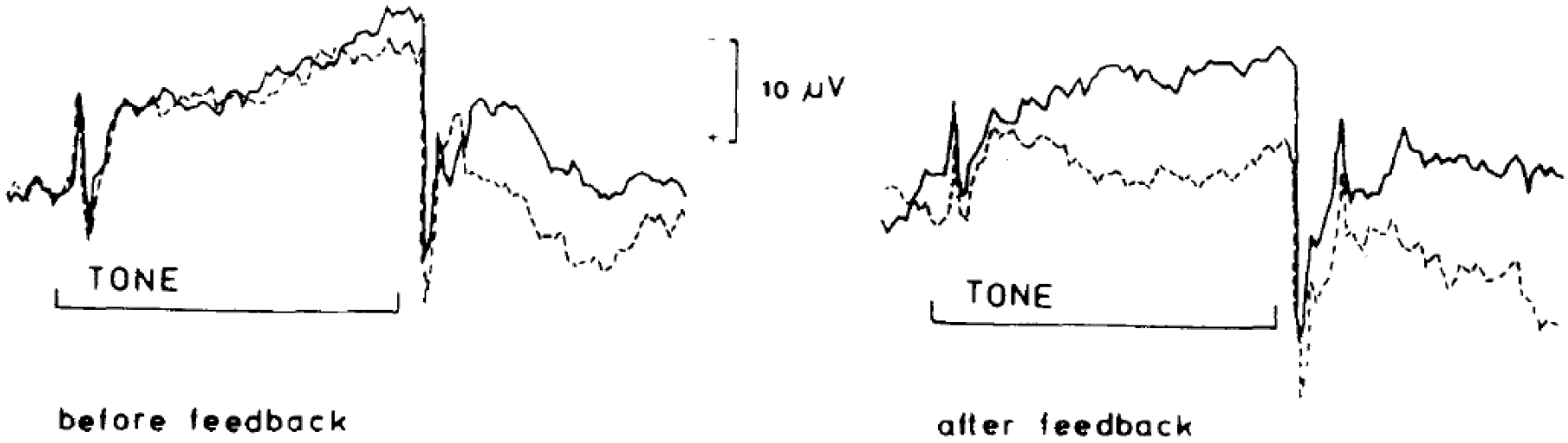


FIGURE 2 Charge carriers flow from a vertex electrode through the head. The dipoles induced by a positively charged vertex electrode have the negative pole directed upwards. Therefore a positive vertex electrode favours a brain polarization corresponding to an internally generated negative cortical shift.

Elbert et al., (1981) The influence of low-level transcortical DC-currents on response speed in humans. *Intern. J. Neuroscience,* 14:101-114.

The CNV can be modulated with neurofeedback



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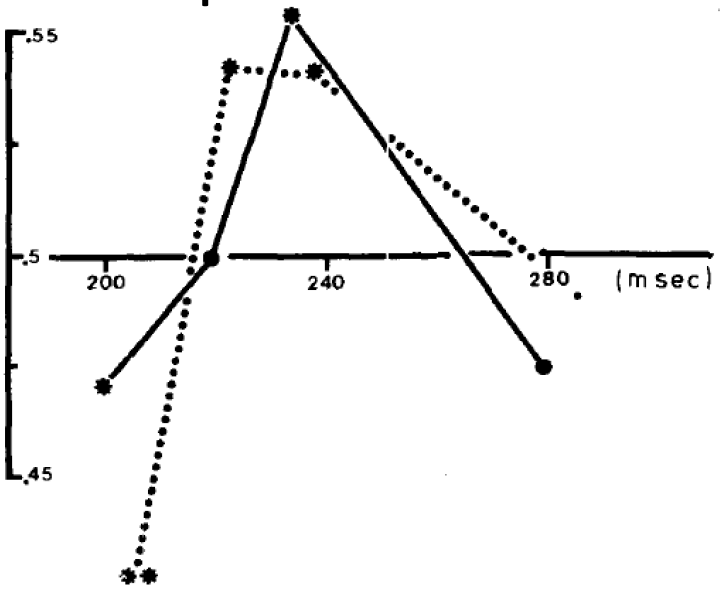

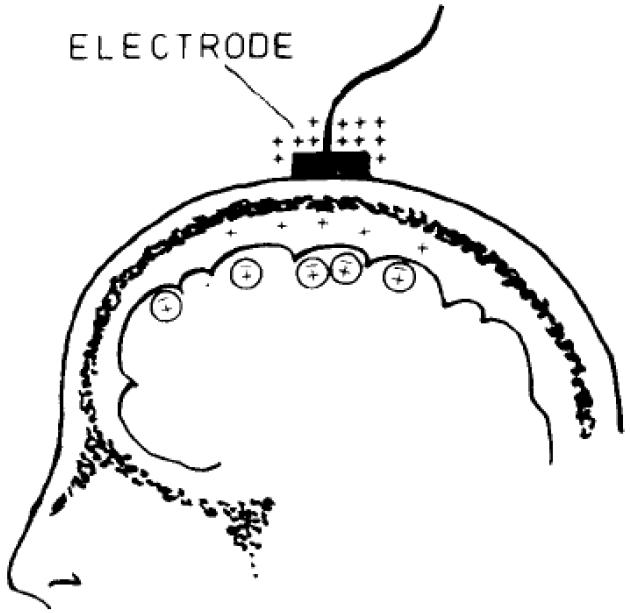

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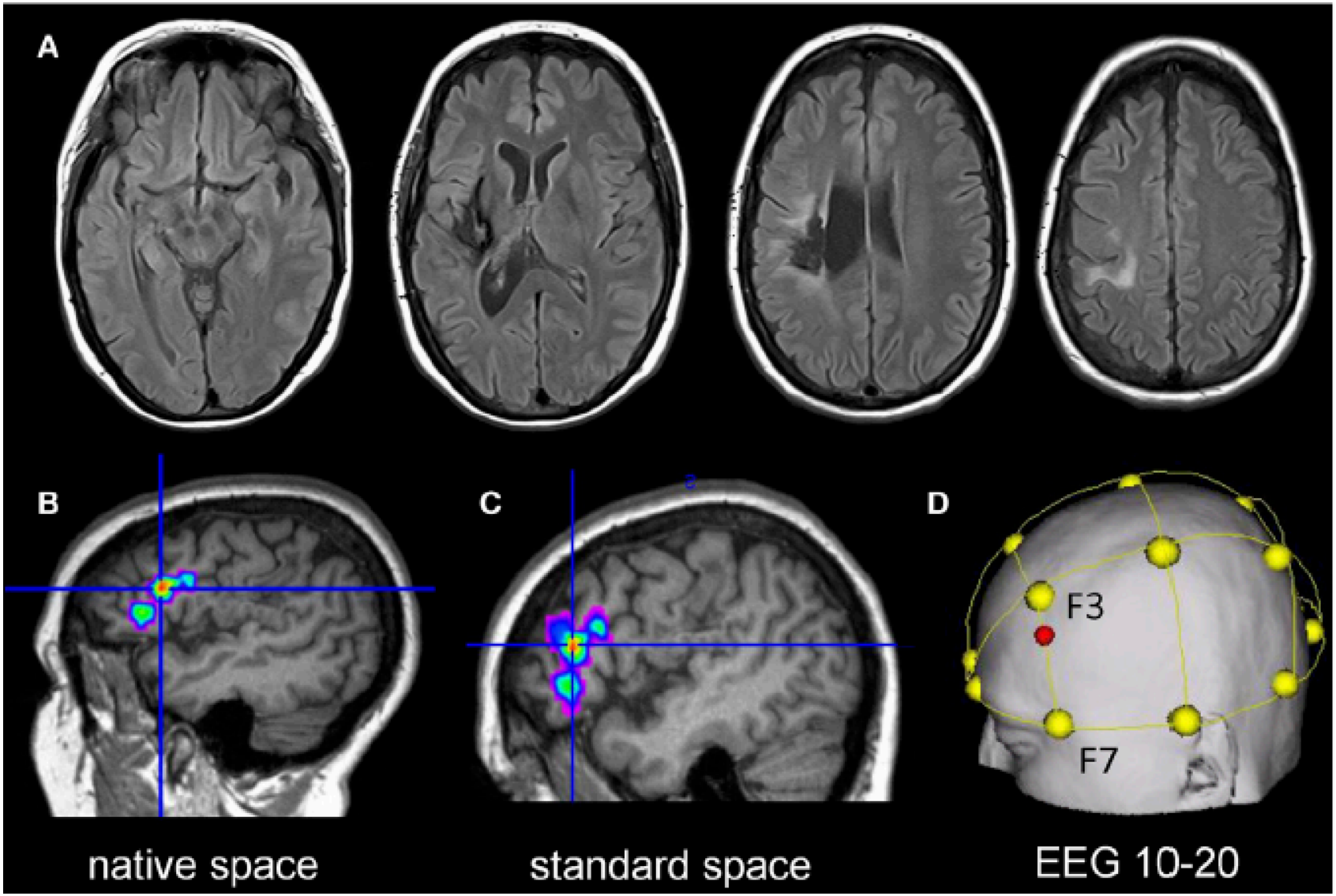
Using neuroimaging to perform individualized stimulation

- Ulm, L. et al. (2015) *Front. Hum. Neurosci.* 9:550 explored effects of tDCS in aphasia during simultaneous fMRI
  - Single subject, cross-over, sham-tDCS controlled design
- Performed picture naming task with fMRI
- Peak fMRI activity was located in the spared left inferior frontal gyrus
  - This area was stimulated with anodal tDCS
  - tDCS increased activity at the stimulation site
- Demonstrated feasibility of targeting an individualized stimulation site in aphasia patients during simultaneous fMRI
- Similar methods may yield information about the variability of tDCS effects on brain function

