Honolulu June 12th 2015

New technologies in transcranial current stimulation

Giulio Ruffini (PhD)
CEO, Starlab
President, Neuroelectrics Corporation

Overview

- Intro to tCS
- Mechanisms, mechanisms: the electric field
- Modeling the electric fields in the brain
- Limitations of classic montages
- MtCS technology
  - MtCS: More focal stimulation
  - MtCS: extended targets. Networks
- Combining EEG and tCS; MtACS and beyond
- Future

Disclosure - Neuroelectrics

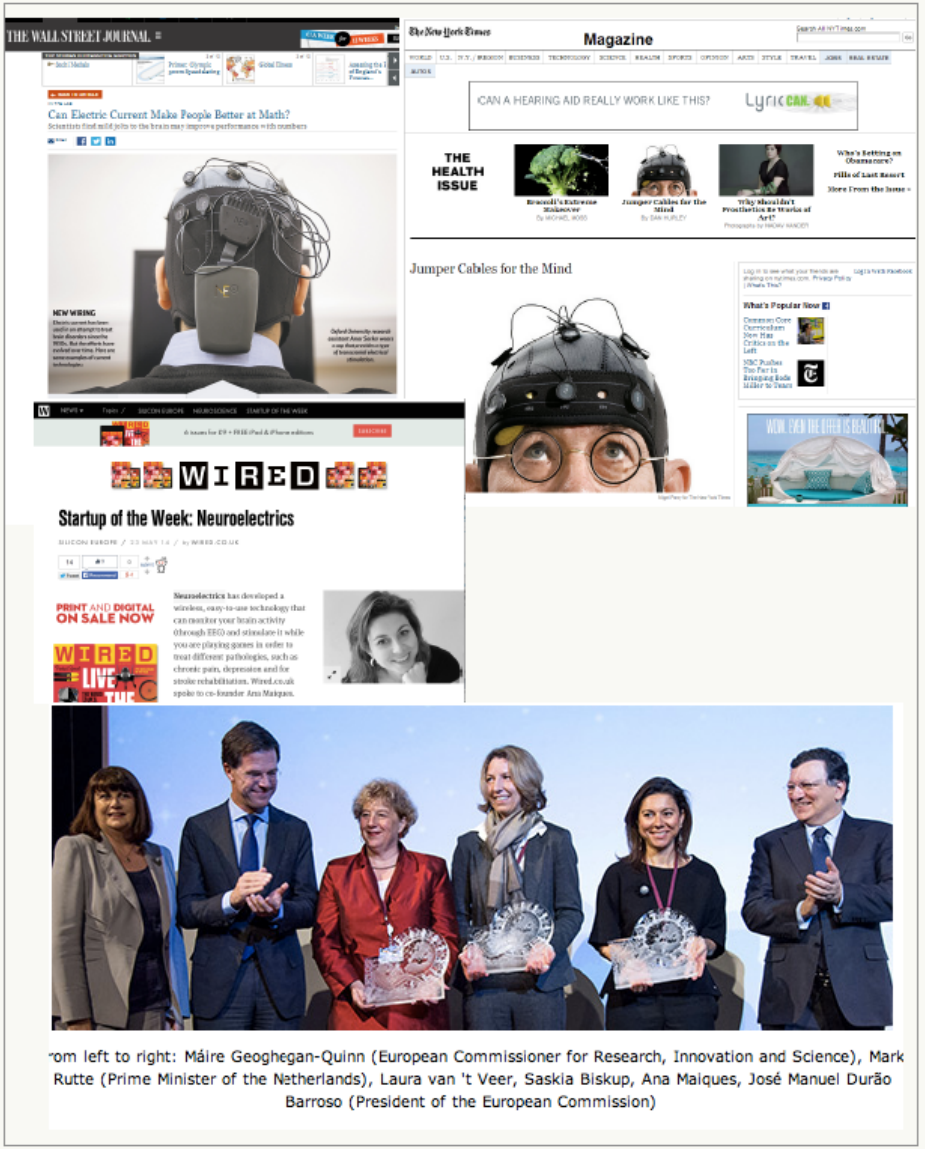
I work for Starlab and Neuroelectrics.

Neuroelectrics is a Starlab Spin-off (2011), child also of FET Open project HIVE (**hive-eu.org**)

Barcelona born and rapidly growing **Cambridge (MA) activity**

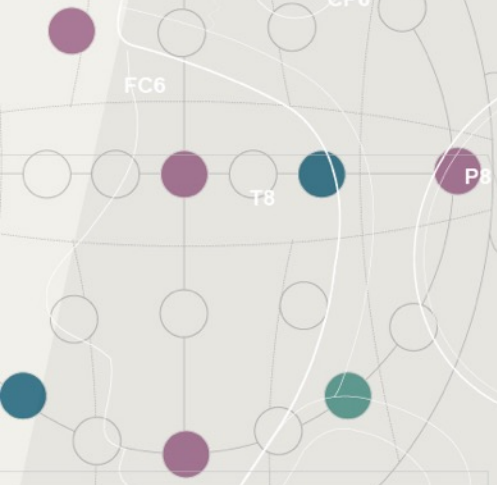
Creating a new paradigm to monitor and stimulate the brain through innovative medical devices and expert knowledge in EEG processing and e-field simulation models

Committed to deliver high quality science based technologies and transforming them into novel therapies and diagnostic tools



From left to right: Máire Geoghegan-Quinn (European Commissioner for Research, Innovation and Science), Mark Rutte (Prime Minister of the Netherlands), Laura van 't Veer, Saskia Biskup, Ana Maiques, José Manuel Durão Barroso (President of the European Commission)

What is tCS?



tCS is… tDCS, tACS, tRNS

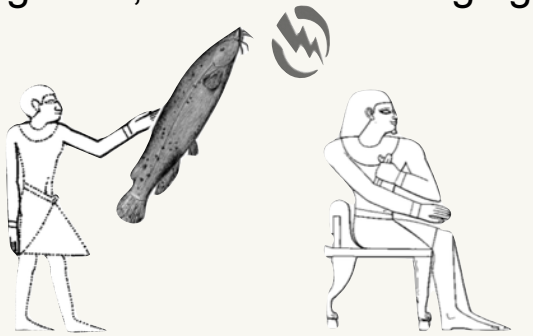
tCS is a form of neurostimulation which uses controlled, low intensity currents delivered non-invasively to the brain area of interest via 2 or more scalp electrodes. tACS and tRNS are similar to tDCS, but with time-varying currents. **tCS** includes all of these.

The current induces intracranial electric fields which can either increase or decrease the neuronal excitability, alter brain function and, ultimately, connectivity.

I use the term tCS (transcranial current stimulation) to emphasize that current is what is controlled …other used terms include tES. "MtCS" sometimes used to highlight the use of more than 2 (small)electrodes.

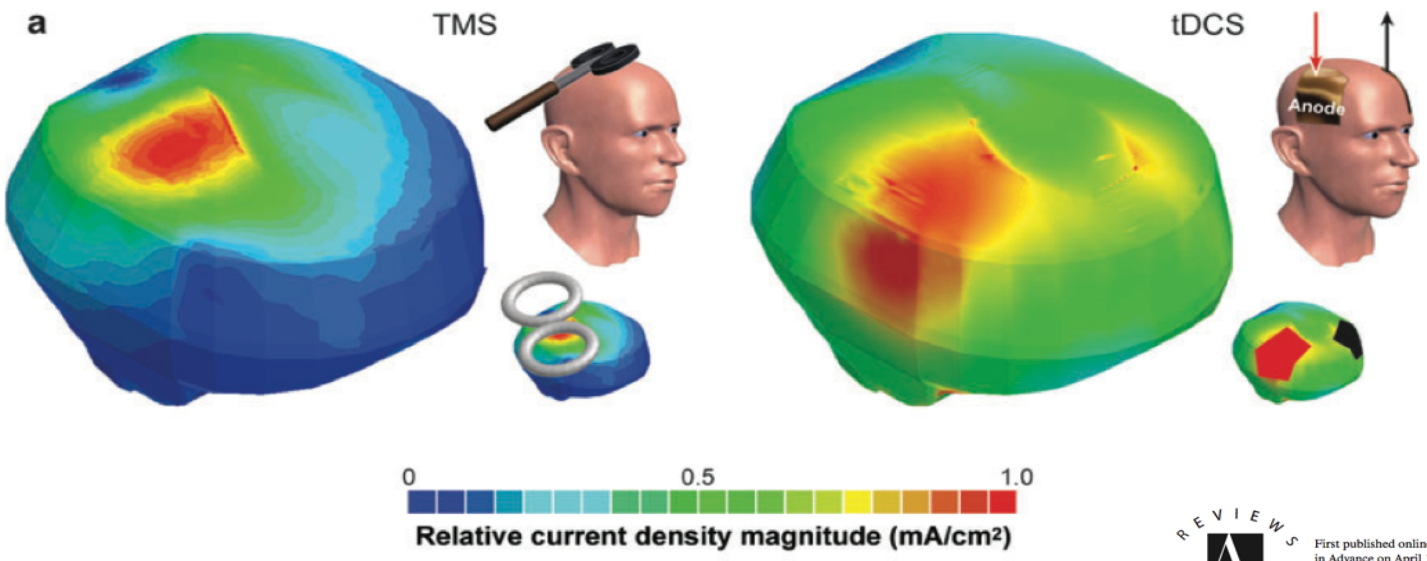
transcranial Current Stimulation (tCS)

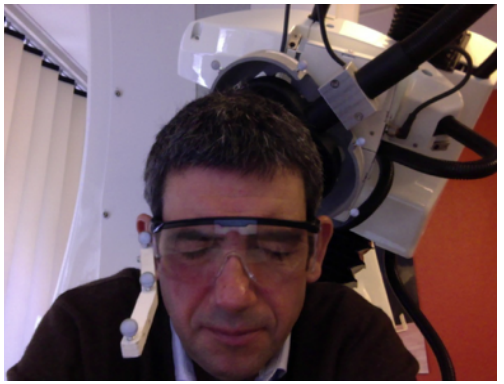
- Non-invasive neuromodulatory technique: sub-threshold – i.e., not initiating action potentials. **Weak electric fields and low frequencies** (quasi-static regime)**.**
- **Small controlled currents** (~1mA) are passed directly through the scalp to modulate activity. Firing rates of the neurons increase when the current is applied in the direction of the axons and decreases if the current is reversed. Plastic effects result.
- Power **dissipated by tDCS devices in head is of the order of 0.05 Watt**. Tiny (& most on scalp).
  [The Federal Communications Commission (FCC) has set a GSM SAR limit of 1.6 W/kg, averaged over a volume of 1 gram of tissue, for the head.]
- The current is normally applied in **repeated 20-40 minute sessions** and some of the applications are: neuropathic chronic pain, major depression, stroke rehabilitation - many others being explored.
- tDCS is most common form. Can also be Alternating Current - **tACS** - random - **tRNS** - , others.
- Know for centuries, but in the last decade with increased interest, mostly due to improved technologies for stimulation and measurements of effects (e.g., using TMS, but also via imaging, etc), new improved protocols.
- Cheaper, simpler, safer than TMS



don't try this at home!

tCS vs TMS





REVIEWS IN ADVANCE
First published online as a Review in Advance on April 19, 2007

Noninvasive Human Brain Stimulation

Timothy Wagner,[1] Antoni Valero-Cabre,[1,2,3] and Alvaro Pascual-Leone[1,4]

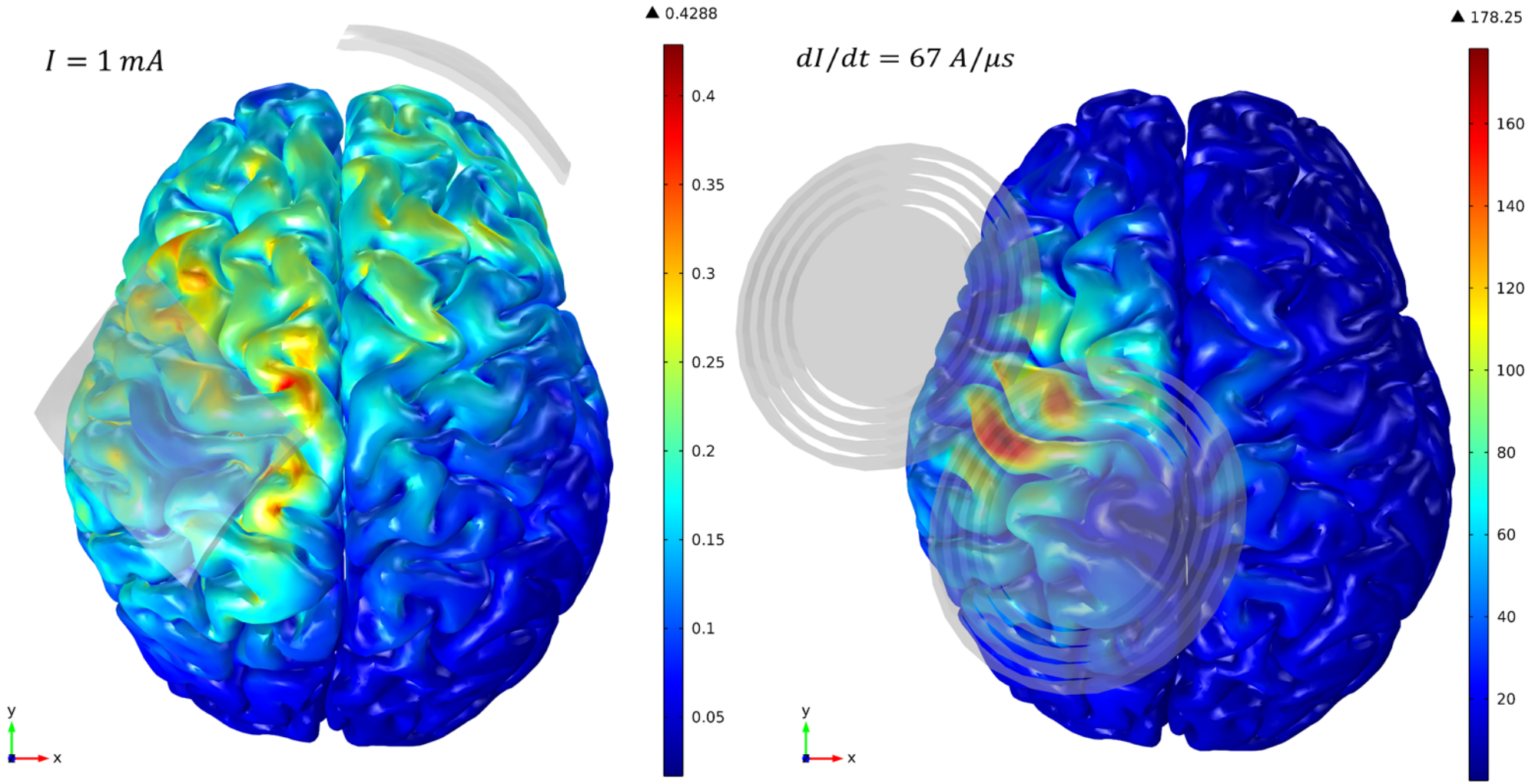
TMS: more focal and higher in intensity and delivered in short pulses

E-field distribution - tDCS

E-field's mag (V/m)

E-field distribution - TMS

E-field mag (V/m)

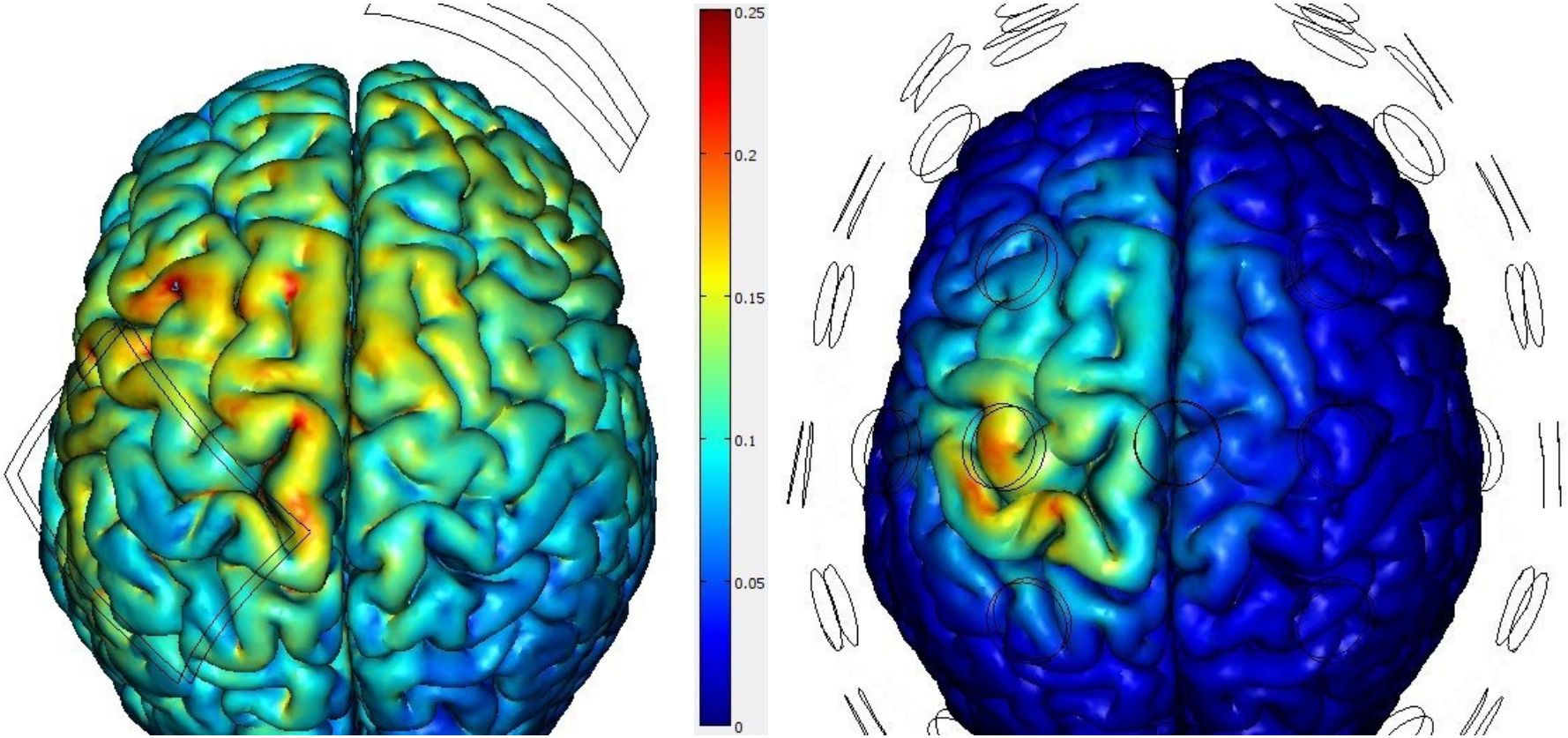


Ricardo Salvador & Pedro Miranda 2015, in prep

Using small electrodes helps

tDCS – two 35 cm² electrodes

MtDCS – five π cm² electrodes



Pedro Miranda, G. Ruffini - with Stimweaver 5 Ch solution

Limitations of bipolar montages with sponges

The use of only two large electrodes is a limitation … Smaller more numerous electrodes (MtCS) provide for more freedom and precision as we will see.

The use of large sponges is troublesome for various reasons:

1. Large impact area of electric fields / shotgun approach probably results in very complex, variable results: most of the cortex affected!
2. Use of square/rectangular sponges requires careful specification of orientation to reproduce set up (normally not done)
3. Sponges are noisy, contaminate concurrent EEG due to sub-optimal electrochemistry which requires more energy

Safety

Short term safety of tDCS - in vivo studies

Clinical Neurophysiology 120 (2009) 1161–1167

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Safety limits of cathodal transcranial direct current stimulation in rats

David Liebetanz [a,*], Reinhard Koch [a], Susanne Mayenfels [a], Fatima König [b], Walter Paulus [a], Michael A. Nitsche [a]

[a] Department of Clinical Neurophysiology, University Medical Center Göttingen, Robert-Koch-Strasse 40, 37099 Göttingen, Germany
[b] Department of Neuropathology, University Medical Center Göttingen, Germany

The results of this systematic animal safety study demonstrate that cathodal tDCS is able to cause severe neuronal damage when it is applied above a certain charge density. For cathodal current densities between 142.9 and 287 A/m^2, no pathological brain lesions were observed below a charge density threshold of 52400 C/m^2. This threshold is at least 2 orders of magnitude higher than those charge densities currently being applied in clinical studies (171– 480C/m^2).

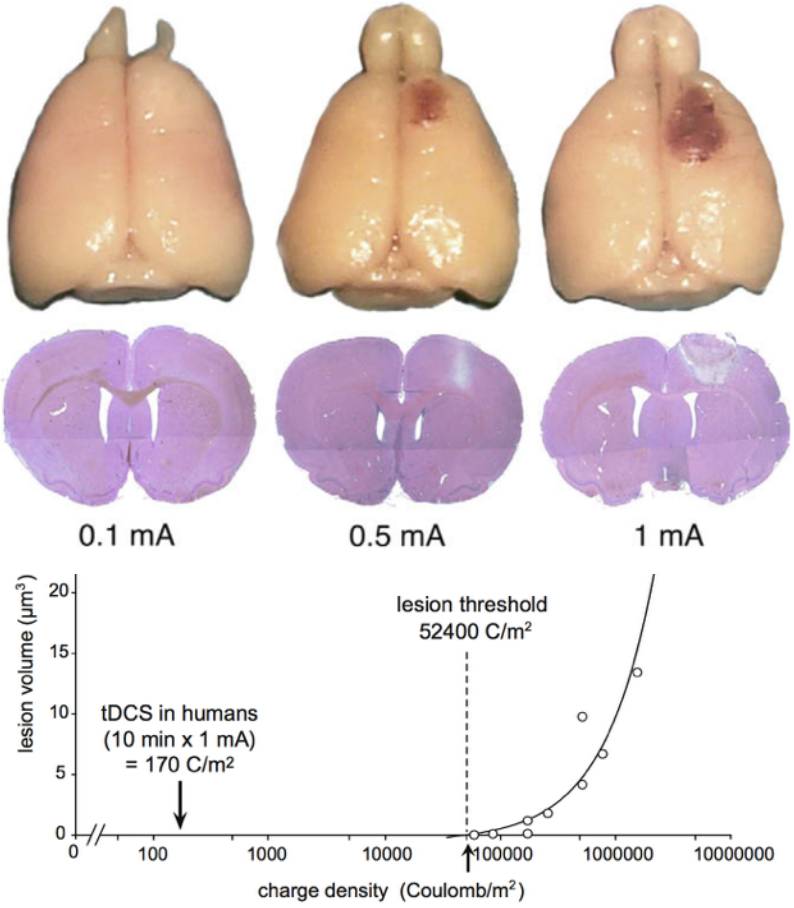
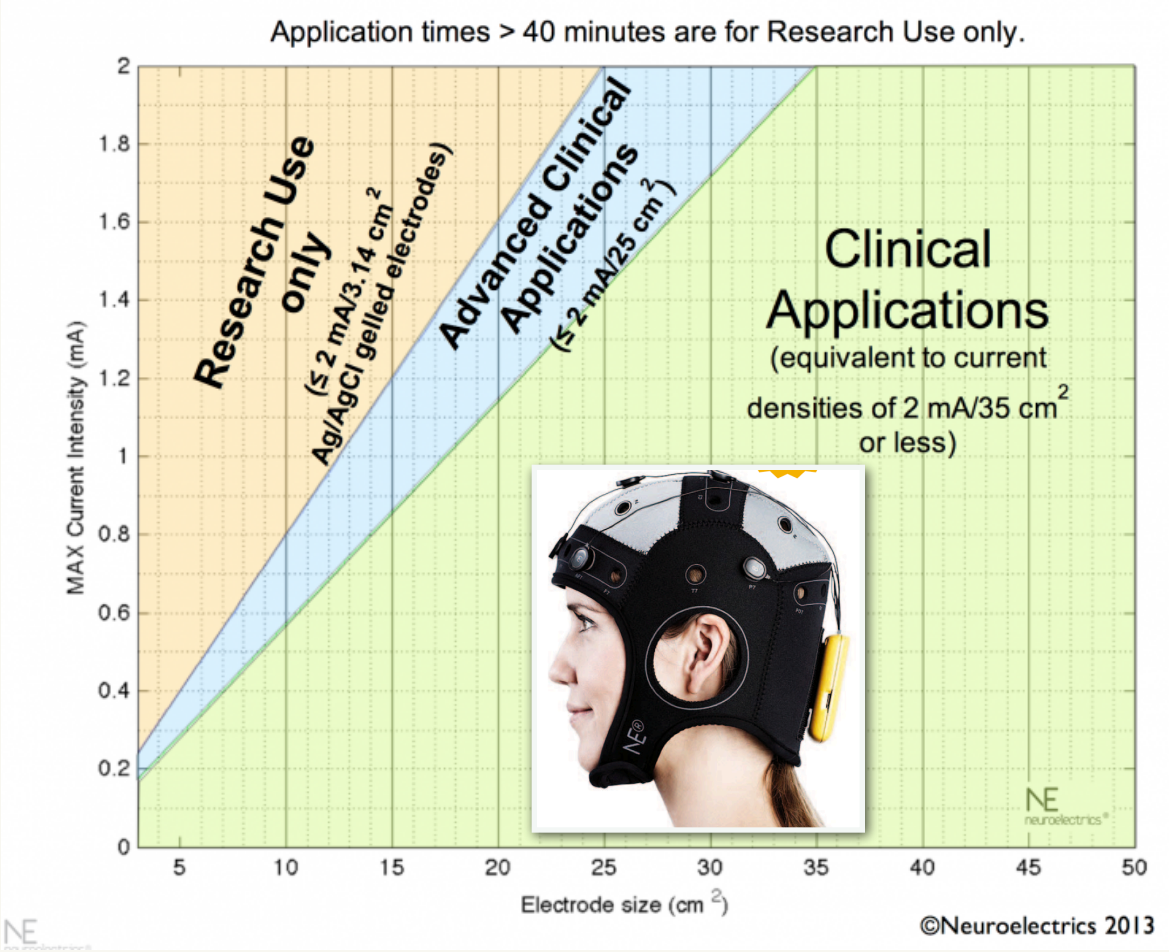


Fig. 4. Threshold estimation from the relation of charge density and lesion size at current intensities of 500–1000 µA. The results of all above-threshold experiments (n = 12) are depicted with respect to the charge density (C/m^2) and the size of the DC-induced brain lesion (µm^3). For better overview, the charge density is scaled logarithmically. The regression analysis indicates a linear relation of charge density and lesion size (r^2 = 0.945, F = 171.33, P < 0.001). The intercept point, at which the lesion size is theoretically zero, corresponds to 52400 C/m^2. The upwards-directed arrow indicates the daily charge density of the group that received repetitive tDCS over 5 days without inducing tissue damage.

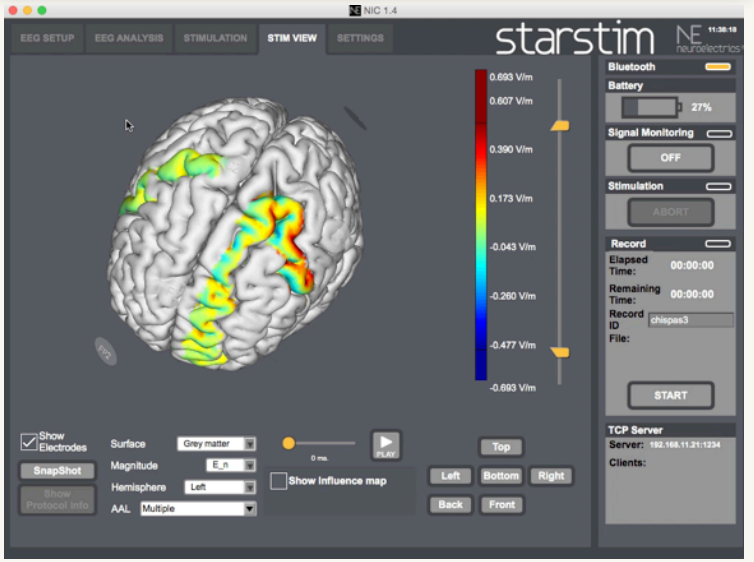
Short term safety of tDCS

- After thousands of hours of stimulation, short term ill effects associated to tCS in <u>controlled</u> settings remain scarce and minor
- Devices need to implement safety measures
- Starstim designed for safety:
  - Current at electrode < 2 mA
  - Max injected current < 4 mA
  - Programmed durations < 1 h
  - Impedance check before stim
  - Impedance check during stim
  - For use with our electrodes only
- Our safety record is excellent!



How to achieve more, safely

- Transition to **tele-monitored home use** to better understand impact of repeated use in natural settings (several NE clients already doing this)
- Use **repeatable montages**; protocols aiming for specificity of stimulation effects (e.g., targeted rather than “shotgun”).
- **[Protocol = specification of electrode type, positions, current type and intensity, duration, session sequencing.]**
- Model electric fields, refine targeting
- Co-registration to study physiological effects such as EEG, fMRI, etc.
- Safety documentation process to continue checking for short term effects, then long term



But are small electrodes safe?

- Short term tDCS safety is very well established using good practices both with sponges
- Use of **small Ag/AgCl electrodes +gel** catching up: Side effects limited to skin irritation or small burns in rare cases (probably due to wrong placement of sponges, with rubber directly contacting skin)
- But note that in any case,
  - Safety verified in adults with intact skulls, no implants, etc. Other groups much less studied.
  - Research studies carefully specify and limit duration, intensity, repetition of sessions. Very controlled scenario.
- Other forms of tCS (such as tACS, tRNS) less studied, but no bad news so far either.

What does the ratio of injected current to electrode area tell us about current density in the brain during tDCS? *Miranda et al, 2009*

Numerical calculation using spherical shell model. Introduces notion of I-A curve (non-linear!)

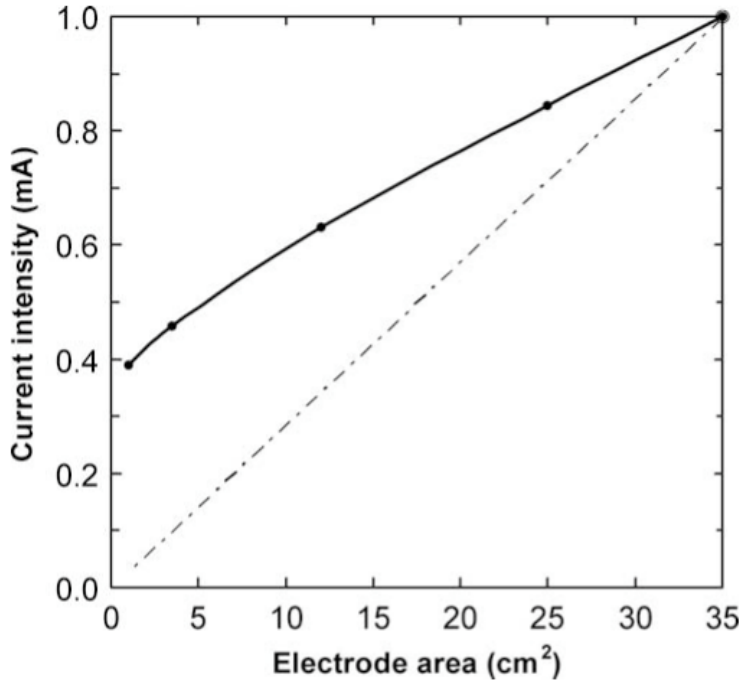
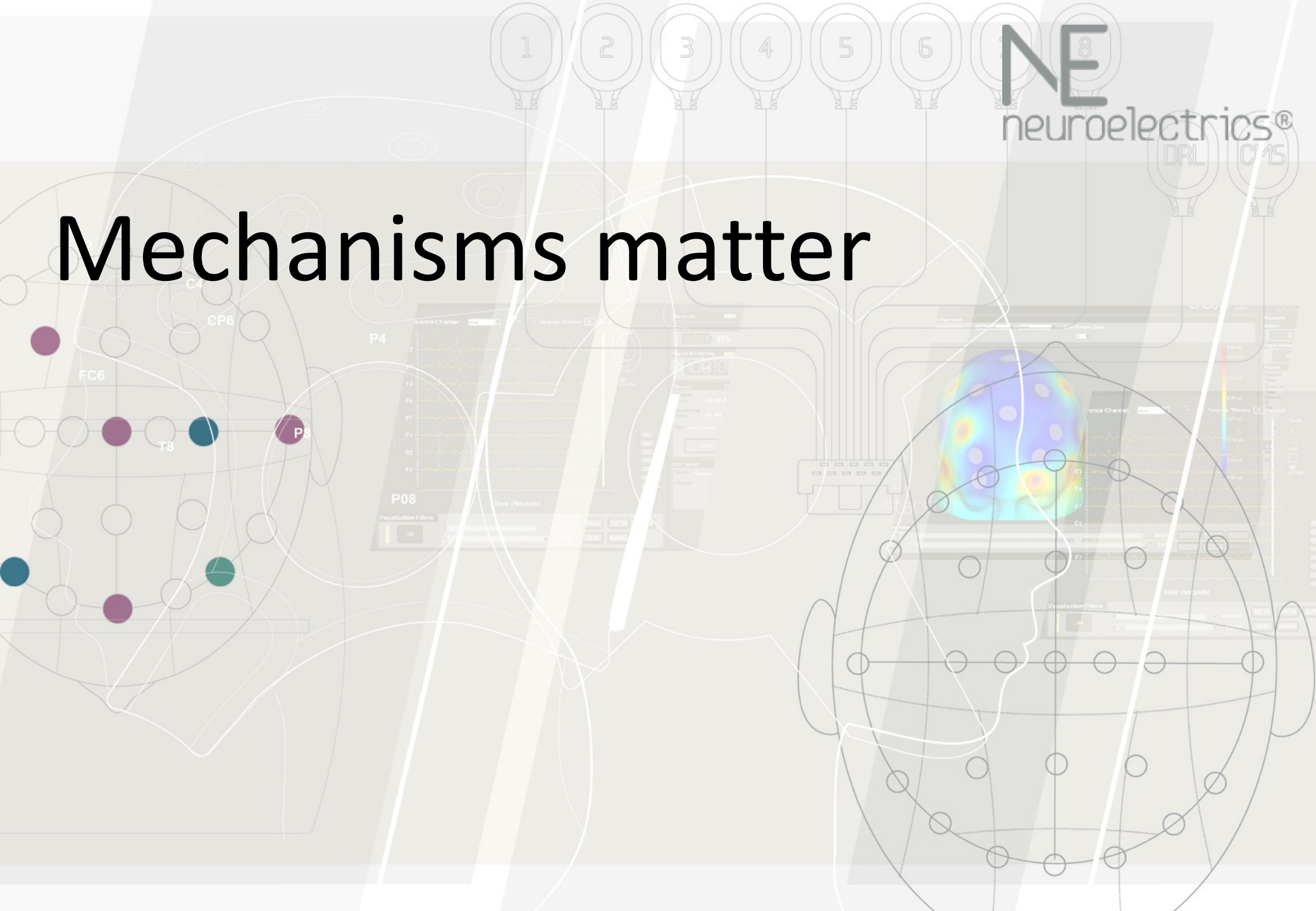


Fig. 4. The current, in mA, that must be injected into the stimulation electrode in order to achieve a constant current density at the target point 12 mm below its center, as a function of electrode area. The calculations were based on a spherical head model. The dotted line has the same meaning as in Fig. 3.