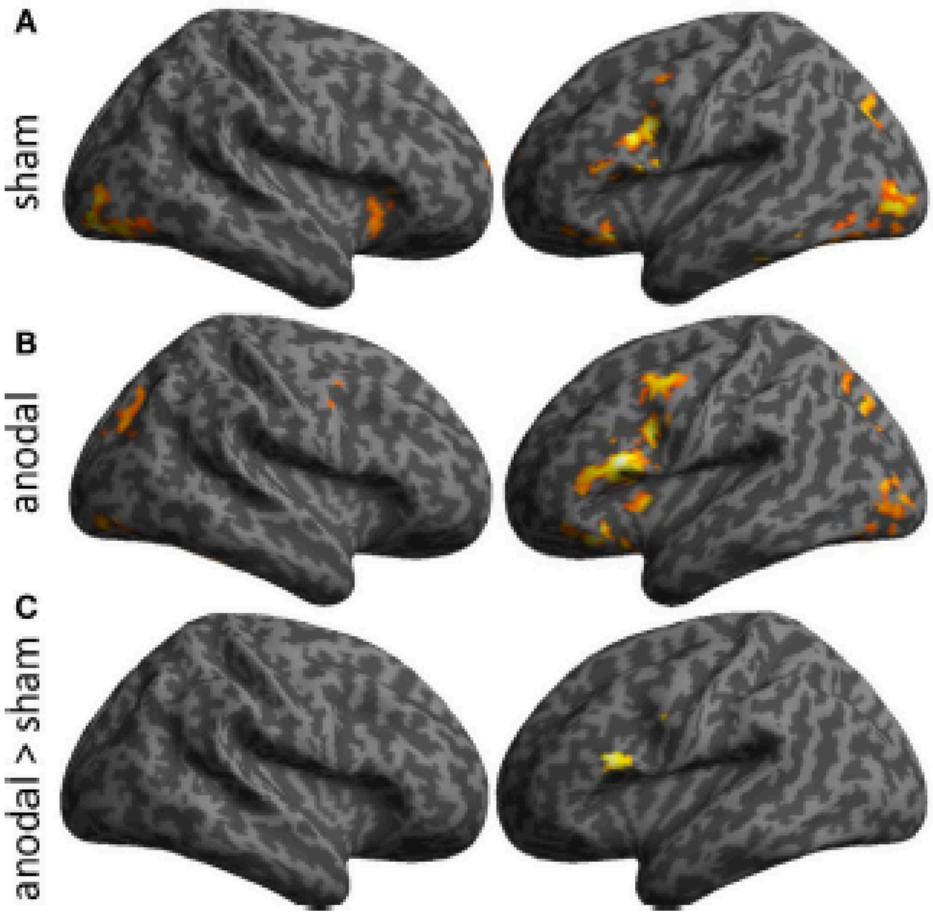
Ulm, L. et al. (2015) Neural mechanisms underlying perilesional transcranial direct current stimulation in aphasia: A feasibility study. *Front. Hum. Neurosci.* 9:550.

Structural lesion, fMRI results and electrode placement



Ulm, L. et al. (2015) Neural mechanisms underlying perilesional transcranial direct current stimulation in aphasia: A feasibility study. *Front. Hum. Neurosci.* 9:550.

Effects of tDCS on fMRI response



Ulm, L. et al. (2015) Neural mechanisms underlying perilesional transcranial direct current stimulation in aphasia: A feasibility study. *Front. Hum. Neurosci.* 9:550.

Using sMRI to model current flow

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 22 October 2012
doi: 10.3389/fpsyt.2012.00091

Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models

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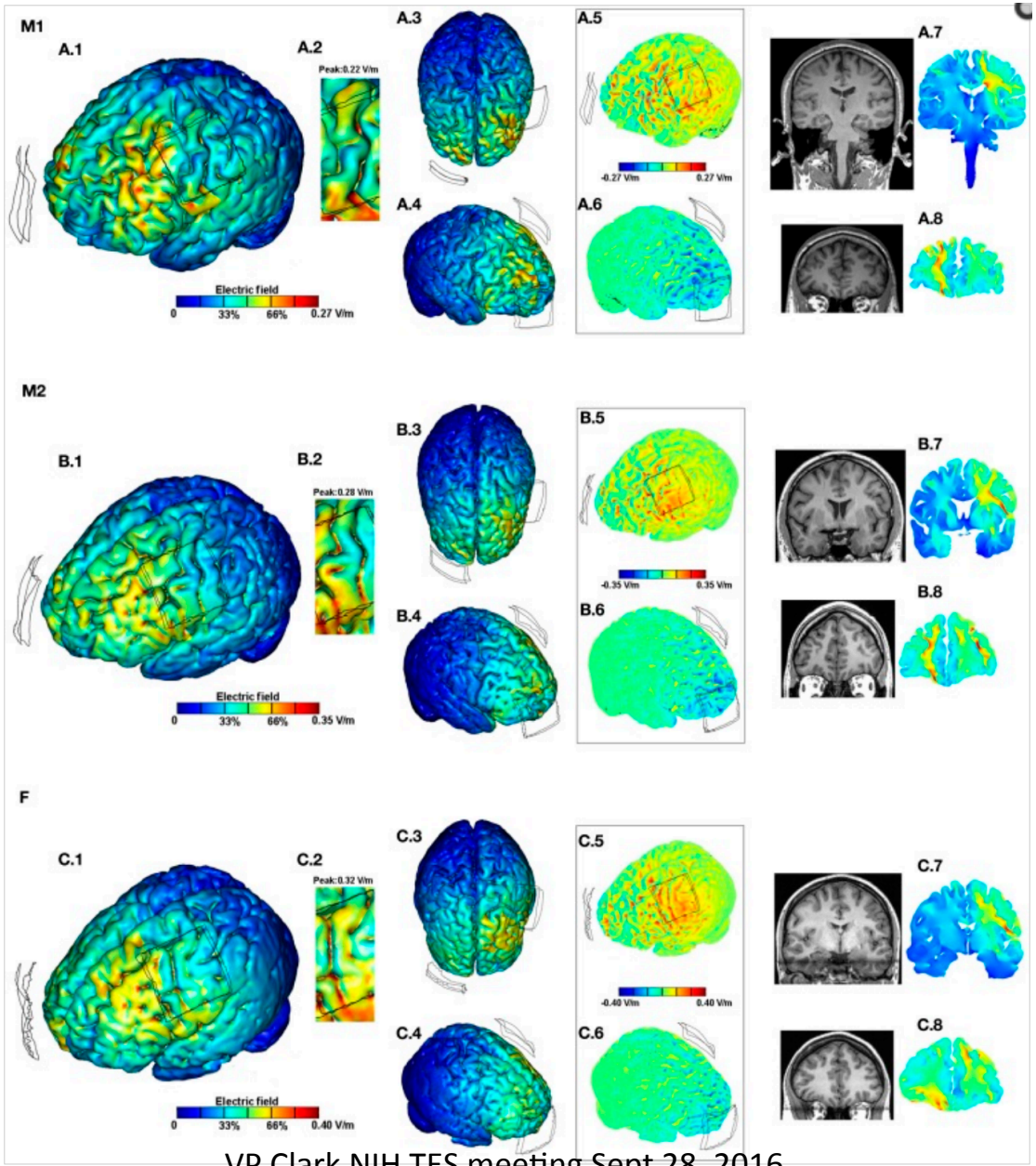
Background: Transcranial Direct Current Stimulation (tDCS) is a non-invasive, versatile, and safe neuromodulation technology under investigation for the treatment of neuropsychiatric disorders, adjunct to rehabilitation, and cognitive enhancement in healthy adults. Despite promising results, there is variability in responsiveness. One potential source of variability is the intensity of current delivered to the brain which is a function of both the operator controlled tDCS dose (electrode montage and total applied current) and subject specific anatomy. We are interested in both the scale of this variability across anatomical typical adults and methods to normalize inter-individual variation by customizing tDCS dose. Computational FEM simulations are a standard technique to predict brain current flow during tDCS and can be based on subject specific anatomical MRI. **Objective:** To investigate this variability, we modeled multiple tDCS montages across three adults (ages 34–41, one female). **Results:** Conventional pad stimulation led to diffuse modulation with maximum current flow between the pads across all subjects. There was high current flow directly under the pad for one subject while the location of peak induced cortical current flow was variable. The High-Definition tDCS montage led to current flow restricted to within the ring perimeter across all subjects. The current flow profile across all subjects and montages was influenced by details in cortical gyri/sulci. **Conclusion:** This data suggests that subject specific modeling can facilitate consistent and more efficacious tDCS.

Keywords: tDCS, head model, HD-tDCS, TMS, tACS, transcranial electrical stimulation

Comparing models from 3 subjects



Imaging might be used to track current flow *in-vivo*

Imaging artifacts induced by electrical stimulation during conventional fMRI of the brain

Andrea Antal [a,*], Marom Bikson [b], Abhishek Datta [b], Belen Lafon [b], Peter Dechent [c], Lucas C. Parra [b,1], Walter Paulus [a,1]

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ARTICLE INFO

Available online xxxx

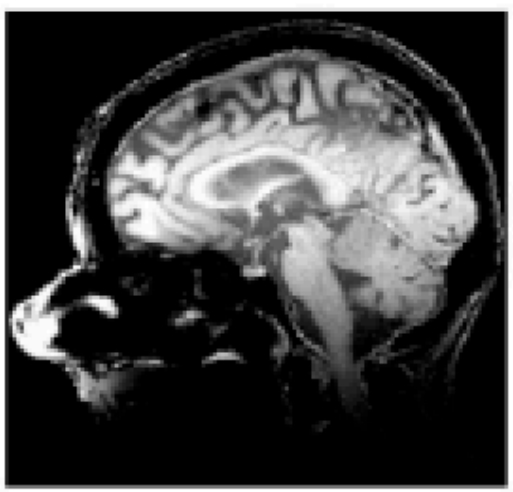
Keywords:
fMRI
Post-mortem
Brain
tDCS
tACS
Modeling