Recent studies using small Ag/AgCl electrodes

- *[Murray2014 et al, Intensity dependent effects of tDCS on corticospinal excitability in chronic Spinal Cord Injury., Arch Phys Med Rehabil. 2014 Nov 22]* : **9 subjects with chronic SCI** and motor disfunction underwent 3 twenty minute sessions of tics with **1-2 mA using 3 cm2 Pi** electrodes (Starstim, Neuroelectrics). No adverse effects were reported with any of the experimental conditions.
- *[Ruffini2015a et al Neuromodec 2015 Conference, NY Jan 2015]*, **20 healthy** subjects underwent **2 mA 20 minutes of stimulation twice with Pi electrodes (3 cm2)** with no adverse effects (Starstim, Neuroelectrics).
- *[Cortes2015 et al, Anodal tDCS decreases total EEG power at rest and alters brain signaling during fatigue in high performance athletes, Neuromodec 2015, NY]*, **4 athletes received 20 minutes of tDCS with Pi Electrodes** (3 cm2) with no ill effects (Starstim, Neuroelectrics).
- *[Boratyn et al. Focal tDCS in Chronic Stroke patients: A pilot study of physiological effects using TMS and concurrent EEG. Clinical Neurophysiology, Volume 124, Issue 10 , pp: 146-147 (October 2013)]*, . **Fifteen chronic stroke patients with hemiparesis following a first single unilateral lesion received 20 min of bilateral 1 mA anodal tDCS over the motor cortex with Pi electrodes (3 cm2)** of the lesioned hemisphere. Bilateral M1 stimulation using small Ag/AgCl (Pi) electrodes is well tolerated and can augment corticospinal excitability in the affected hemisphere (Starstim, Neuroelectrics).
- *[Borkardt2012 et al A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. The Journal of Pain. 2012;13(2):112-120.]*, t**wenty-four healthy adult** volunteers underwent quantitative sensory testing before and after **20 minutes of real (n = 13) or sham (n = 11) 2 mA HD-tDCS over the motor cortex (1 cm2 electrodes).** No adverse events occurred and no side effects were reported.
- *[Faria2012 et al, Feasibility of focal transcranial DC polarization with simultaneous EEG recording: preliminary assessment in healthy subjects and human epilepsy, Epilepsy Behav. 2012 Nov;25(3):417-25.]* report good tolerability in **15 healthy subjects** and preliminary effects of its use, testing repeated 1 mA tDCS sessions using small EEG electrodes, and in **two patients** with drug-refractory Continuous Spike-Wave Discharges

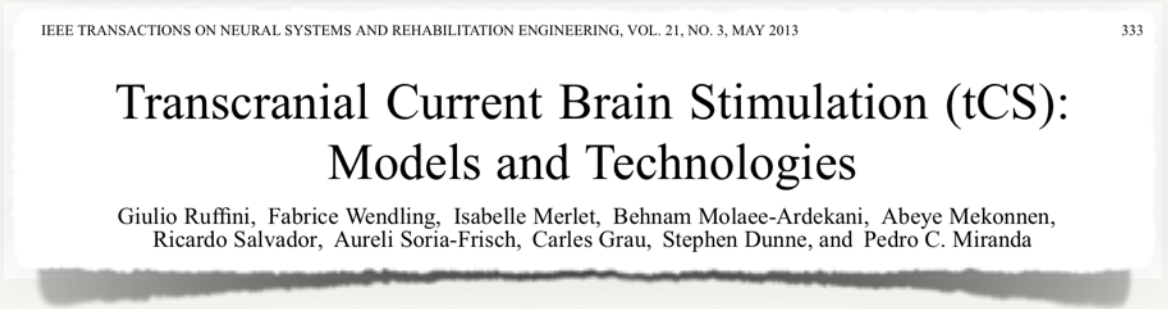
Mechanisms matter



The concurrent and aftereffects of tCS

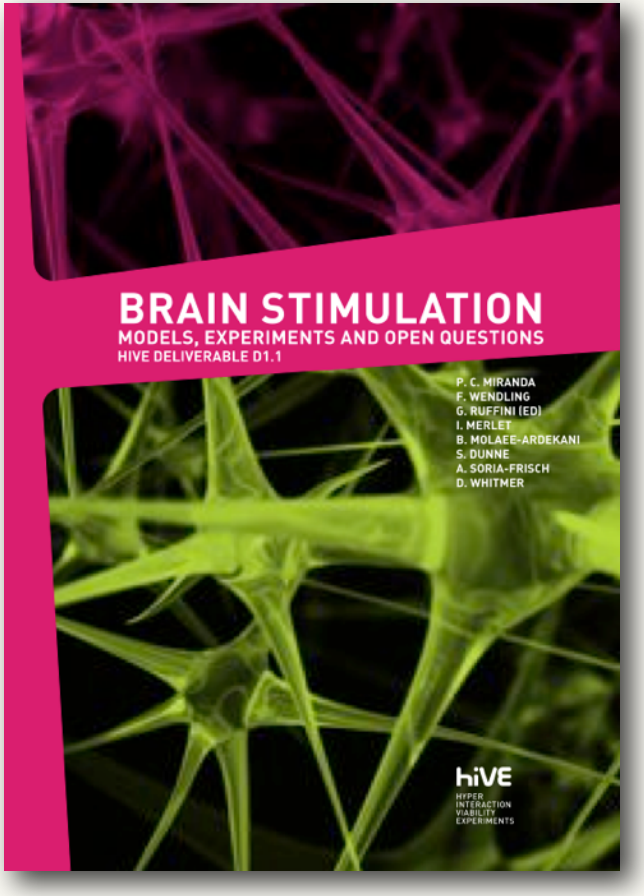
Work now available for many years in vitro and in vivo shows:

- Weak E fields from tCS alter / modulate neuronal firing rates (concurrent effects) up or down
- The effects last longer than the stimulation (aftereffects)
- Brain connectivity altered


IEEE TRANSACTIONS ON NEURAL SYSTEMS AND REHABILITATION ENGINEERING, VOL. 21, NO. 3, MAY 2013 333

Transcranial Current Brain Stimulation (tCS): Models and Technologies

Giulio Ruffini, Fabrice Wendling, Isabelle Merlet, Behnam Molaee-Ardekani, Abeye Mekonnen, Ricardo Salvador, Aureli Soria-Frisch, Carles Grau, Stephen Dunne, and Pedro C. Miranda



wiki.neuroelectrics.com

Effects on firing rates. Linear dependence of firing rates on field

MEASUREMENT OF IMPOSED VOLTAGE GRADIENT ADEQUATE TO MODULATE NEURONAL FIRING*

BY C. A. TERZUOLO AND T. H. BULLOCK

DEPARTMENT OF ZOÖLOGY, UNIVERSITY OF CALIFORNIA, LOS ANGELES

Communicated by H. W. Magoun, July 6, 1956

Many authors[1-31] have described the effects of polarization by imposed electric current upon nerve cells. We have not seen in the literature, however, a quantitative evaluation of the sensitivity of nerve cells to electric fields in terms of voltage gradient across some appropriate dimension of the neuron. We have undertaken to estimate the threshold value as being the unique value of greatest interest and have found this to be far lower for modulation of the frequency of an already active neuron than for the excitation of a silent one.

3. In the most effective axis of polarization, it was found that a voltage gradient in the neighborhood of 0.1 mv/100 μ markedly influenced active cells. Currents of more than 20 times this value are required to fire a silent cell, even if it has been poised, i.e., the adapting stretch receptor, under a physiological degree of stretch.

In vitro, crayfish and lobster

Weak Electric fields seen to modulate ongoing activity, but cannot start it

Orientation-dependence seen

EXPERIMENTAL NEUROLOGY 5, 436-452 (1962)

cat encephale isole

Influence of Transcortical d-c Currents on Cortical Neuronal Activity

OTTO D. CREUTZFELDT, GERHARD H. FROMM, AND HERMANN KAPP[1]

Abteilung für Klinische Neurophysiologie, University of Freiburg, Freiburg i. Br., Germany

Received October 23, 1961; and January 30, 1962

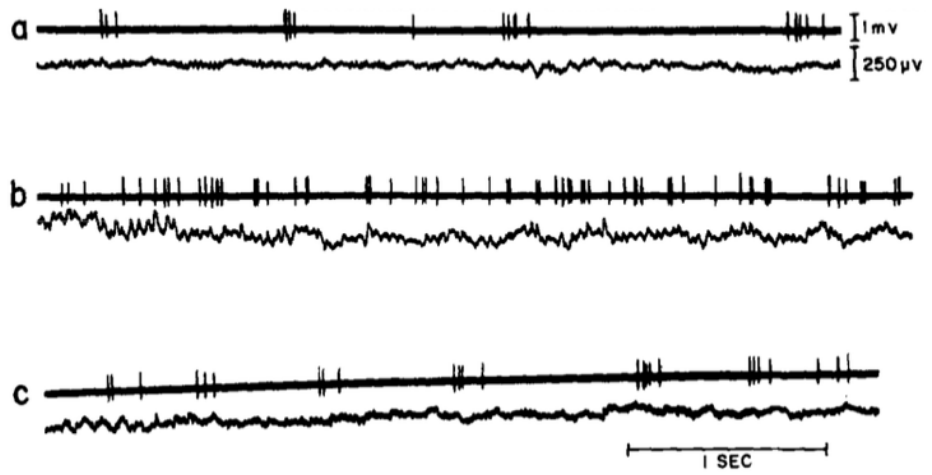
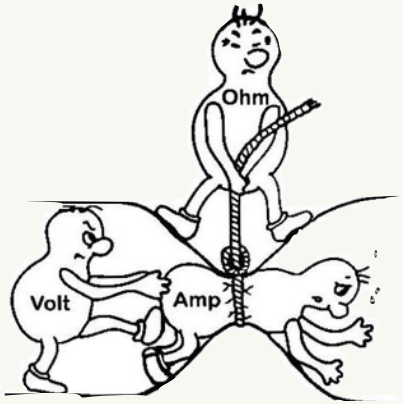


FIG. 1. Effect of transcortical d-c current on spontaneous neuron activity and EEG in the motor cortex; *a*, control; *b*, 1,000 µa inward (surface-positive); *c*, control, 20 sec after *b*.

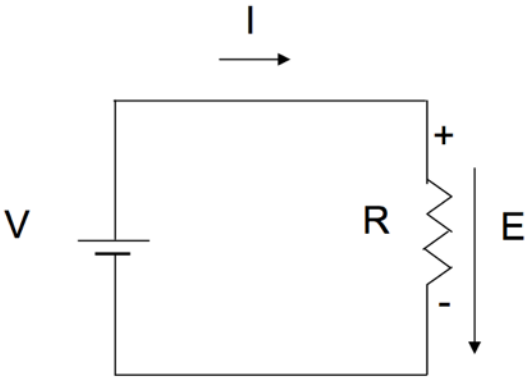
A bit of physics: current and electric vector fields



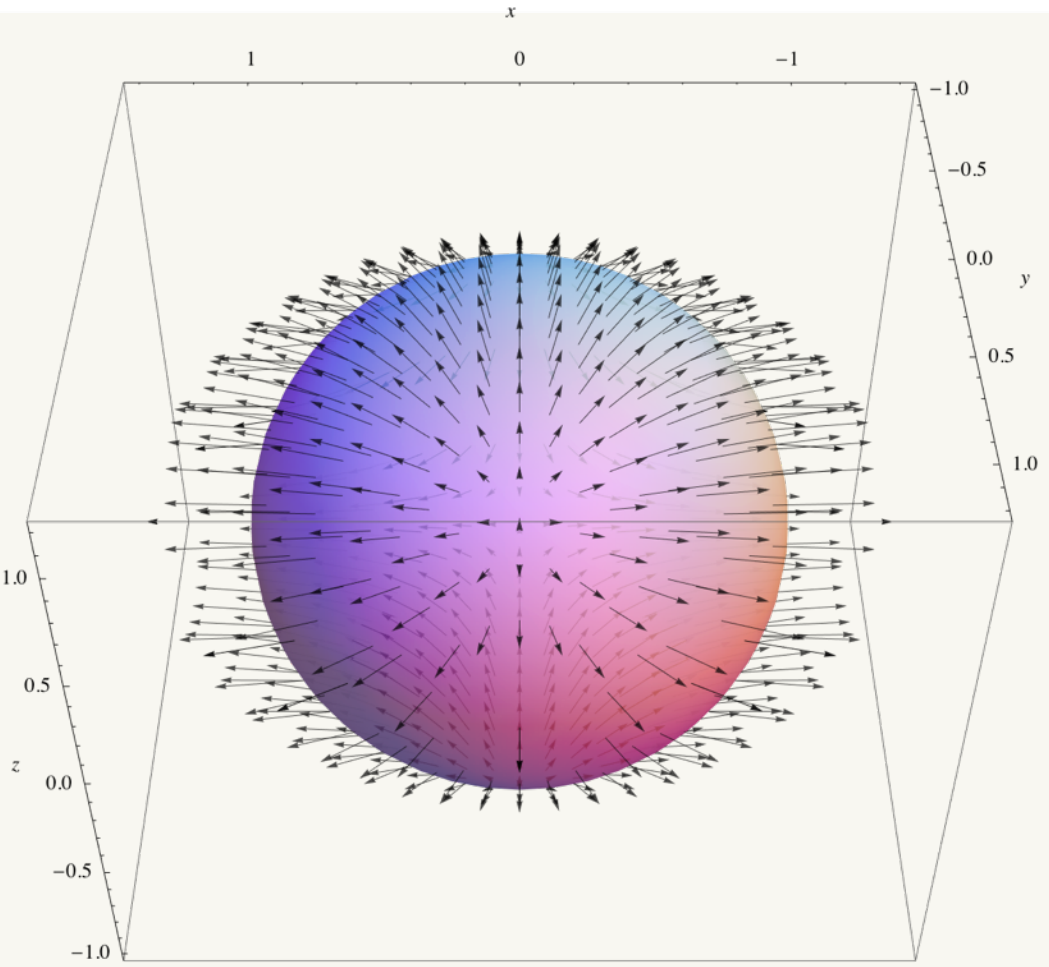
Ohm's law,
V= I R is the same as

$$J = \sigma E,$$

Current and electric vectors are proportional to each other.