ABSTRACT

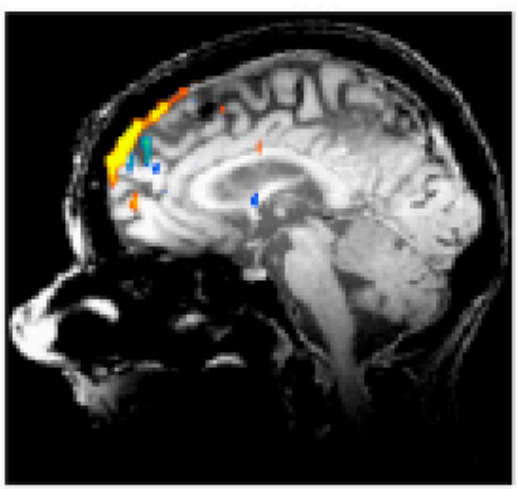
Functional magnetic resonance imaging (fMRI) of brain activation during transcranial electrical stimulation is used to provide insight into the mechanisms of neuromodulation and targeting of particular brain structures. However, the passage of current through the body may interfere with the concurrent detection of blood oxygen level-dependent (BOLD) signal, which is sensitive to local magnetic fields. To test whether these currents can affect concurrent fMRI recordings we performed conventional gradient echo-planar imaging (EPI) during transcranial direct current (tDCS) and alternating current stimulation (tACS) on two post-mortem subjects. tDCS induced signals in both superficial and deep structures. The signal was specific to the electrode montage, with the strongest signal near cerebrospinal fluid (CSF) and scalp. The direction of change relative to non-stimulation reversed with tDCS stimulation polarity. For tACS there was no net effect of the MRI signal. High-resolution individualized modeling of current flow and induced static magnetic fields suggested a strong coincidence of the change EPI signal with regions of large current density and magnetic fields. These initial results indicate that (1) fMRI studies of tDCS must consider this potentially confounding interference from current flow and (2) conventional MRI imaging protocols can be potentially used to measure current flow during transcranial electrical stimulation. The optimization of current measurement and artifact correction techniques, including consideration of the underlying physics, remains to be addressed.

Antal et al. (2014) Imaging artifacts induced by electrical stimulation during conventional fMRI of the brain. *NeuroImage* 85(3):1040-1047.

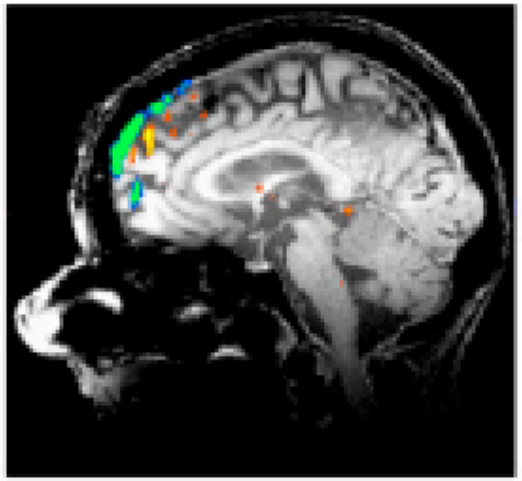
Anodal vs. cathodal current



M1-AC



M1-ANODAL

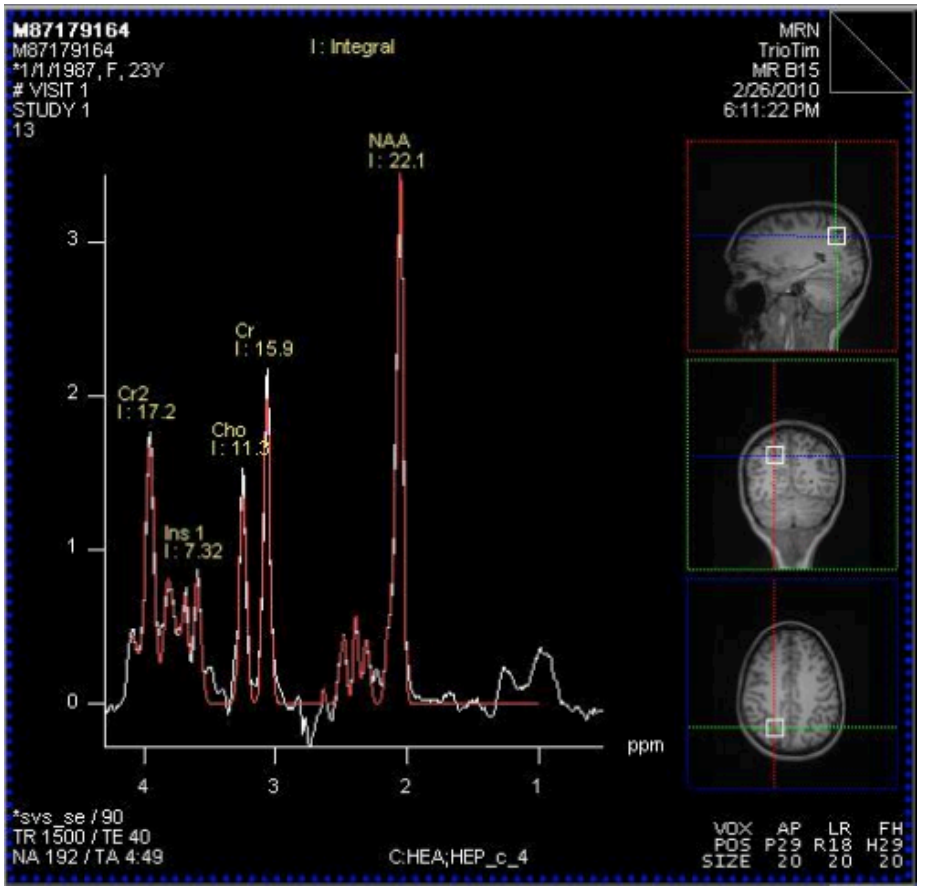


M1-CATHODAL

Antal et al. (2014) Imaging artifacts induced by electrical stimulation during conventional fMRI of the brain. *NeuroImage* 85(3):1040-1047.

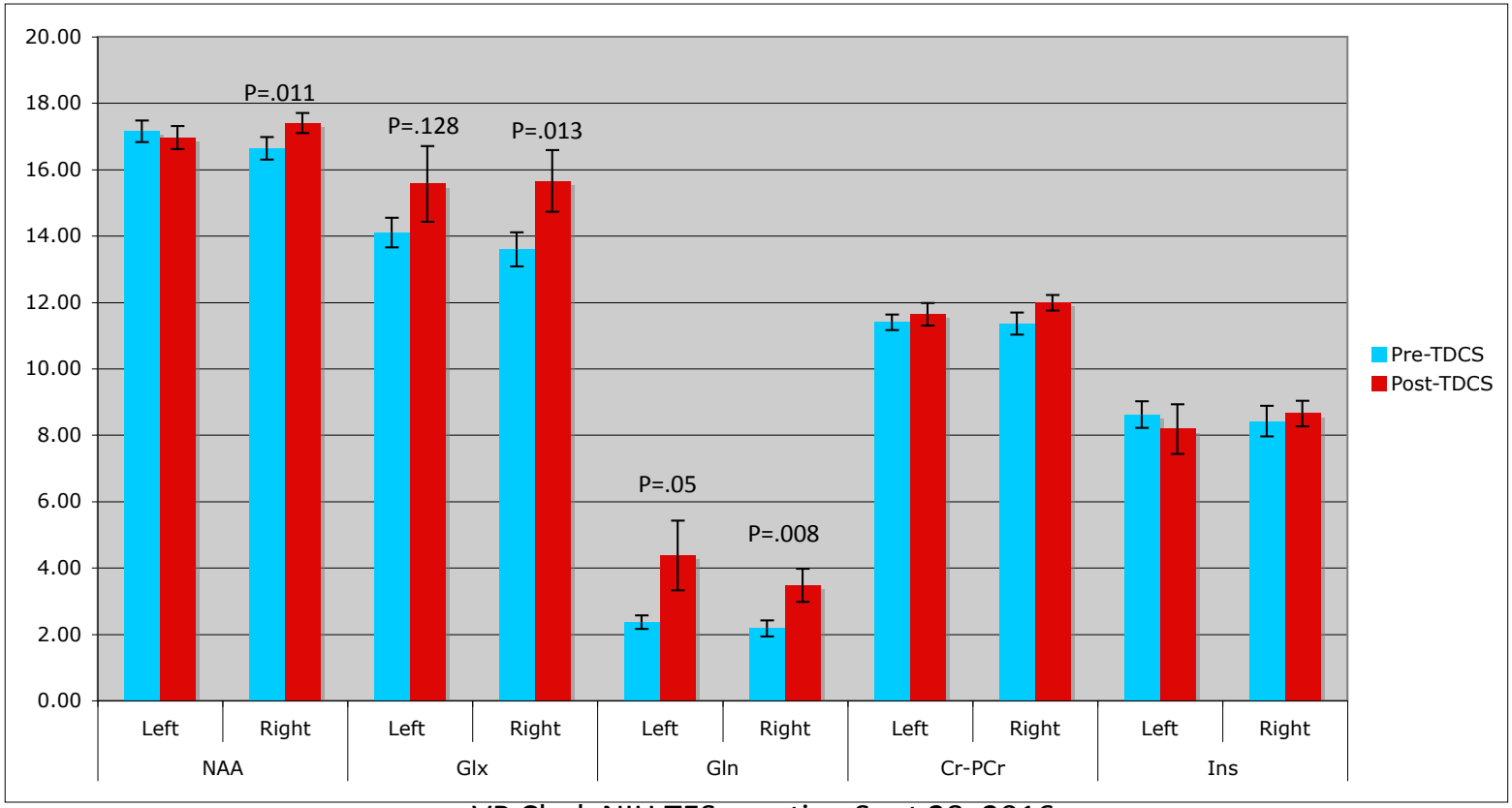
What are the neurochemical effects of tDCS?

- Tesla Siemens Trio MRI, tested before and after tDCS
- 2 single voxel 1H-MRS acquisitions, centered on the parietal sulcus of each hemisphere
- PRESS with and without water suppression; TR/TE=1.5s/40ms; 8 cm^3
- 30 minutes of 2.0 mA anodal tDCS over P4, cathode placed on the upper left arm.



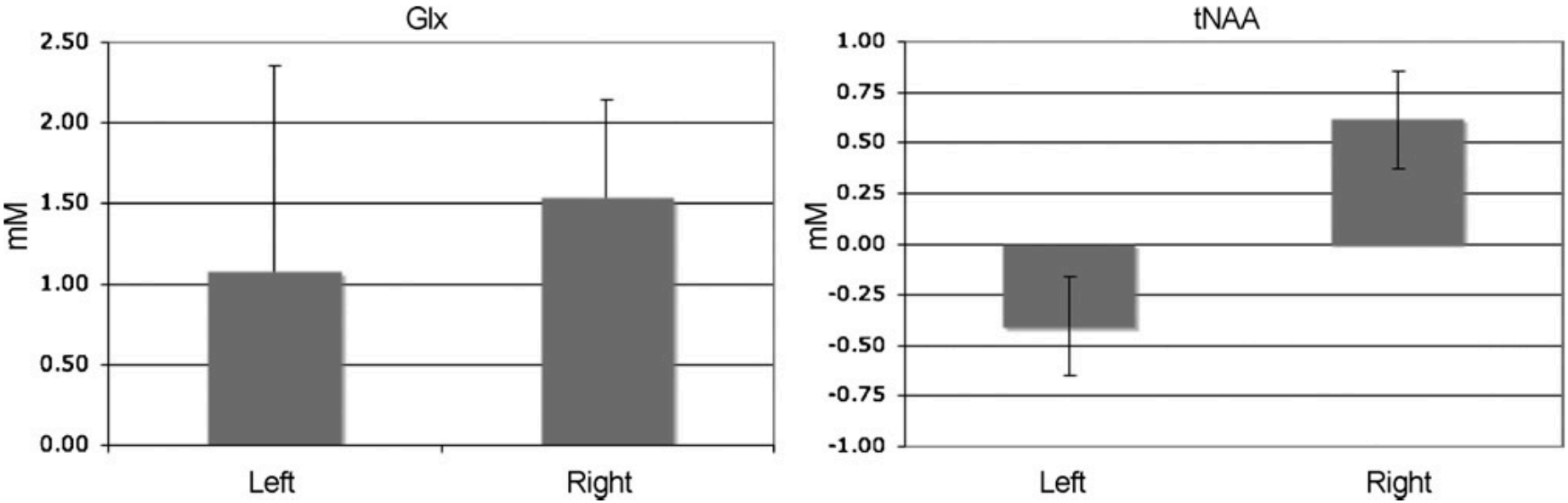
tDCS increases Glu/Gln and NAA

- Combined glutamine and glutamate (Glx) concentration
  - Glx significantly higher in the right voxel after tDCS (15.7 mM) relative to before 13.6 mM
    - t=2.87, p=0.01, not contralateral hemisphere (t=1.61, N.S.)
- Combined N-acetylaspartate and N-acetylaspartylglutamate (tNAA) concentrations
  - Higher in right parietal cortex (17.4 mM vs. before 16.64 mM, t=2.91, p=0.011)
  - Not in left parietal cortex (t=1.12, N.S.).
- No significant changes in creatine or inositol
- Results not confounded by gray matter fraction



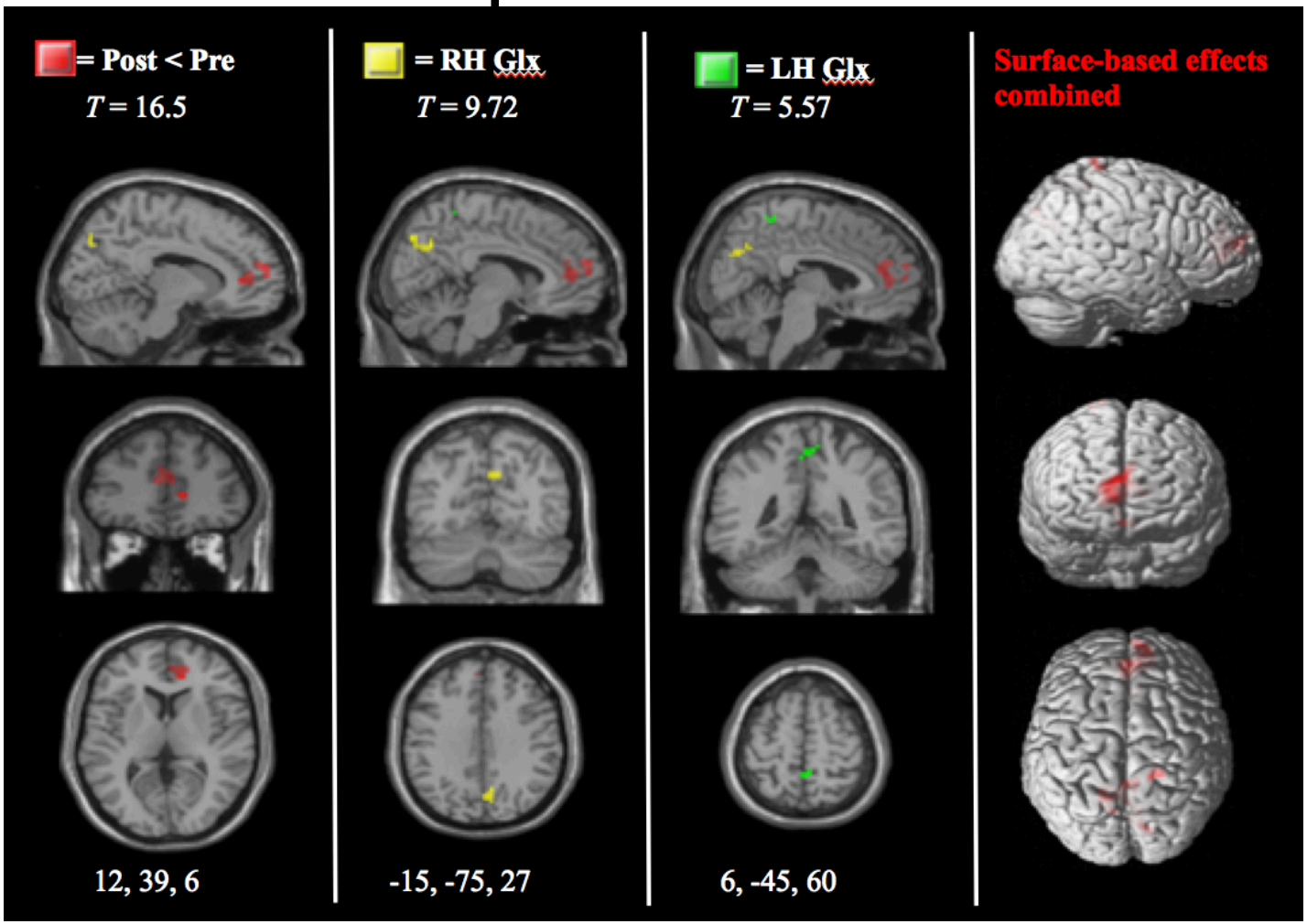
Changes in combined Glutamate & Glutamine (Glx) and tNAA with tDCS

V.P. Clark et al. / Neuroscience Letters 500 (2011) 67–71



- MRS study of brain metabolites in response to tDCS over right parietal cortex
- Significant increase in Glx ($F_{(1,6)} = 9.40$, $p = 0.022$) and tNAA ($F_{(1,6)} = 9.24$, $p = 0.023$) under electrode, but not in opposite hemisphere
- Significant interaction between right and left hemispheres for tNAA ($F_{(1,6)} = 9.673$, $p = 0.020$)
- **Increased glutamatergic activity (Glx) and increased metabolism (tNAA) together suggest that tDCS may lead to increased plasticity.**

Functional network connectivity correlates with post-tDCS Glx



Hunter, M.A., Coffman, B.A., Gasparovic, C., Calhoun, V.D., Trumbo, M.C., Clark, V.P. (2015). Baseline effects of transcranial direct current stimulation on glutamatergic neurotransmission and large-scale network connectivity. *Brain Research*, 1594:92-107.

Archival Report

Biological Psychiatry

Online Effects of Transcranial Direct Current Stimulation in Real Time on Human Prefrontal and Striatal Metabolites

Antoine Hone-Blanchet, Richard A. Edden, and Shirley Fecteau

ABSTRACT

BACKGROUND: Studies have reported that transcranial direct current stimulation (tDCS) can modulate human behaviors, symptoms, and neural activity; however, the neural effects during stimulation are unknown. Most studies compared the effects of tDCS before and after stimulation. The objective of our study was to measure the neurobiological effect of a single tDCS dose during stimulation.

METHODS: We conducted an online and offline protocol combining tDCS and magnetic resonance spectroscopy (MRS) in 17 healthy participants. We applied anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) and cathodal tDCS over the right DLPFC for 30 minutes, one of the most common montages used with tDCS. We collected MRS measurements in the left DLPFC and left striatum during tDCS and an additional MRS measurement in the left DLPFC immediately after the end of stimulation.

RESULTS: During stimulation, active tDCS, as compared with sham tDCS, elevated prefrontal *N*-acetylaspartate and striatal glutamate + glutamine but did not induce significant differences in prefrontal or striatal gamma-aminobutyric acid level. Immediately after stimulation, active tDCS, as compared with sham tDCS, did not significantly induce differences in glutamate + glutamine, *N*-acetylaspartate, or gamma-aminobutyric acid levels in the left DLPFC.

CONCLUSIONS: These observations indicate that tDCS over the DLPFC has fast excitatory effects, acting on prefrontal and striatal transmissions, and these effects are short lived. One may postulate that repeated sessions of tDCS might induce similar longer lasting effects of elevated prefrontal *N*-acetylaspartate and striatal glutamate + glutamine levels, which may contribute to its behavioral and clinical effects.