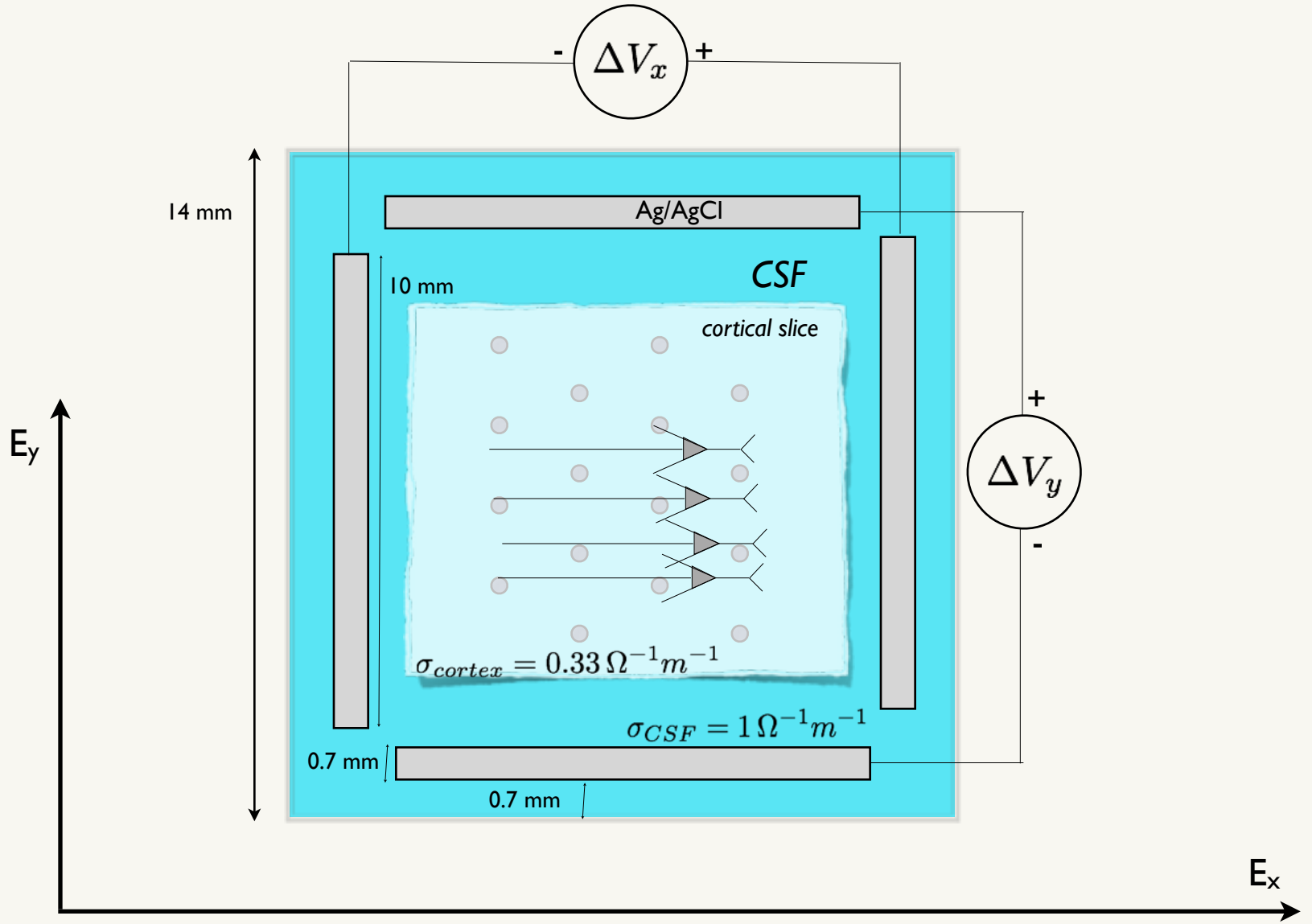


Charges accumulate at boundaries

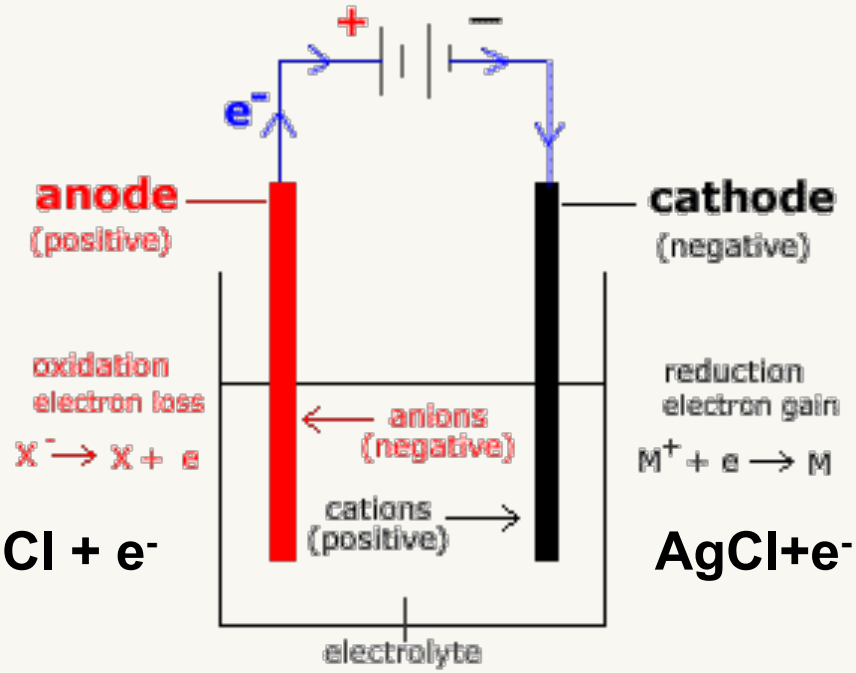


"Vector Field on a Sphere" by Glosser.ca - Own work.
Licensed under Public Domain via Wikimedia Commons

Fields and neurons in flatland



The head as an electrolyte



Ag+Cl$^-$ ☞ AgCl + e$^-$

AgCl+e$^-$ ☞ Ag + Cl$^-$

⇐ Cl$^-$

Where is the electron? It depends.

Chemical reactions take place.

Orientation of Electric field is important

J. Physiol. (1981), **319**, *pp.* 143–152
With 5 text-figures
Printed in Great Britain

INFLUENCE OF ELECTRIC FIELDS ON THE EXCITABILITY OF GRANULE CELLS IN GUINEA-PIG HIPPOCAMPAL SLICES

By J. G. R. JEFFERYS

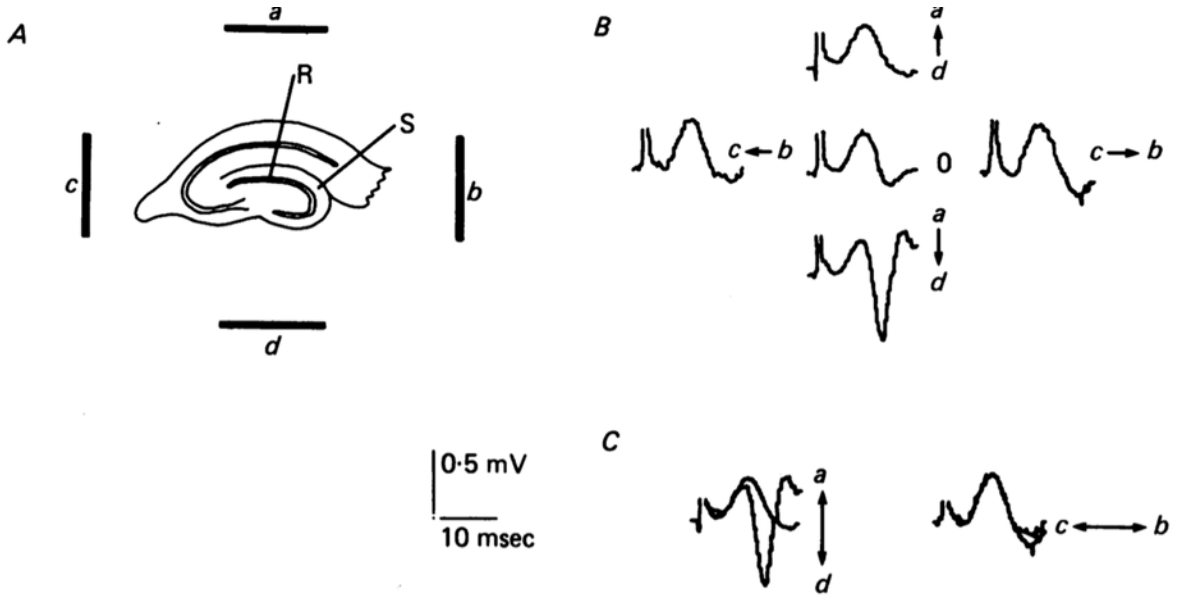
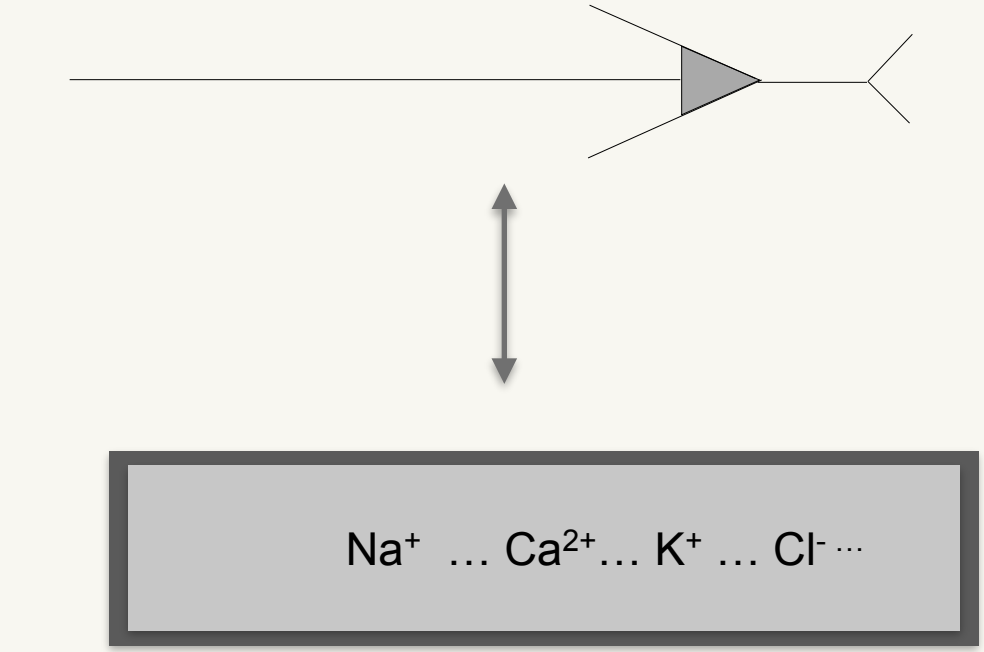
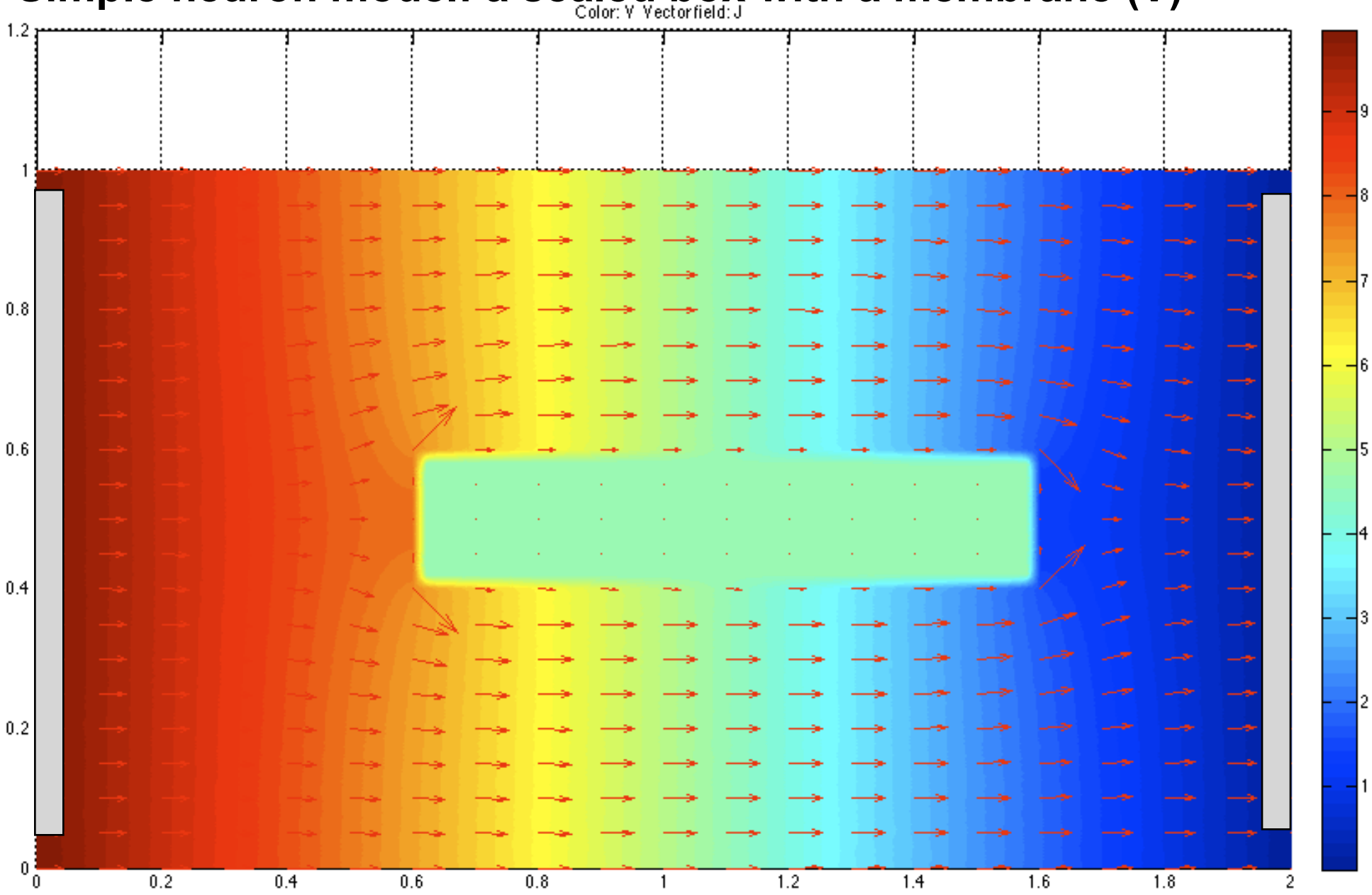


Fig. 1. Effect of direction of polarizing current. *A*, polarization currents were passed across a transverse slice, between gross electrodes positioned in the artificial c.s.f. at sites *a* and *d* or *b* and *c* (S, stimulus, site; R, recording site). The polarization potential gradient was 17 mV/mm, measured over a 250 μm track in the slice. Responses to afferent volleys were recorded from the cell body layer and are labelled with the direction of conventional current (*B*). To aid comparison, responses under both directions of current have been superimposed for each electrode pair (*C*). Temperature was 27 °C.

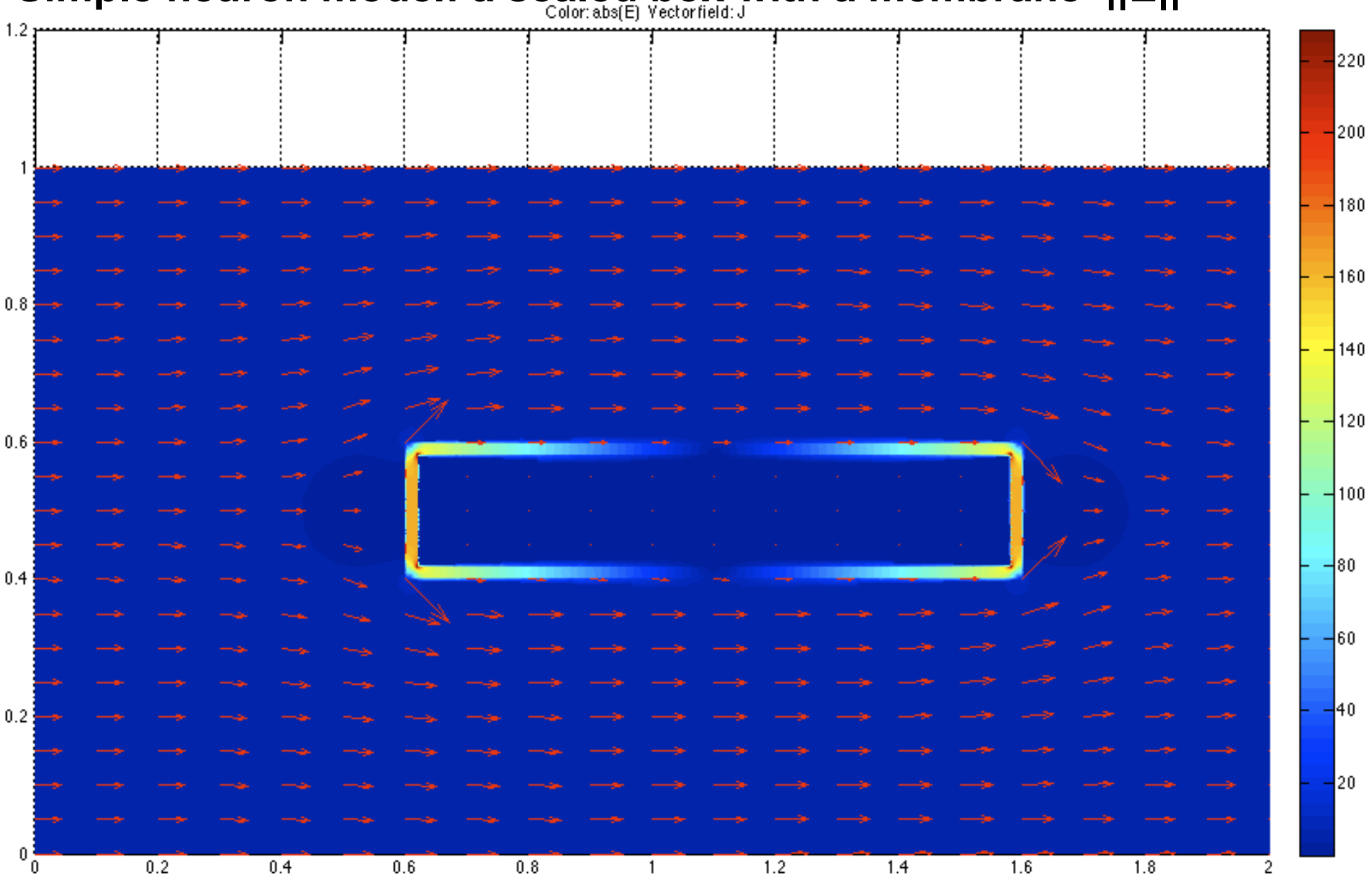


Simple neuron model: a sealed (ok, leaky) box with a membrane

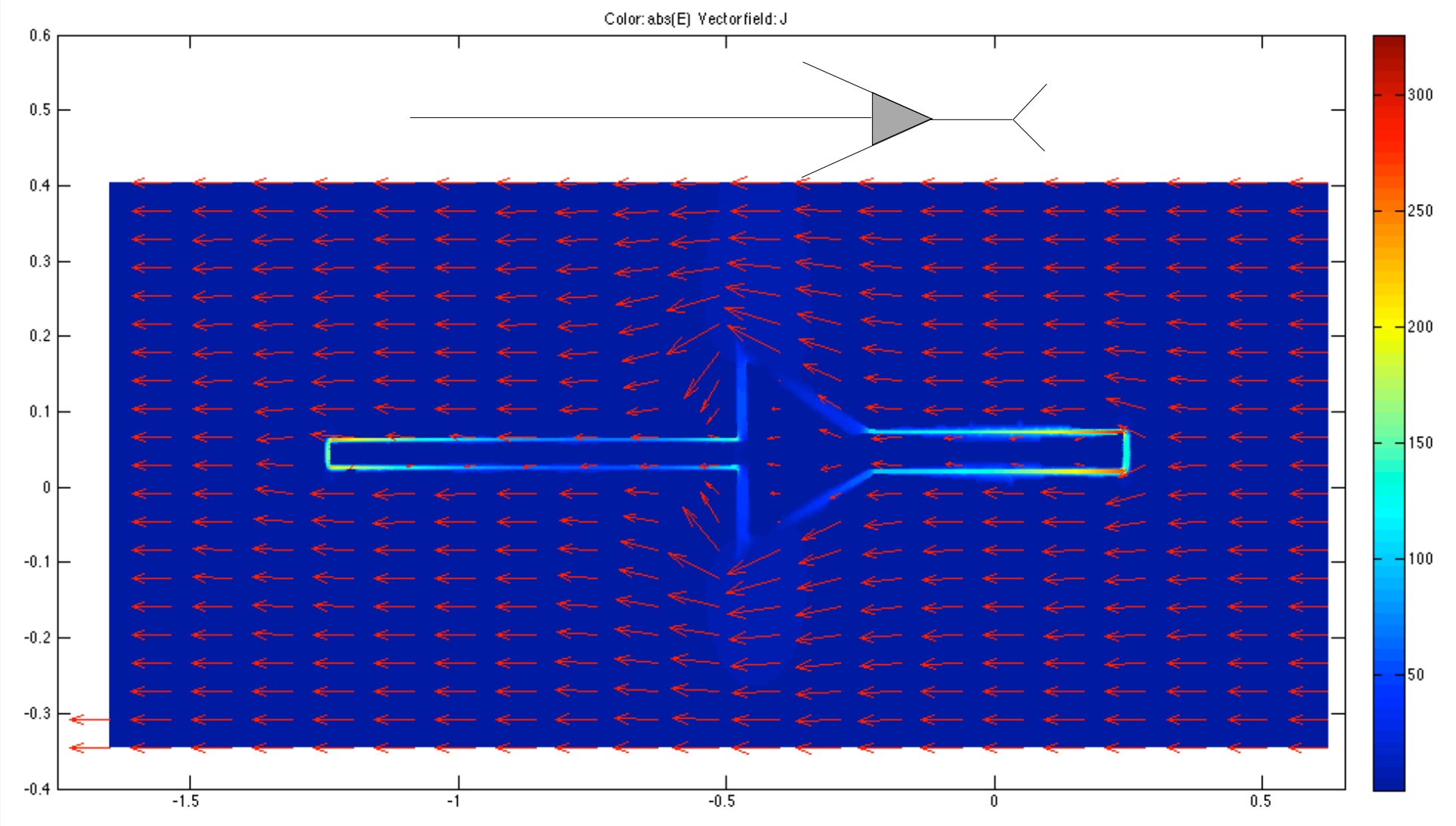
Simple neuron model: a sealed box with a membrane (V)



Simple neuron model: a sealed box with a membrane ||E||



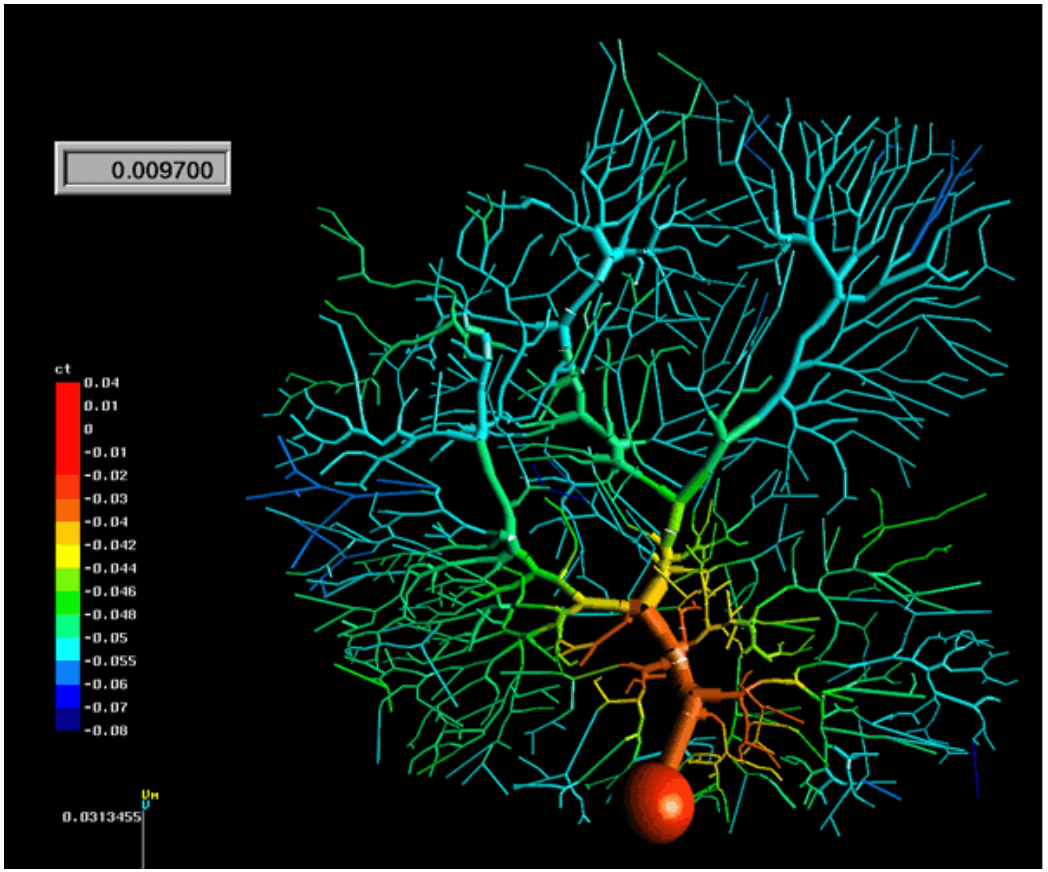
A bit more realistic neuron model (||E||)



Going beyond…is hard. But needed.

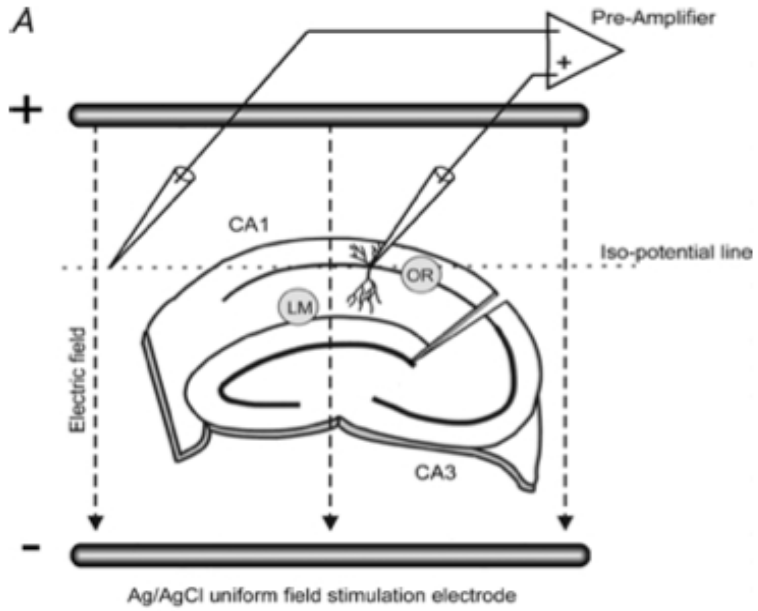
Purkinje cell		DCN neuron	
surface area:	261,000 μm^2	• surface area:	11,056 μm^2
number of synapses (ex/in):	175,000 / 5,000	• number of synapses (ex/in):	5,000 / 15,000
number of inputs / s	350,000 / 10,000	• number of inputs / s	25,000 / 750,000

The Book of GENESIS
Exploring Realistic Neural Models
with the GEneral NEural SImulation System

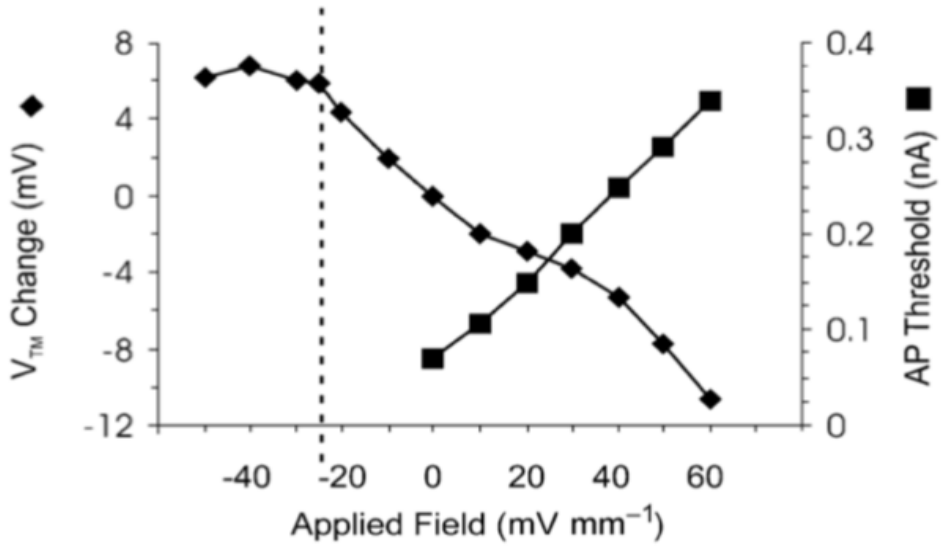


http://www.brains-minds-media.org/archive/222

The E-field and the transmembrane potential (linearity)



Rat hippocampal slices

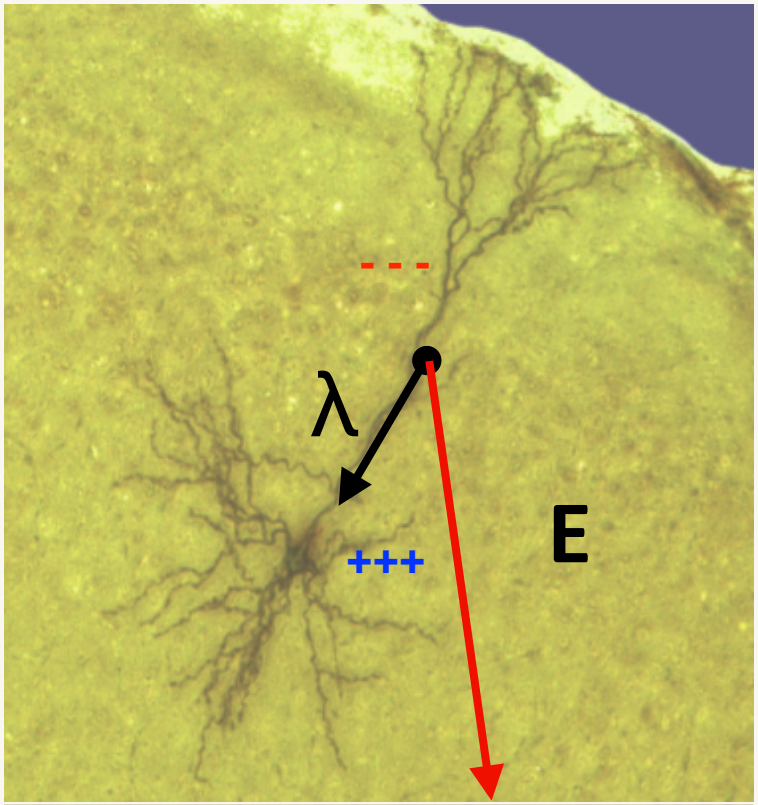


J Physiol 557.1 (2004) pp 175–190

Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices *in vitro*

Marom Bikson[1], Masashi Inoue[2], Hiroki Akiyama[2], Jackie K. Deans[1], John E. Fox[1], Hiroyoshi Miyakawa[2] and John G. R. Jefferys[1]

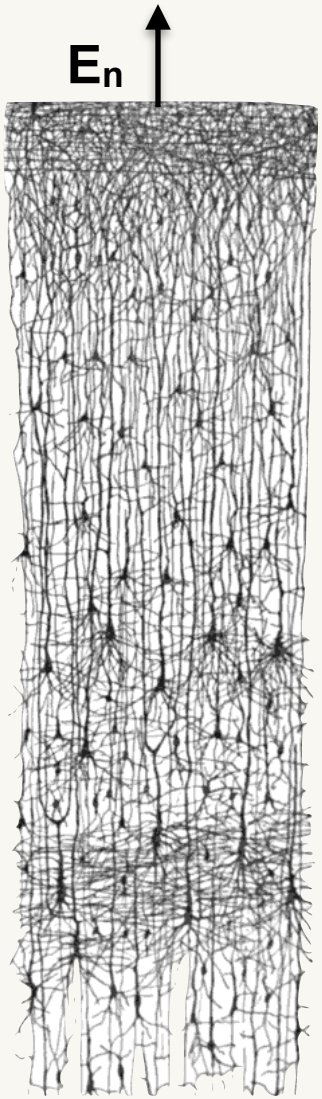
A linear, orientation dependent model

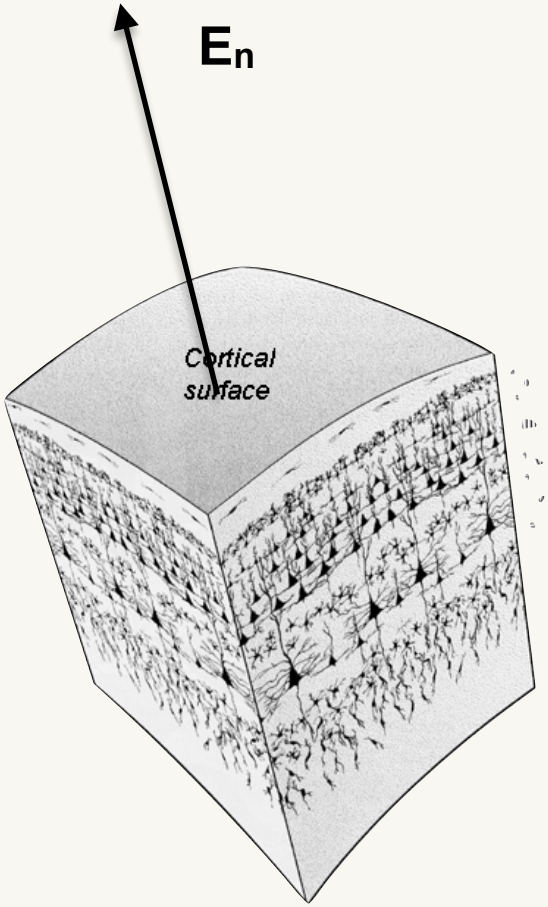


- **λ** points from tree to axon termination
- First order effect from dot product of E and λ
- Units of $\delta\Phi = E \cdot \lambda$ are Volts