Keywords: Dorsolateral prefrontal cortex, Glx, Magnetic resonance spectroscopy, *N*-acetylaspartate, Striatum, Transcranial direct current stimulation

http://dx.doi.org/10.1016/j.biopsych.2015.11.008

Hone-Blanchet, A. et al. (2016) Online Effects of Transcranial Direct Current Stimulation in Real Time on Human Prefrontal and Striatal Metabolites. Biol Psychiatry. 80(6):432-438.

MRS voxels

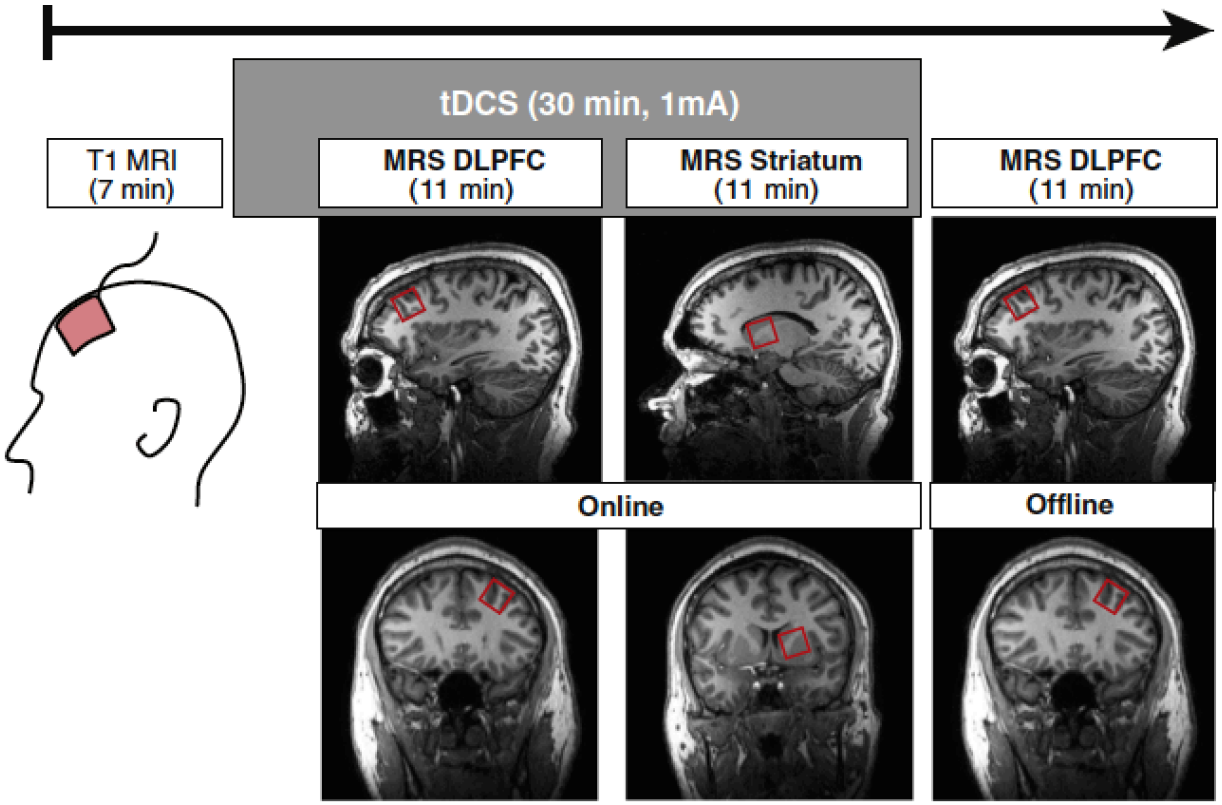


Figure 1. Experimental timeline. Following the acquisition of a T1-weighted anatomic image, we delivered active or sham stimulation to the dorsolateral prefrontal cortex (DLPFC) with the anode electrode over the left DLPFC and the cathode electrode over the right DLPFC. We acquired glutamate + glutamine, *N*-acetylaspartate, and gamma-aminobutyric acid levels in the left DLPFC (ipsilateral to the anode) and in the left striatum beginning 5 minutes after the start of stimulation. We acquired the same metabolites in the left DLPFC immediately after stimulation. MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; tDCS, transcranial direct current stimulation.

Hone-Blanchet, A. et al. (2016) Online Effects of Transcranial Direct Current Stimulation in Real Time on Human Prefrontal and Striatal Metabolites. Biol Psychiatry, 80(6):432-438.

VP Clark NIH TES meeting Sept 28, 2016

MRS results – Elevation of NAA and Glx

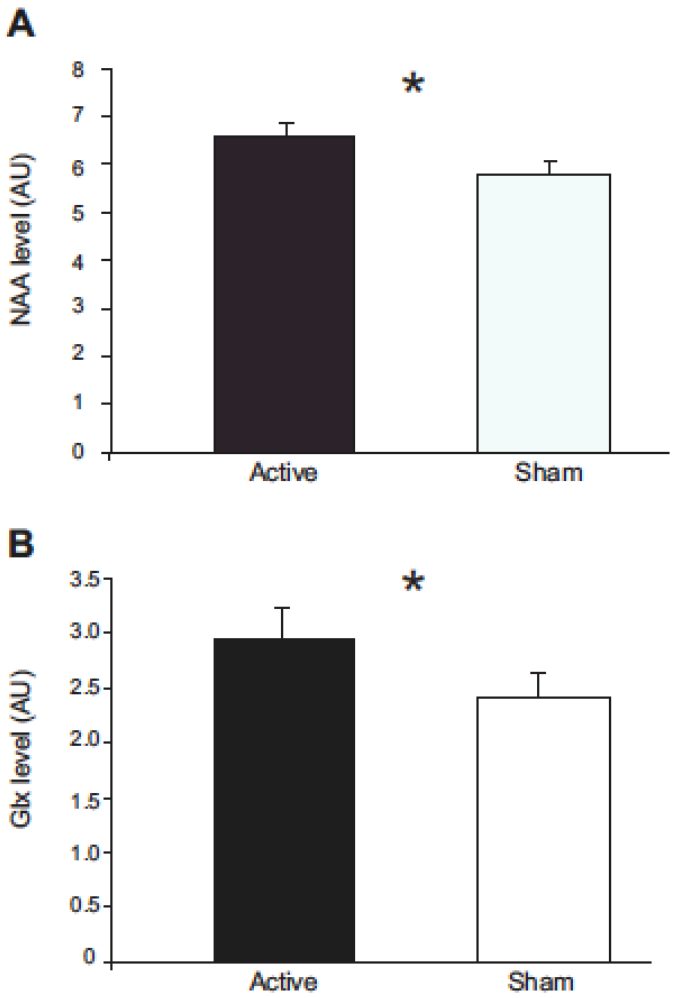


Figure 3. Elevation of prefrontal *N*-acetylaspartate (NAA) and striatal glutamate + glutamine (Glx) levels by transcranial direct current stimulation (tDCS) applied over the dorsolateral prefrontal cortex. **(A)** NAA levels (n = 14) in the left dorsolateral prefrontal cortex during active and sham tDCS. **(B)** Glx levels (n = 15) in the left striatum during active and sham tDCS. Light gray bars represent group averages for active and sham stimulation. Results are in arbitrary units (AU). Error bars represent SEM. *$p < .05$.

Hone-Blanchet, A. et al. (2016) Online Effects of Transcranial Direct Current Stimulation in Real Time on Human Prefrontal and Striatal Metabolites. Biol Psychiatry, 80(6):432-438.

Restorative Neurology and Neuroscience 34 (2016) 587–602
DOI 10.3233/RNN-150569
IOS Press

The effects of bi-hemispheric M1-M1 transcranial direct current stimulation on primary motor cortex neurophysiology and metabolite concentration

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[b]*Centre de recherche du Centre Hospitalier Universitaire de l'Hôpital Sainte-Justine, Montréal, Canada*
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[d]*McGill University, Montréal, Canada*
[e]*Center for Magnetic Resonance Research and Department of Radiology, University of Minnesota, Minneapolis, USA*

Abstract.
Purpose: The aim of the present study was to assess, in healthy individuals, the impact of M1-M1 tDCS on primary motor cortex excitability using transcranial magnetic stimulation and sensorimotor metabolite concentration using ^{1}H-MRS.
Methods: For both experiments, each participant received the three following interventions (20 min tDCS, 1 mA): left-anodal/right-cathodal, left-cathodal/right-anodal, sham. The effects of tDCS were assessed via motor evoked potentials (experiment 1) and metabolite concentrations (experiment 2) immediately after and 12 minutes following the end of stimulation and compared to baseline measurement.
Results: No effect of M1-M1 tDCS on corticospinal excitability was found. Similarly, M1-M1 tDCS did not significantly modulate metabolite concentrations. High inter-subject variability was noted. Response rate analysis showed a tendency towards inhibition following left-anodal/right-cathodal tDCS in 50% of participants and increased GABA levels in 45% of participants.
Conclusion: In line with recent studies showing important inter-subject variability following M1-supraorbital tDCS, the present data show that M1-M1 stimulation is also associated with large response variability. The absence of significant effects suggests that current measures may lack sensitivity to assess changes in M1 neurophysiology and metabolism associated with M1-M1 tDCS.