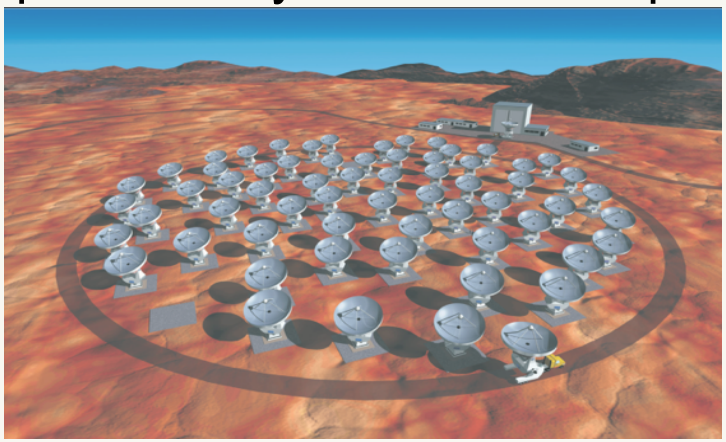
$$\delta\Phi = \lambda \cdot E$$

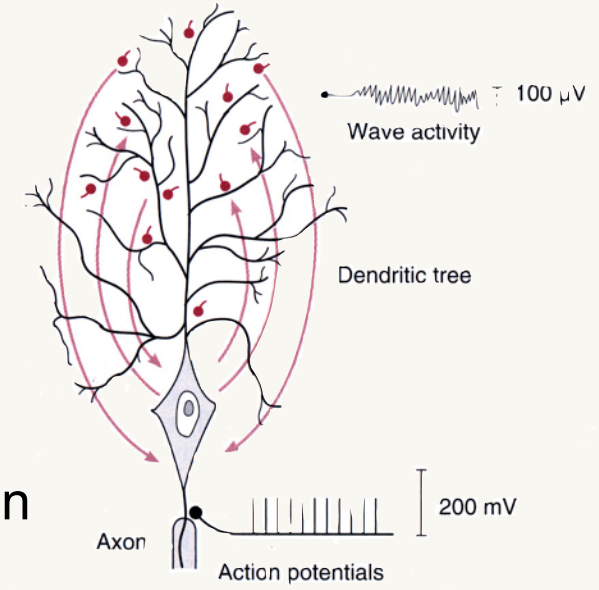
Coherence enhances everything





phase array - radio telescope





EEG generation

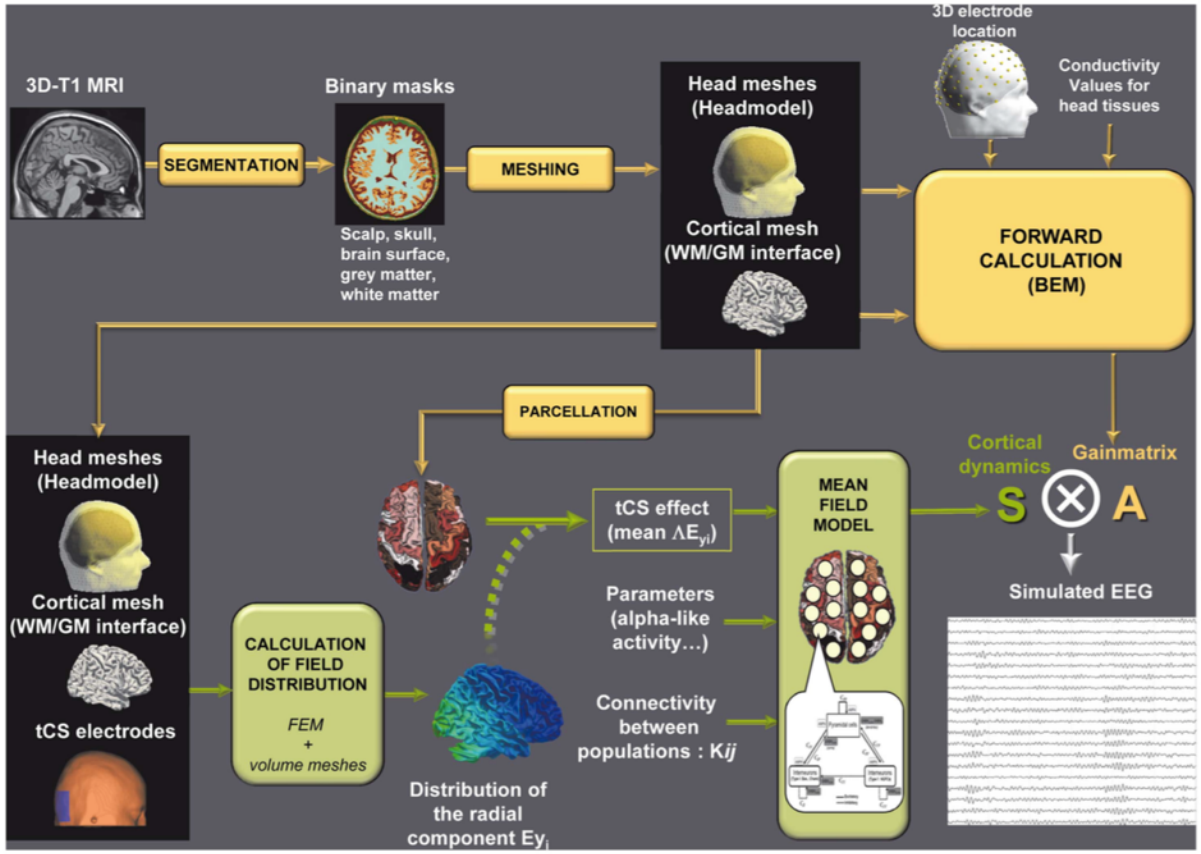
Merlet et al 2013 (tCS+EEG modeling)

OPEN ACCESS Freely available online

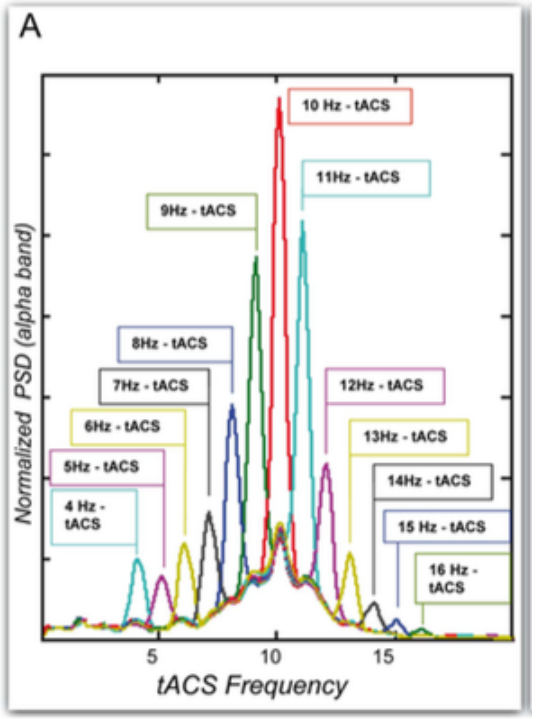
PLOS | ONE

From Oscillatory Transcranial Current Stimulation to Scalp EEG Changes: A Biophysical and Physiological Modeling Study

Isabelle Merlet[1,2*], Gwénaël Birot[1,2], Ricardo Salvador[3], Behnam Molaee-Ardekani[1,2], Abeye Mekonnen[3], Aureli Soria-Frish[4], Giulio Ruffini[4], Pedro C. Miranda[3,5], Fabrice Wendling[1,2]



Connecting stimulation and EEG response: modeling can help to guide and interpret tCS experiments.



After-effects

J. Physiol (1964), **172**, *pp.* 369–382
With 9 text-figures
Printed in Great Britain

THE ACTION OF BRIEF POLARIZING CURRENTS ON THE CEREBRAL CORTEX OF THE RAT (1) DURING CURRENT FLOW AND (2) IN THE PRODUCTION OF LONG-LASTING AFTER-EFFECTS

BY LYNN J. BINDMAN*, O. C. J. LIPPOLD AND J. W. T. REDFEARN
From the Department of Physiology, University College London

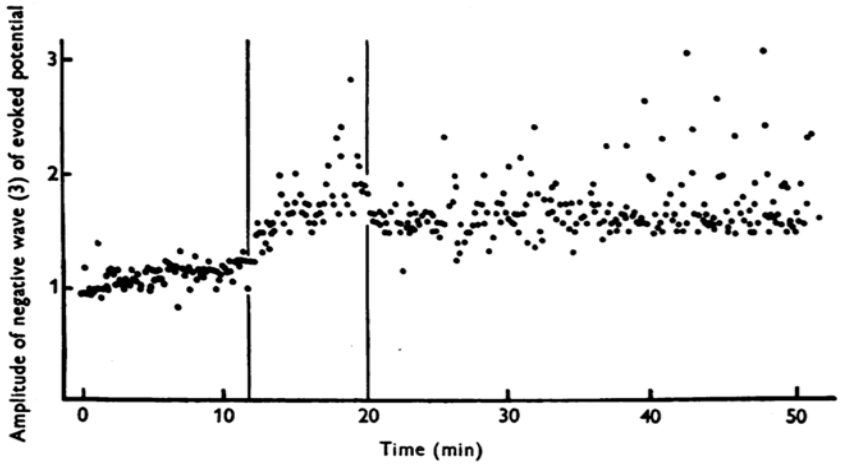


Fig. 4. The after-effect of surface-positive polarization on the peak amplitude (mV) of the evoked potential. (Negative wave (3), recorded from the depth of minimum latency.) Between the 12th and 20th min a current of 25 μA was passed radially through the somatosensory cortex. Area of exposed pia 12 mm^2.

Recent history: TMS used to study tDCS after-effects in humans

11055 *Journal of Physiology* (2000), **527.3**, *pp.*633–639 633

Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation

M. A. Nitsche and W. Paulus

Department of Clinical Neurophysiology, University of Goettingen, Robert Koch Strasse 40, 37075 Goettingen, Germany

(Received 8 May 2000; accepted after revision 5 June 2000)

1. In this paper we demonstrate in the intact human the possibility of a non-invasive modulation of motor cortex excitability by the application of weak direct current through the scalp.
2. Excitability changes of up to 40%, revealed by transcranial magnetic stimulation, were accomplished and lasted for several minutes after the end of current stimulation.
3. Excitation could be achieved selectively by anodal stimulation, and inhibition by cathodal stimulation.
4. By varying the current intensity and duration, the strength and duration of the after-effects could be controlled.
5. The effects were probably induced by modification of membrane polarisation. Functional alterations related to post-tetanic potentiation, short-term potentiation and processes similar to postexcitatory central inhibition are the likely candidates for the excitability changes after the end of stimulation. Transcranial electrical stimulation using weak current may thus be a promising tool to modulate cerebral excitability in a non-invasive, painless, reversible, selective and focal way.

- **Long-term effects** are due to Hebbian learning: *neurons that fire together, wire together.*
- This is the basis for brain plasticity and memory
- With tDCS modulation of firing rates we can thus alter the connections of neurons

Current understanding of after effects

Modulation of firing rates means Hebbian processes such as LTD/ LTP are affected.

tCS polarization changes will no doubt increase “coincidence” of connected neurons.

Glutamate receptors such as NMDA involved.

Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation

M. A. Nitsche, K. Fricke, U. Henschke, A. Schlitterlau, D. Liebetanz, N. Lang, S. Henning, F. Tergau and W. Paulus

Department of Clinical Neurophysiology, Georg-August-University, Goettingen, Germany

Transcranial direct current stimulation (tDCS) of the human motor cortex results in polarity-specific shifts of cortical excitability during and after stimulation. Anodal tDCS enhances and cathodal stimulation reduces excitability. Animal experiments have demonstrated that the effect of anodal tDCS is caused by neuronal depolarisation, while cathodal tDCS hyperpolarises cortical neurones. However, not much is known about the ion channels and receptors involved in these effects. Thus, the impact of the sodium channel blocker carbamazepine, the calcium channel blocker flunarizine and the NMDA receptor antagonist dextromethorphane on tDCS-elicited motor cortical excitability changes of healthy human subjects were tested. tDCS-protocols inducing excitability alterations (1) only during tDCS and (2) eliciting long-lasting after-effects were applied after drug administration. Carbamazepine selectively eliminated the excitability enhancement induced by anodal stimulation during and after tDCS. Flunarizine resulted in similar changes. Antagonising NMDA receptors did not alter current-generated excitability changes during a short stimulation, which elicits no after-effects, but prevented the induction of long-lasting after-effects independent of their direction. These results suggest that, like in other animals, cortical excitability shifts induced during tDCS in humans also depend on membrane polarisation, thus modulating the conductance of sodium and calcium channels. Moreover, they suggest that the after-effects may be NMDA receptor dependent. Since NMDA receptors are involved in neuroplastic changes, the results suggest a possible application of tDCS in the modulation or induction of these processes in a clinical setting. The selective elimination of tDCS-driven excitability enhancements by carbamazepine proposes a role for this drug in focussing the effects of cathodal tDCS, which may have important future clinical applications.

(Received 24 June 2003; accepted after revision 26 August 2003; first published online 29 August 2003)

Some things to remember

What matters is the electric field, not the current density (although they are related). **Orientation matters.**

Electric fields move charges around. These accumulate at “bottlenecks” and create local secondary electric fields. E.g., at cell membranes.

However, when you keep control over the current density, we control also the electric field.

To control the transmembrane potentials of neurons, use electric fields. To generate them with transcranial currents, use **current-controlled** systems (not voltage controlled).

Our neuron model is very simple! Will apply better to long neuronal populations such cortical pyramidal cells.

tCS is mostly cortical. Focus on normal component of electric field (orthogonal to cortical surface), aligned with cortical pyramidal neurons.

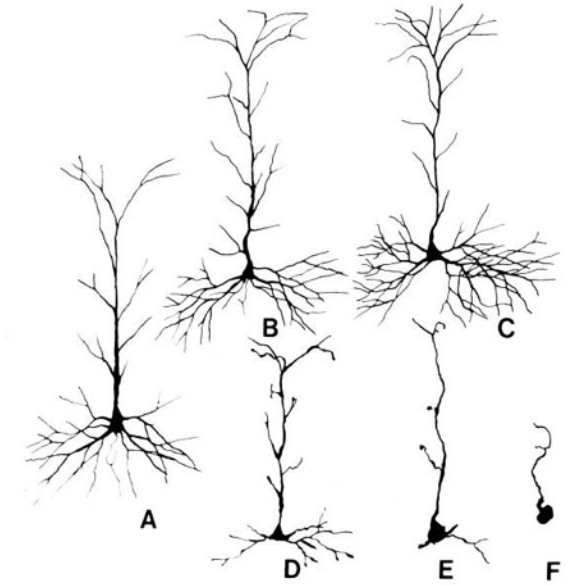
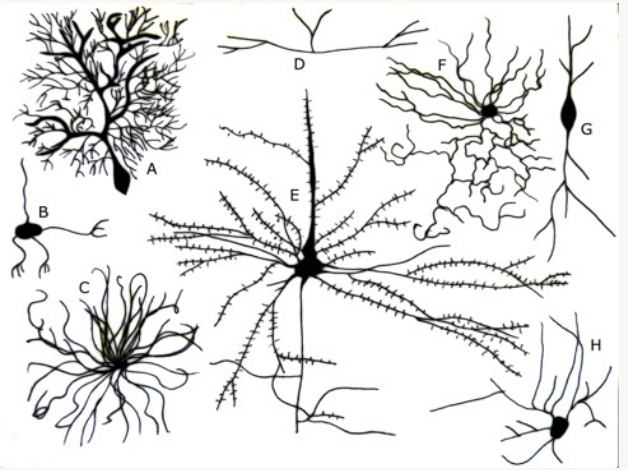
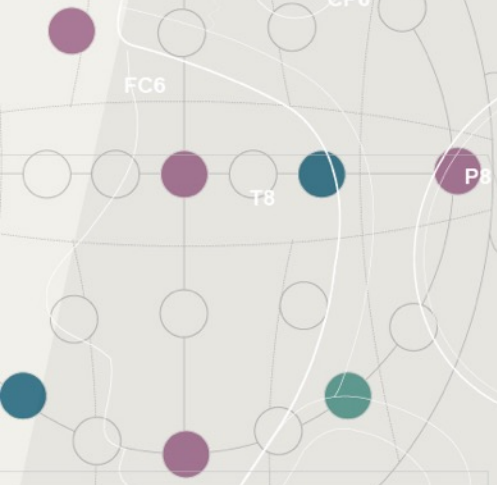
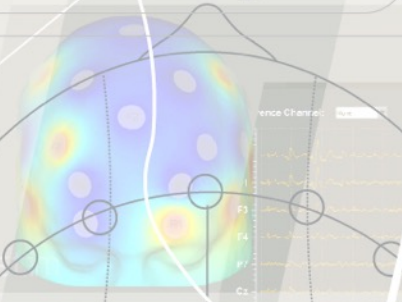


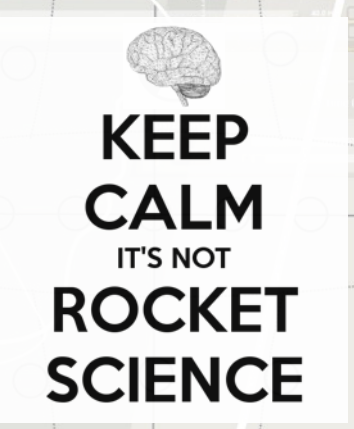
Figure 1. Two possible patterns of age-related alterations in cortical pyramidal cells. The normal mature neuron (A) may show regressive dendritic changes characterized by loss of basilar dendritic branches and eventual loss of the entire dendritic tree (D, E, F). Other neurons (B, C) may show progressive increase in dendritic branching. Drawing based on Golgi impregnations.