Keywords: Magnetic resonance spectroscopy, transcranial direct current stimulation, motor cortex, GABA, glutamate

JOURNAL OF NEUROTRAUMA 33: 1–10 (XXXX 00, 2016)
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DOI: 10.1089/neu.2016.4399

Original Article

No Effect of Anodal Transcranial Direct Current Stimulation on Gamma-Aminobutyric Acid Levels in Patients with Recurrent Mild Traumatic Brain Injury

Skadi Wilke,[1,*] Jonathan List,[1,*] Ralf Mekle,[4] Robert Lindenberg,[1] Martin Bukowski,[1] Stefanie Ott,[1] Florian Schubert,[4] Bernd Ittermann,[4] and Agnes Flöel[1–3]

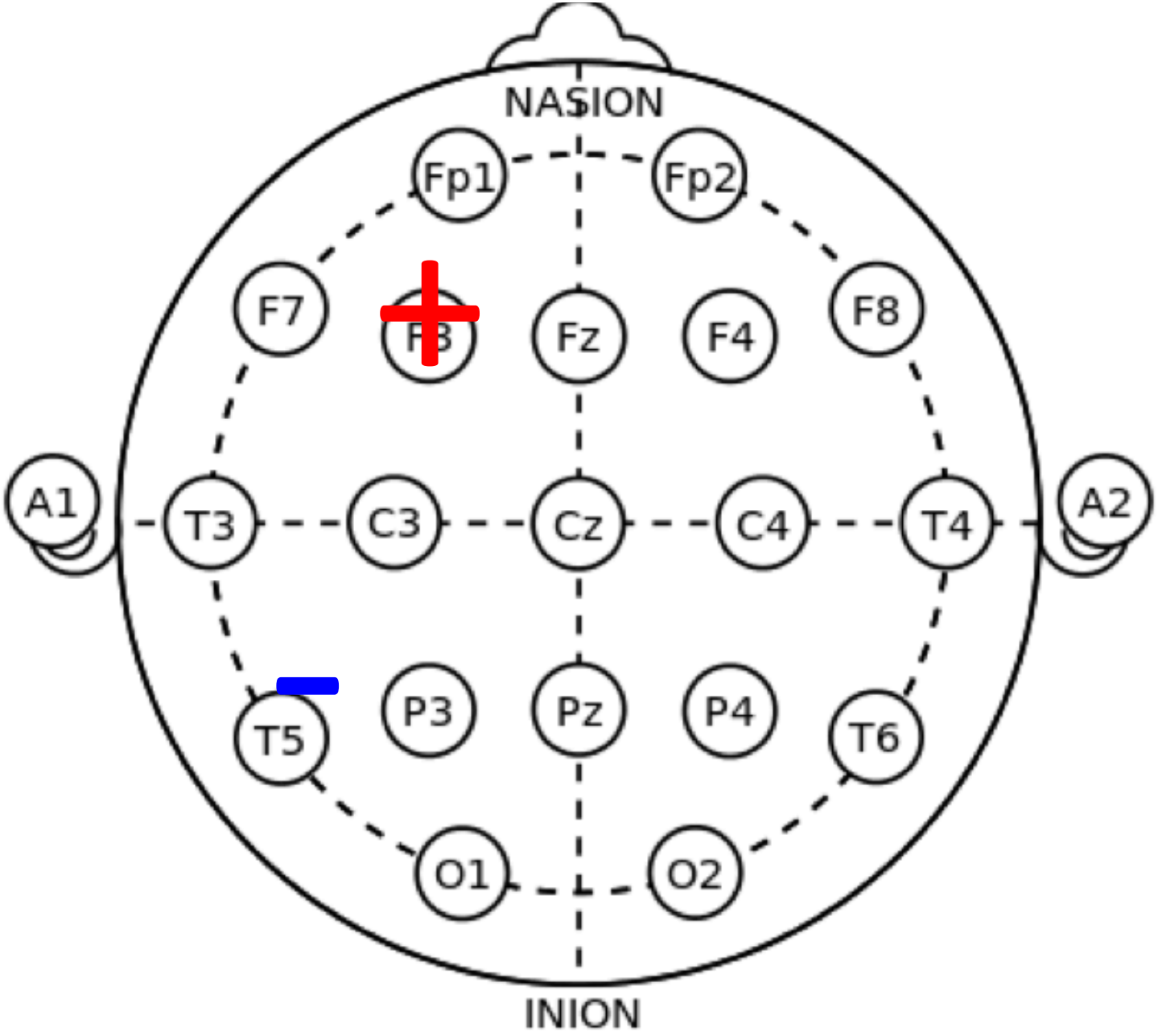
Abstract

In patients in the chronic phase after recurrent mild traumatic brain injury (mTBI), alterations in gamma-aminobutyric acid (GABA) concentration and receptor activity have been reported, possibly mediating subtle but persistent cognitive deficits and increased rate of dementia in older age. We evaluated whether anodal transcranial direct current stimulation (atDCS) over the primary motor cortex reduces GABA concentration and $GABA_B$ receptor activity in patients with recurrent mTBI. Seventeen patients (mean age 25, two women) in the chronic phase after recurrent mTBI and 22 healthy control subjects (mean age 26, two women) were included. All participants received comprehensive cognitive testing and detailed questionnaires on post-concussive symptoms at baseline. Subsequently, they participated in four experimental sessions, consisting of either magnetic resonance spectroscopy (MRS)/atDCS/MRS, transcranial magnetic stimulation (TMS)/atDCS/TMS, MRS/sham/MRS, or TMS/sham/TMS to determine GABA concentration (from MRS) and $GABA_B$ receptor activity (from TMS) after atDCS and after sham stimulation. Patients with mTBI scored significantly lower on verbal fluency tasks compared with healthy control subjects. GABA concentration at baseline was associated with the number of mTBI, although no group differences in GABA concentration and $GABA_B$ receptor activity were found. Moreover, no effects of atDCS on GABA concentration and receptor activity were seen in patients with mTBI or healthy control subjects. GABA concentration may increase with the number of mTBI, but atDCS did not modulate GABA concentration and receptor activity, as has been reported previously. Specifics of experimental design and analysis, but also characteristics of the respective samples, may account for these differential findings, and should be addressed in future larger studies.

Brunelin AVH protocol

- Anode over left DLPFC, cathode over left temporoparietal cortex (TPC) to reduce auditory verbal hallucinations (AVH; Brunelin et al., 2012)
  - 30 Sz pts
  - 20 min per session, 2 sessions per day for 5 days
  - Reduced AVH for up to three months, with a reduction of negative symptoms and improved insight

Brunelin et al. (2012) Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatry; 169:719–724



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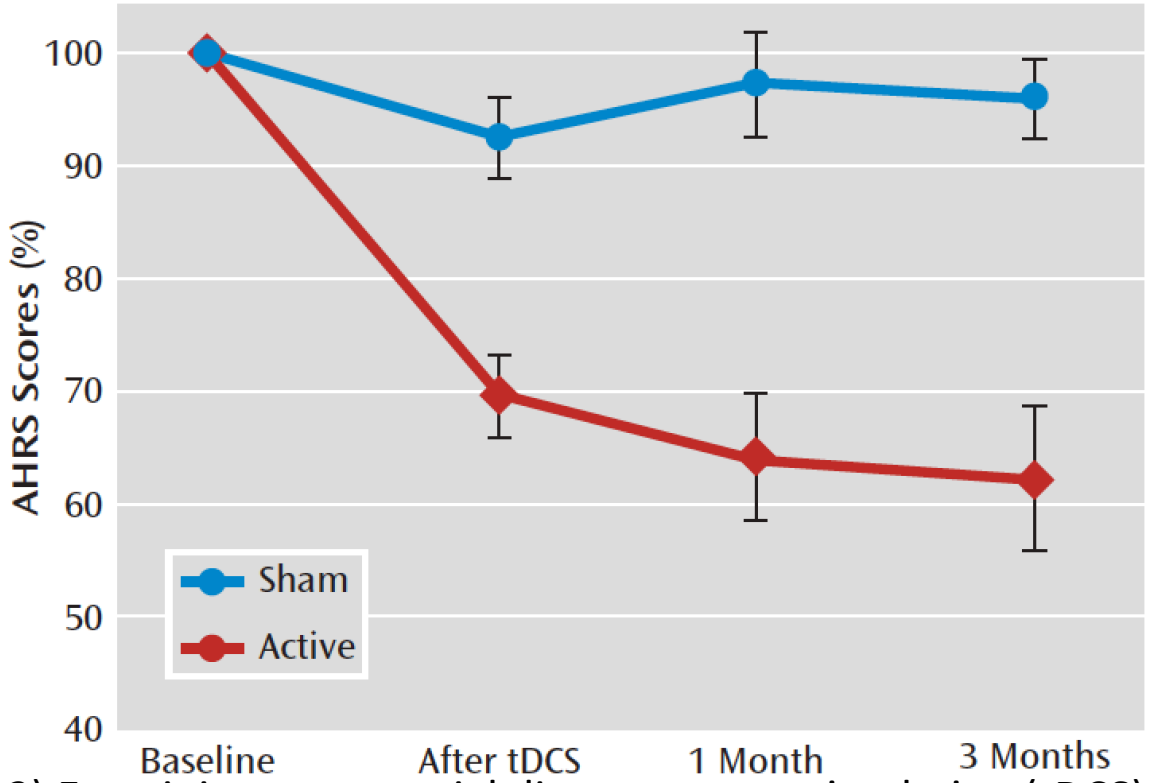
Brunelin et al. (2012), *Am J Psychiatry* 169:719–724

FIGURE 1. Effect of Active and Sham Transcranial Direct-Current Stimulation (tDCS) on the Severity of Auditory Verbal Hallucinations[a]



Brunelin et al. (2012) Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatry; 169:719–724

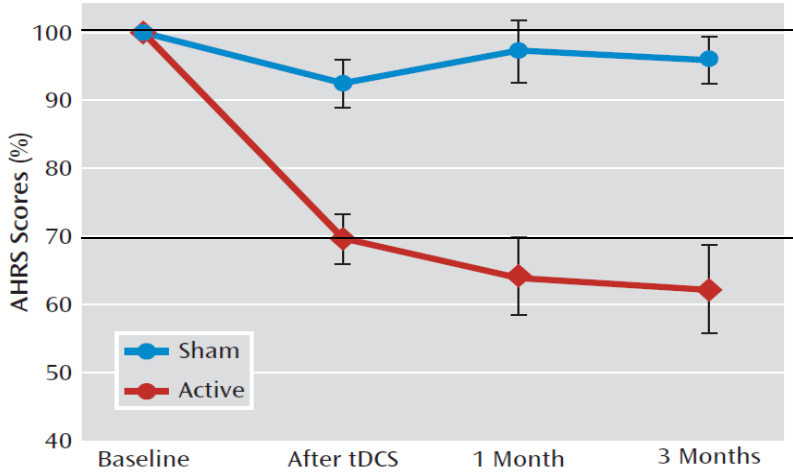
Looking for effects of stimulation

- PI: Robert Thoma, PhD
- Replicating Brunelin et al. 2012
  - 2.0 mA, 20 min., 2x day, (10 sessions over 1 week)
  - 7x5 cm (35 cm^2) sponge electrodes
  - Anode over the left DLPFC
    - midway between F3 and FP1
  - Cathode over left temporo-parietal cortex
    - midway between T3 and P3