Modeling the electric field







Two bits of physics

Current and Electric field are proportional to each other (Ohm's law). If we include EEG generated currents($\boldsymbol{J^I}$), we can relate current density J and electric field E vectors by

$$J = J^I + \sigma E,$$

☞ **Controlling the current means we control the electric field.**

Currents and electric fields obey Poisson's equation. If you know tissue parameters and geometry of brain structures, it is possible to model quite precisely currents and fields:

$$\nabla \cdot J^I + \nabla \cdot (\sigma E) = 0.$$

The same equation governs tCS and EEG generated electric fields.

What about tACS, tRNS … ?

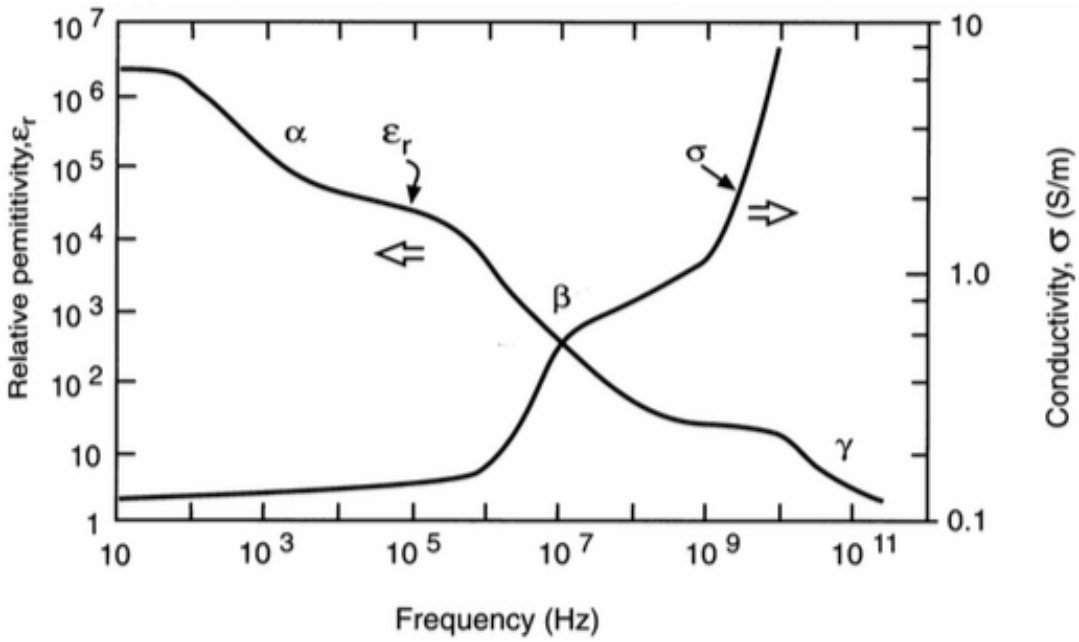


Figure 2.1 – Frequency variation of dielectric properties of typical soft tissue (from [Reilly:1998aa])

Quasistatic approximation < 10-100 KHz

History - pre FEM - The spherical brain

IEEE TRANSACTIONS ON BIO-MEDICAL ENGINEERING, VOL. BME-16, NO. 1, JANUARY 1969 15

EEG Electrode Sensitivity—An Application of Reciprocity

STANLEY RUSH, SENIOR MEMBER, IEEE, AND DANIEL A. DRISCOLL, STUDENT MEMBER, IEEE

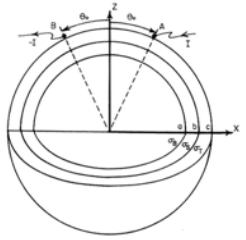


Fig. 5. Geometry for the three-concentric-sphere proof.

Annals of Biomedical Engineering, Vol. 19, pp. 317-328, 1991
Printed in the USA.
0090-6964/91 $3.00 + .00

ELSEVIER

Computers in Biology and Medicine

Computers in Biology and Medicine 35 (2005) 133–155
http://www.intl.elsevierhealth.com/journals/cobm

Transcranial electric stimulation of motor pathways: a theoretical analysis☆

Mark M. Stecker*

Department of Neurology, Geisinger Medical Center, 100 N Academy Rd., Danville, PA 17821, USA

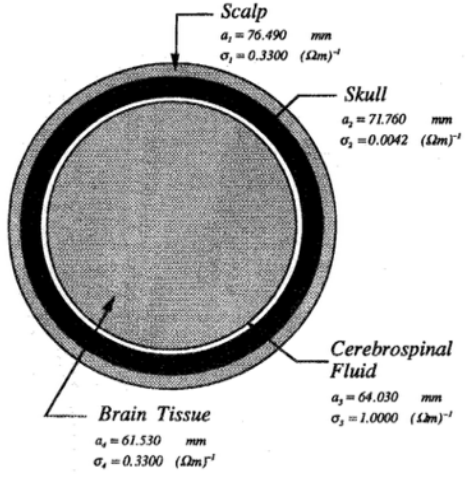
A Theoretical Comparison of Electric and Magnetic Stimulation of the Brain

Joshua M. Saypol,* Bradley J. Roth,* Leonardo G. Cohen,† and Mark Hallett†

IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, VOL. 43, NO. 9, SEPTEMBER 1996

Potential and Current Density Distributions of Cranial Electrotherapy Stimulation (CES) in a Four-Concentric-Spheres Model

Mohammed Ferdjallah, *Member, IEEE*, Francis X. Bostick, Jr., and Ronald E. Barr,* *Member, IEEE*



FEM modeling!

NE neuroelectrics ®

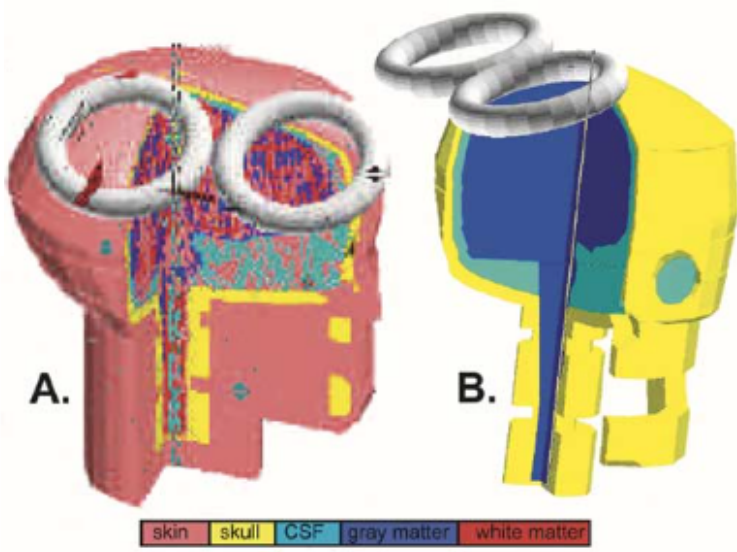
Three-Dimensional Head Model Simulation of Transcranial Magnetic Stimulation

Tim A. Wagner*, Markus Zahn, *Fellow, IEEE*, Alan J. Grodzinsky, and Alvaro Pascual-Leone

ELSEVIER

Clinical Neurophysiology 117 (2006) 1623–1629

www.elsevier.com/locate/clinph



Modeling the current distribution during transcranial direct current stimulation

Pedro Cavaleiro Miranda [a,*], Mikhail Lomarev [b], Mark Hallett [b]

[a] *Faculty of Sciences, Institute of Biophysics and Biomedical Engineering, University of Lisbon, Campo Grande, 1749-016 Lisbon, Portugal*
[b] *Human Motor Control Section, MNB, NINDS, National Institutes of Health, Bethesda, MD 20892-1428, USA*

Accepted 7 April 2006

IOP PUBLISHING JOURNAL OF NEURAL ENGINEERING

J. Neural Eng. **5** (2008) 163–174 doi:10.1088/1741-2560/5/2/007

Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis

Abhishek Datta[1], Maged Elwassif[1], Fortunato Battaglia[2] and Marom Bikson[1,3]

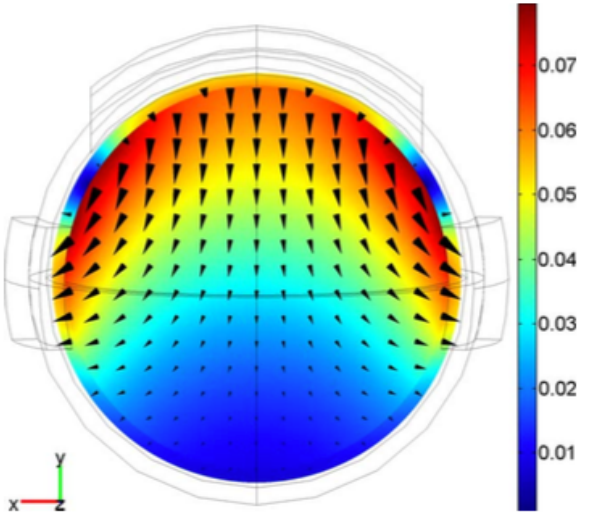


Fig. 5. The magnitude and direction of the current density in the brain and

Modeling comes of age: realistic FEM models

neuroelectrics®

32nd Annual International Conference of the IEEE EMBS
Buenos Aires, Argentina, August 31 - September 4, 2010

Modeling the electric field induced in a high resolution realistic head model during transcranial current stimulation

R. Salvador, A. Mekonnen, G. Ruffini, P. C. Miranda

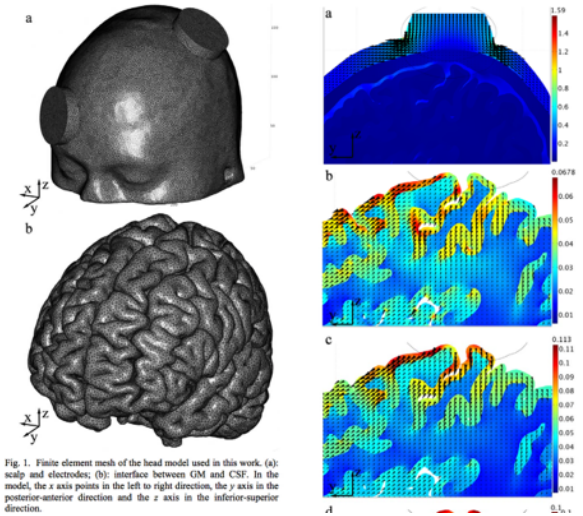


Fig. 1. Finite element mesh of the head model used in this work. (a): scalp and electrodes; (b): interface between GM and CSF. In the model, the *x* axis points in the left to right direction, the *y* axis in the posterior-anterior direction and the *z* axis in the inferior-superior direction.

Brain Stimulation (2011) 4, 169–74

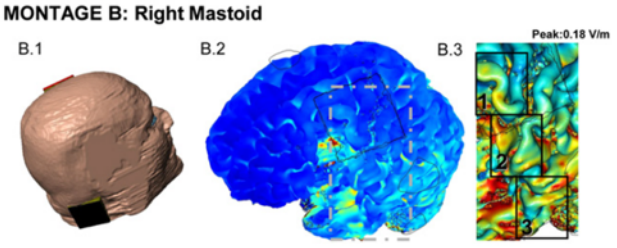
ELSEVIER

BRAIN
STIMULATION

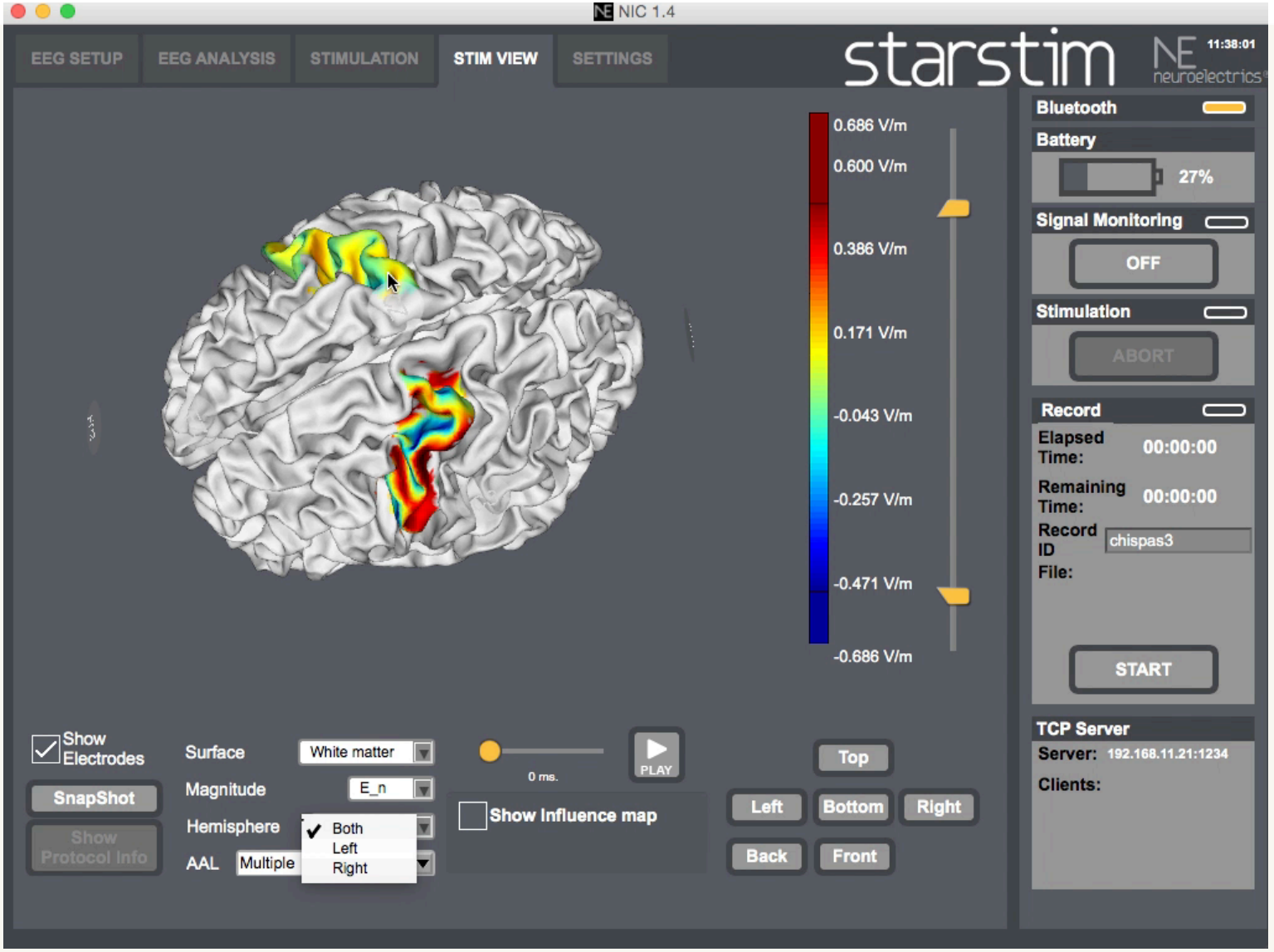
www.brainstimjrnl.com

Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient

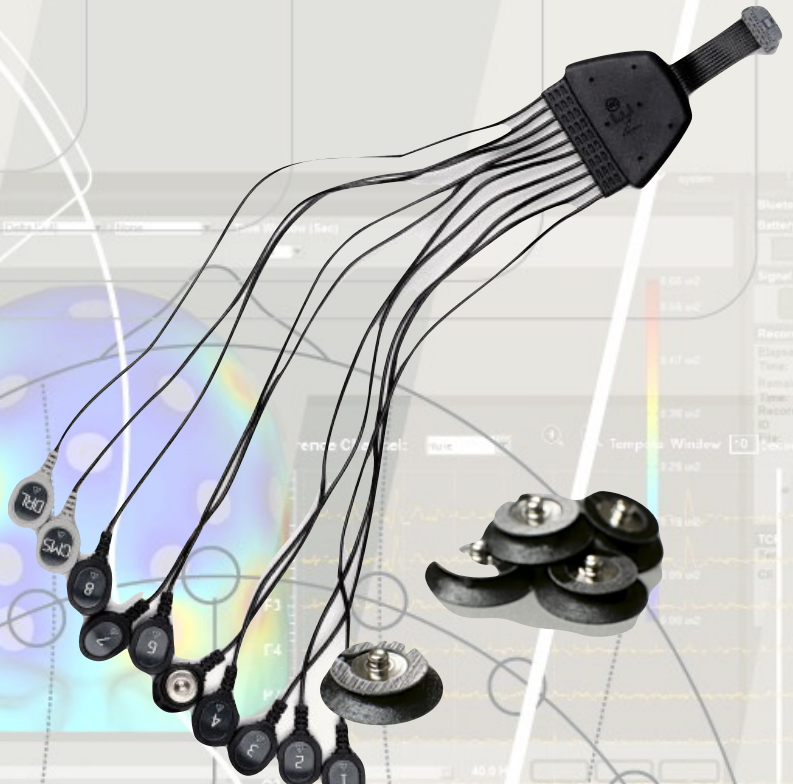
Abhishek Datta,[a] Julie M. Baker,[b] Marom Bikson,[a] Julius Fridriksson[b]