Comparison with Brunelin

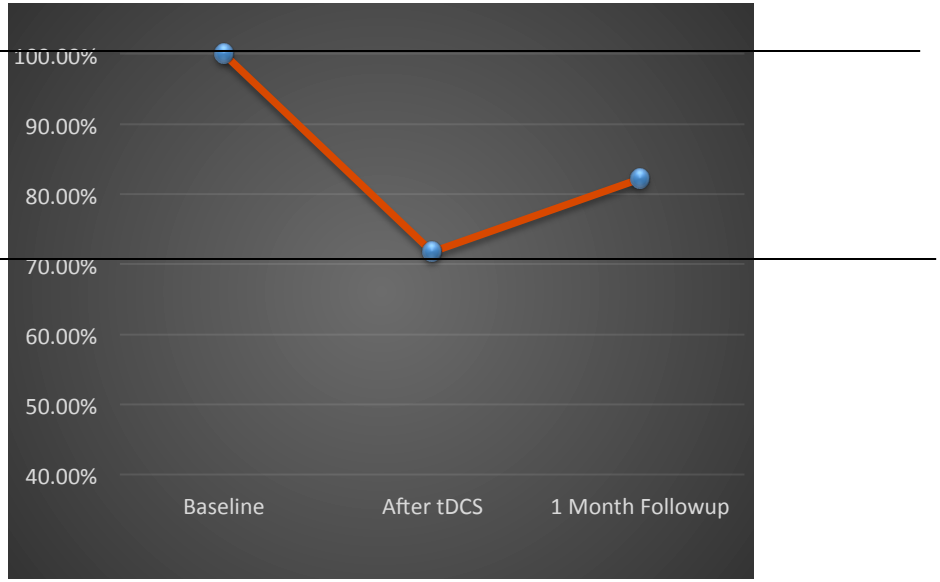
Brunelin et al., 2012

FIGURE 1. Effect of Active and Sham Transcranial Direct-Current Stimulation (tDCS) on the Severity of Auditory Verbal Hallucinations[a]



[a] The graph illustrates the significant interaction between the mean percentage change in Auditory Hallucination Rating Scale (AHRS) score in the two groups across the four assessments ($F=10.97$, $df=3, 84$, $p<0.0001$). Post hoc analyses showed significant differences between groups at each postbaseline assessment: after tDCS, $t=-4.45$, $p<0.001$; 1 month after treatment, $t=-4.48$, $p<0.001$; 3 months after treatment, $t=-4.58$, $p<0.001$. Error bars indicate standard error.

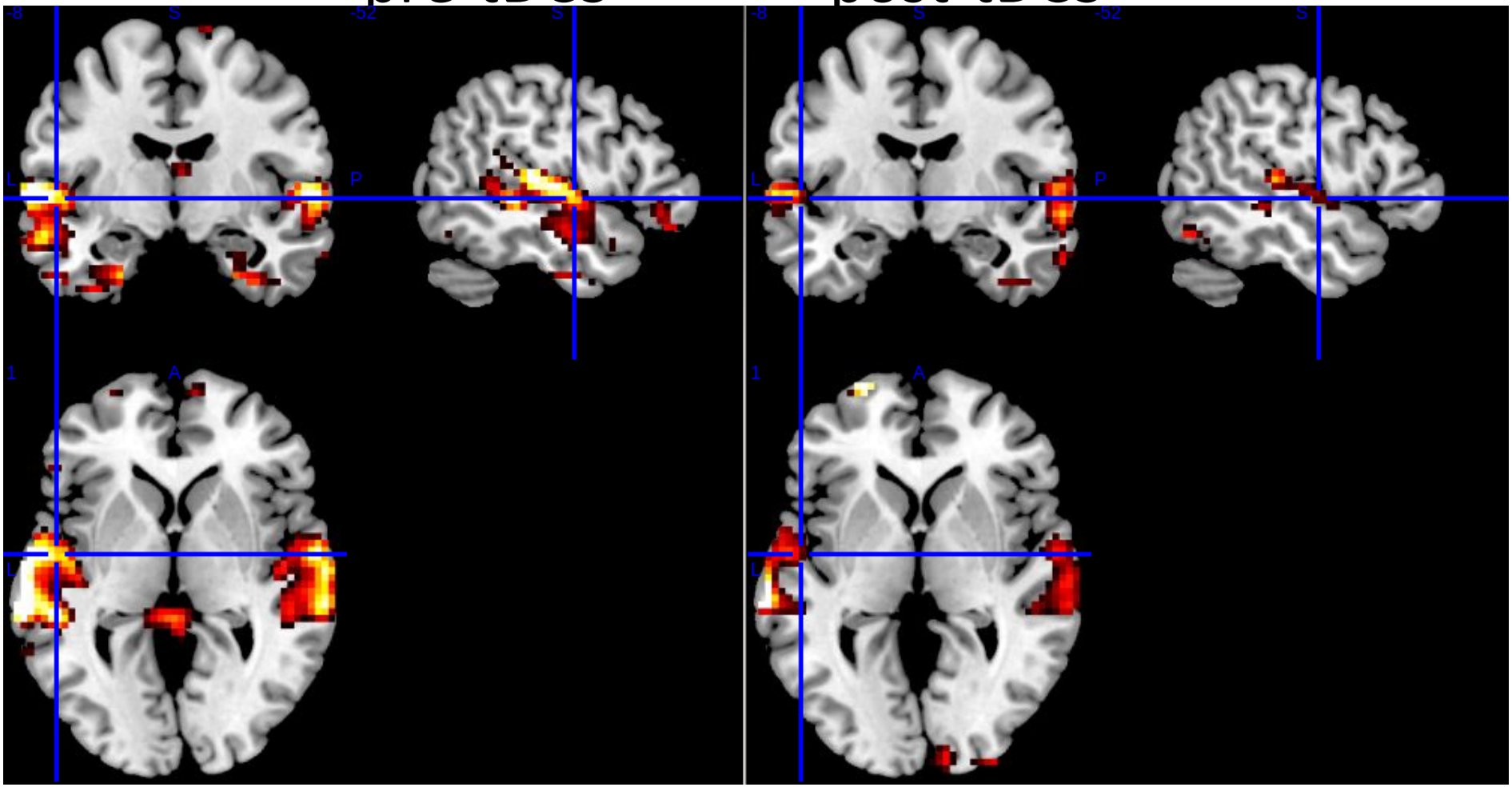
Bob Thoma pilot replication —PSYRATS total score



fMRI effects

Reduction in fMRI response to recorded voices after tDCS (N = 5)

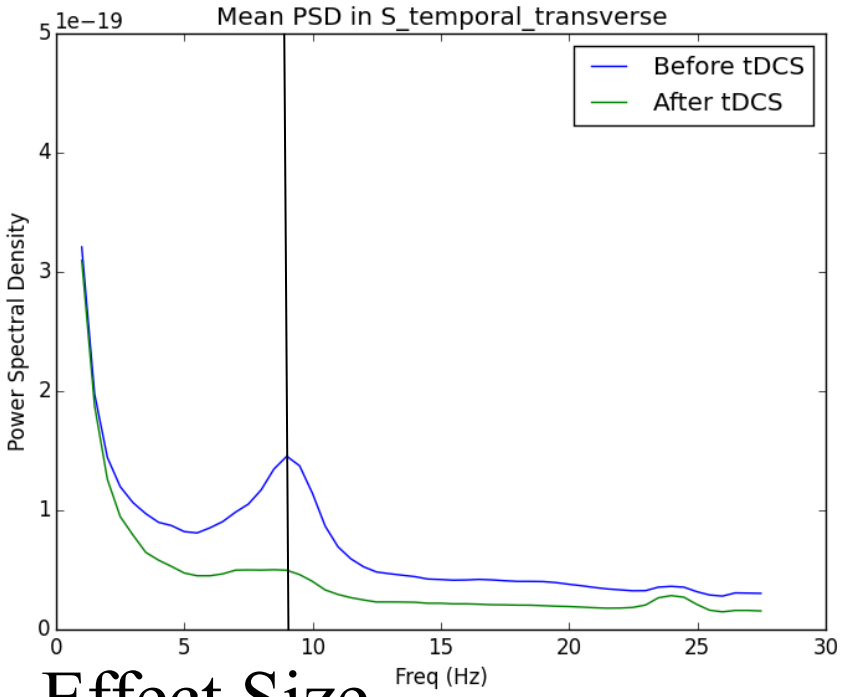
pre-tDCS post-tDCS



MEG effects

- MRN Electa Neuromag 306-channel MEG at 1200 Hz sampling rate
- *Reduction* in spectral density data after tDCS (N = 5)

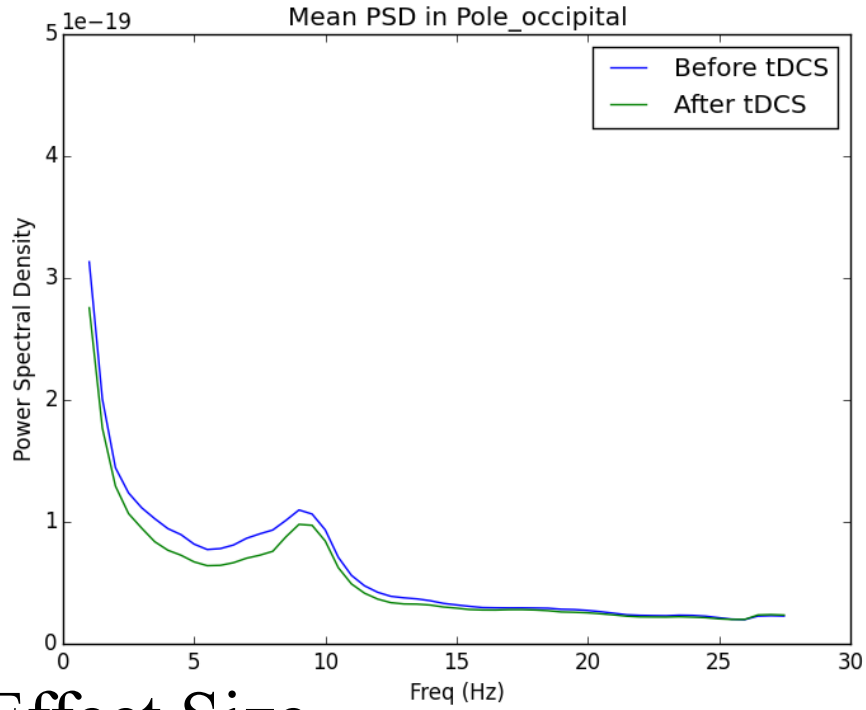
Auditory Cortex



Effect Size

Cohen's d = .78

Visual Cortex



Effect Size

Cohen's d = .015

How many possible tDCS protocols are there?

- Unique electrode locations (2 electrodes, at least 1 on the scalp): [6,142 to 153,180]
  - 10-20 system = 74 unique scalp locations
  - "10-5" system = 345 (Oostenveld & Praamstra '01)
  - Cephalic but non-scalp "return" locations (avoiding the heart): 8-100
- Electrode size (Current density, 2 electrodes): [10–1032]
  - 1 cm^2 to 226 cm^2 (List of Amrex sizes / 1 cm^2 increments)
- Electrode number [2-128]
- Current strengths: [5-25]
  - 0.1 to 2.5 mA (0.5 mA increments / 0.1 mA increments)
- Polarities: 2
- Durations: [5-35]
  - 5 to 40 minutes (5 minute increments / 1 min increments)

Minimum: 6,142*5*2*7*10 = 4,299,400

Maximum (?): 153,180*25*2*40*226*126 = 8,723,907,360,000

-OR-

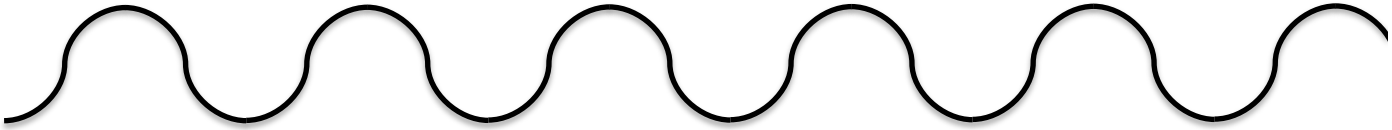
4.3 million to 8.7 trillion

VP Clark NIH TES meeting Sept 28, 2016

What different types of current modulation are there?

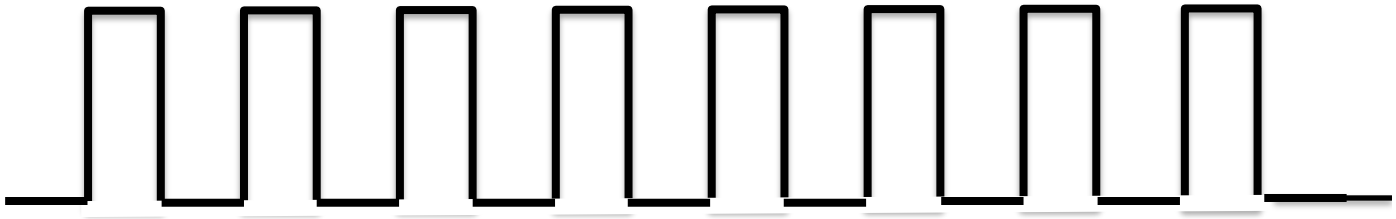
- tDCS

- tACS



- tRNS

- Pulsed



- … and many others

How many tES protocols?

- Combining DC, AC, Noise (RN) and pulsed protocols
  - tDCS protocols: [4,299,401 - 8,723,907,360,000]
  - tACS:
    - Frequency: [101-10,001]
      - 0.01 – 100 Hz (1 Hz increments / 0.01 Hz increments)
    - Note: high current amplitudes are better tolerated using AC
  - tRNS: [2-101]
    - Pink/white/etc.
  - Pulsed: [2-101]

Minimum: 1,736,958,004

Maximum: 890,014,782,372,579,000,000

- Or -

Up to 890 quintillion unique tES protocols

VP Clark NIH TES meeting Sept 28, 2016

How many other forms of neuromodulation are there?

- Ultrasound
  - – Location, emitter area and "focusing" angle, frequencies, duration, amplitude…
- Magnetic Stimulation
  - – TMS (Single-pulse, Paired-pulse, Low frequency, High frequency, Theta burst)
  - – Low field magnetic stimulation (LFMS)
- Electromagnetic radiation (light)
  - – Location, frequency, duration, amplitude…
- Physical pressure
  - – Acupuncture, Acupressure, Massage, Chiropractic, Cranio-sacral therapy, Kinesiology,…
- Meditation/Mindfulness, Yoga, Hypnotism, …

Why combine imaging and stimulation?

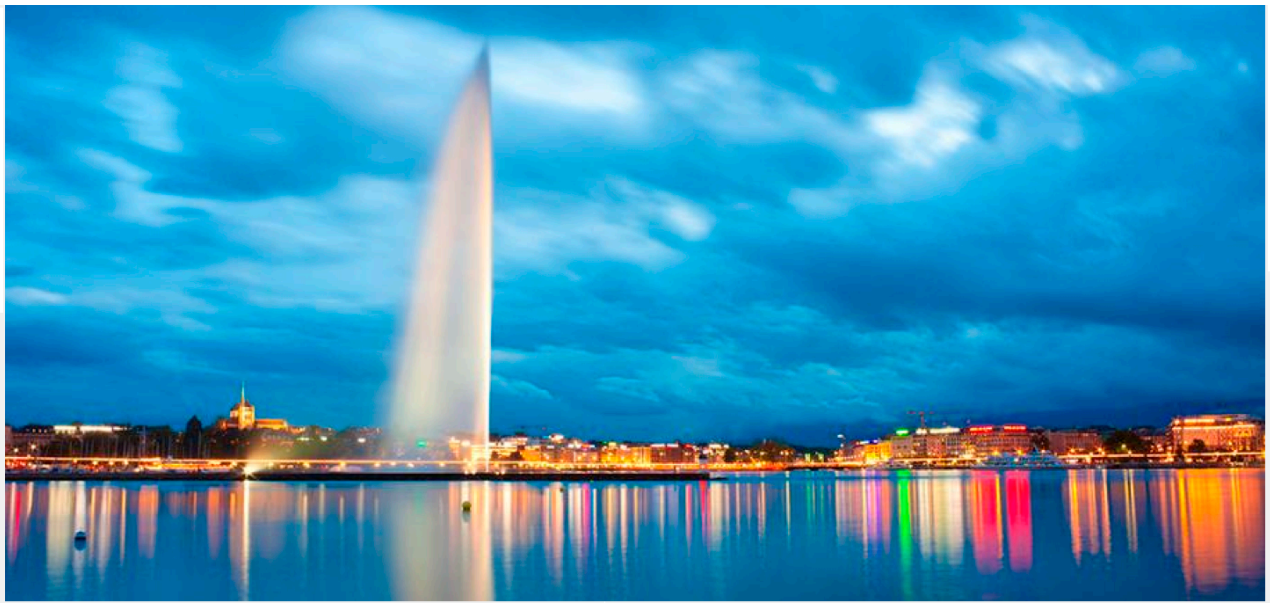
- Together they might provide a better understanding of human brain organization
  - Stimulation can be used to test hypotheses derived from brain imaging
  - Imaging can be used to better understand the neural mechanisms of stimulation on behavior
- Imaging might be used to choose better stimulation protocols
  - A nearly infinite number are possible, can only use one at a time
  - Individualized stimulation
- Ultimately could lead to safer, cheaper and more effective treatments for brain and mental illness, and turn decades of our hard work into real-world benefits

Hawai'i Brain Stimulation and Imaging Meeting

June 12-13, 2015

Speakers: Peter Fox, Peter Bandettini, Marom Bikson, Michael Nitsche, others

Geneva Brain Stimulation and Imaging Meeting



Campus Biotech, Geneva, Switzerland, June 24-25, 2016

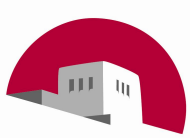
Speakers: Sarah Lisanby, Michael Fox, Peter Tass, Ashesh Mehta, Christoph Herrmann, Don Tucker, Pedro Cavaleiro Miranda, others.

Announcing the Vancouver Brain Stimulation and Imaging Meeting June 23-24, 2017

Take-home summary slide

- There are many ways that neuroimaging can be used to improve neurostimulation, and conversely, that neurostimulation can benefit the efforts of neuroimaging
- We need to find markers for predicting variability in tDCS response
- We must be careful not to over-generalize relationships
  - There are nearly infinite ways to apply electrical current, each may have different effects
- Large, boring studies on effects of stimulation parameters must be done
  - We need to be really thorough in looking for relationships

Many Thanks…



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- Rose Bigelow
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- Elizabeth Browning
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- Mike Weisend
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The Mind RESEARCH NETWORK For Neurodiagnostic Discovery

The City College of New York

- **Marom Bikson**

National Institute of Neurological Disorders and Stroke, NIH

- **Eric Wassermann**

Sandia National Laboratories

- **Elaine Raybourn**

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Thank You