Visualizing the E field



Going Multichannel (MtCS)



Back in 2008 … we wanted:

Stimulate:

- Controlled - safe - multi-site stimulation (frequencies, intensities, phase relationships control)
- Independent current control at each electrode
- Use EEG like electrodes (more precise)

Measure:

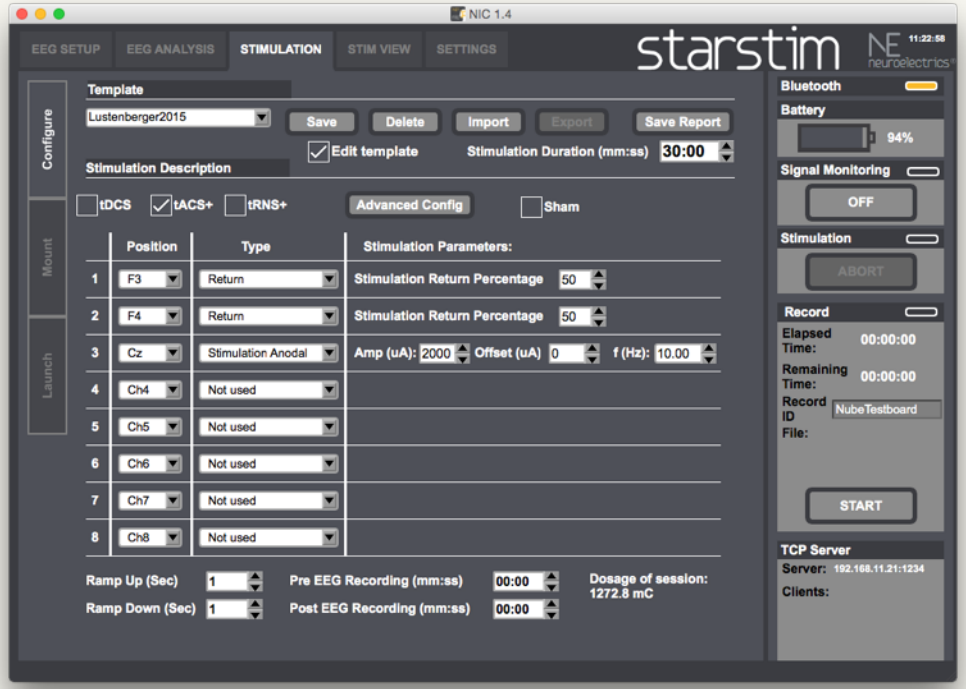
- Dual-use electrodes (stimulation + EEG)
- Measure while stimulating

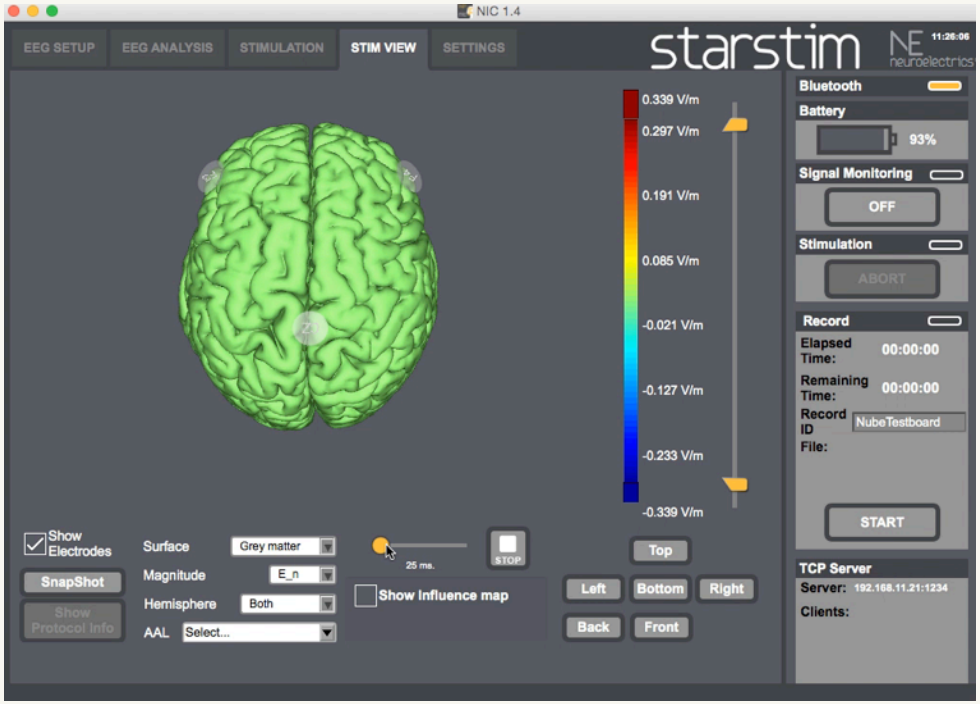
Visualize and adapt:

- Simulate E-fields generated
- Provide EEG features online, visualization and feedback
- Provide data services
- Eventually close the loop

HIVE - EU FET OPEN Project (2008-2012)

Lustenberger et al 2015: MtACS





CORTEX 67 (2015) 74–82

Available online at www.sciencedirect.com

ScienceDirect

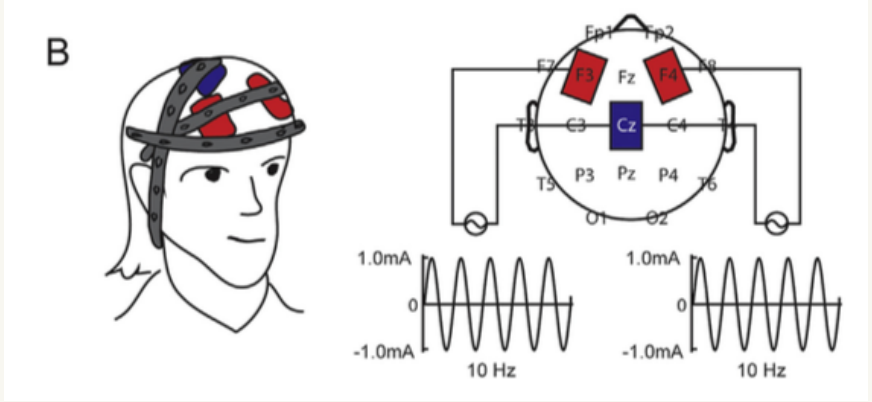
Journal homepage: www.elsevier.com/locate/cortex

ELSEVIER

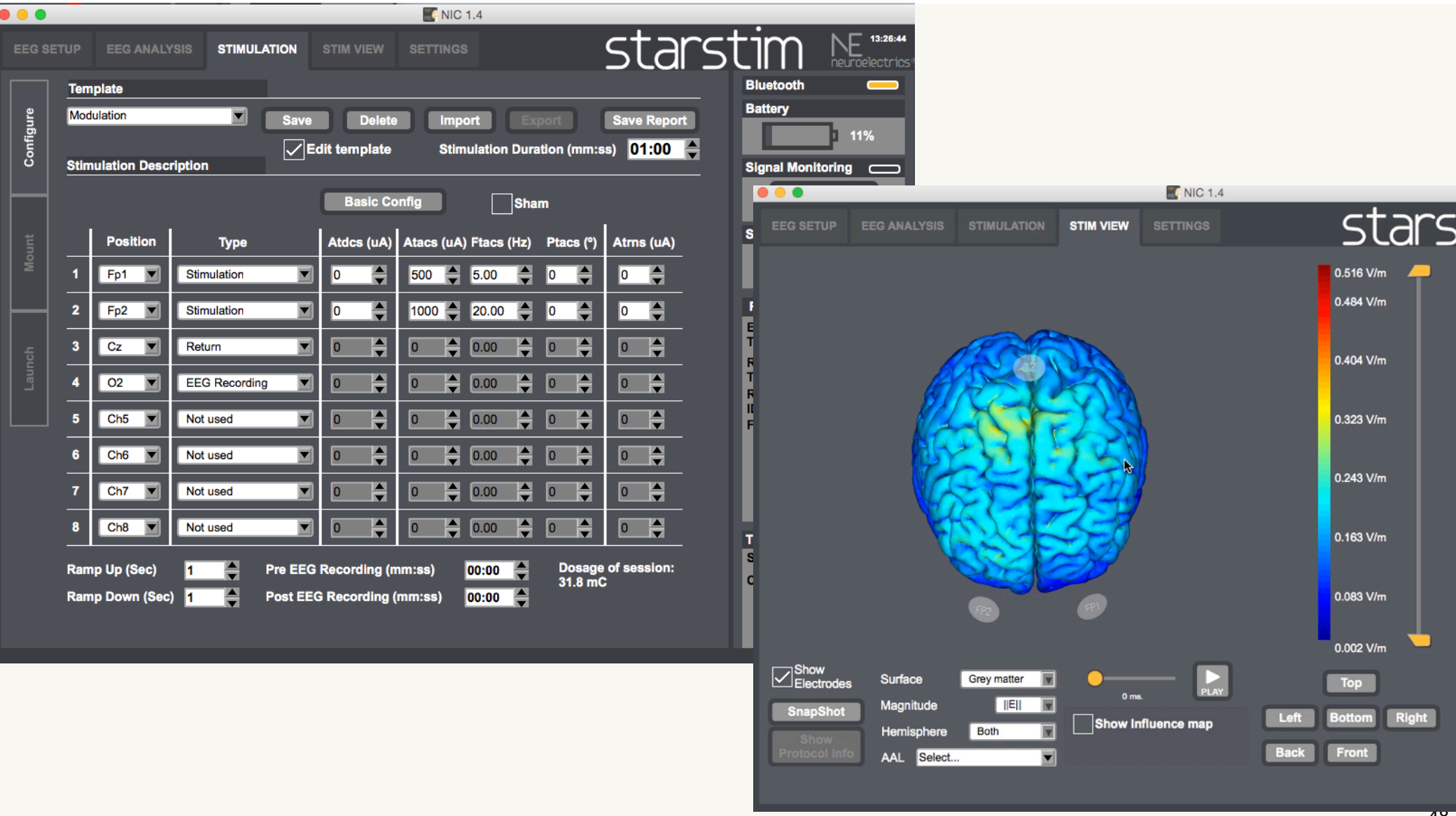
Research report

Functional role of frontal alpha oscillations in creativity

Caroline Lustenberger [a], *Michael R. Boyle* [a,b], *A. Alban Foulser* [c], *Juliann M. Mellin* [a] *and Flavio Fröhlich* [a,b,d,e,f,*]

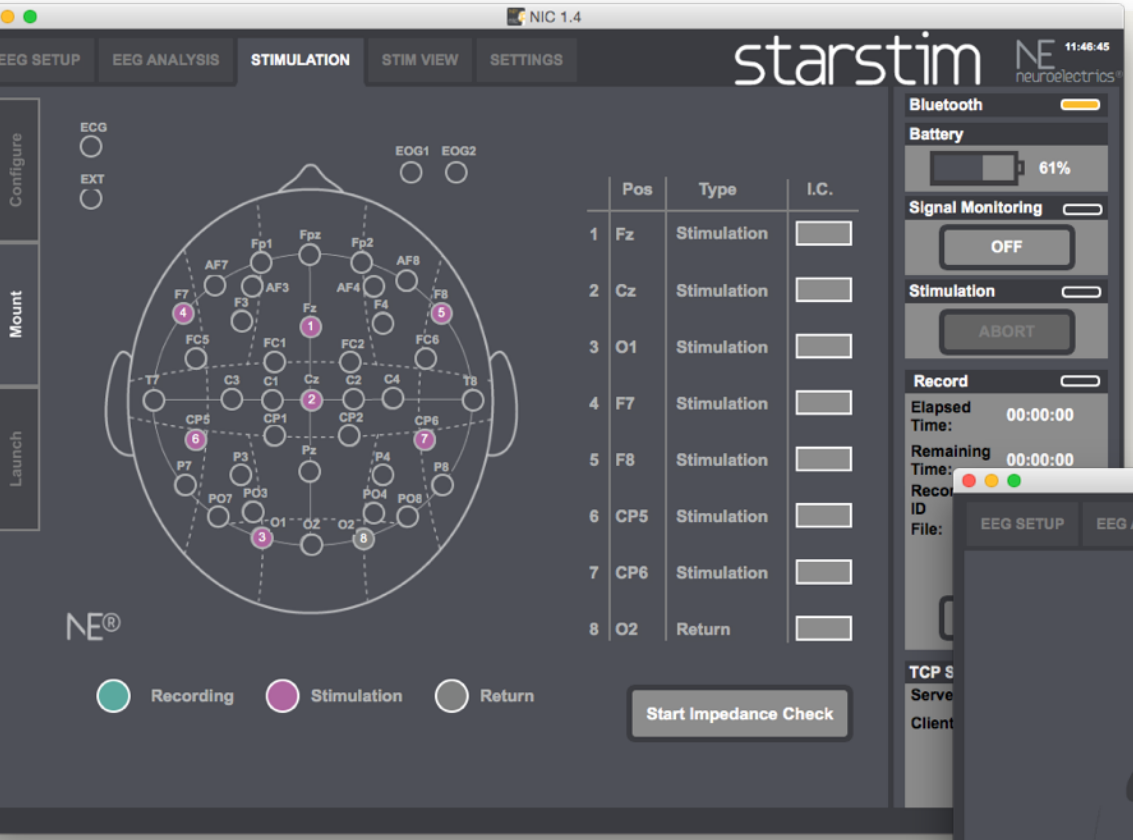


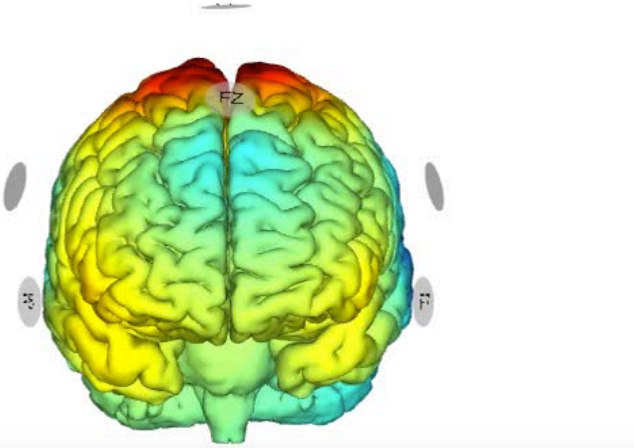
Adding different frequency current waveforms

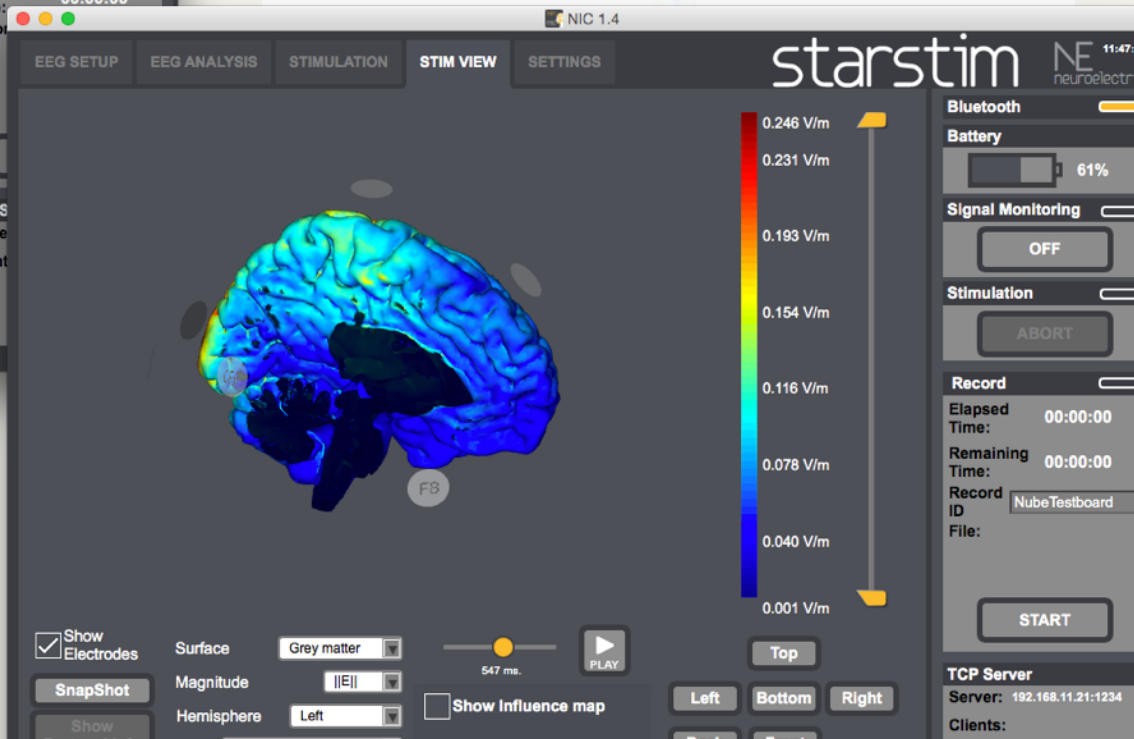


MtCS protocol configuration: phase control

MtCS protocol configuration: phase control

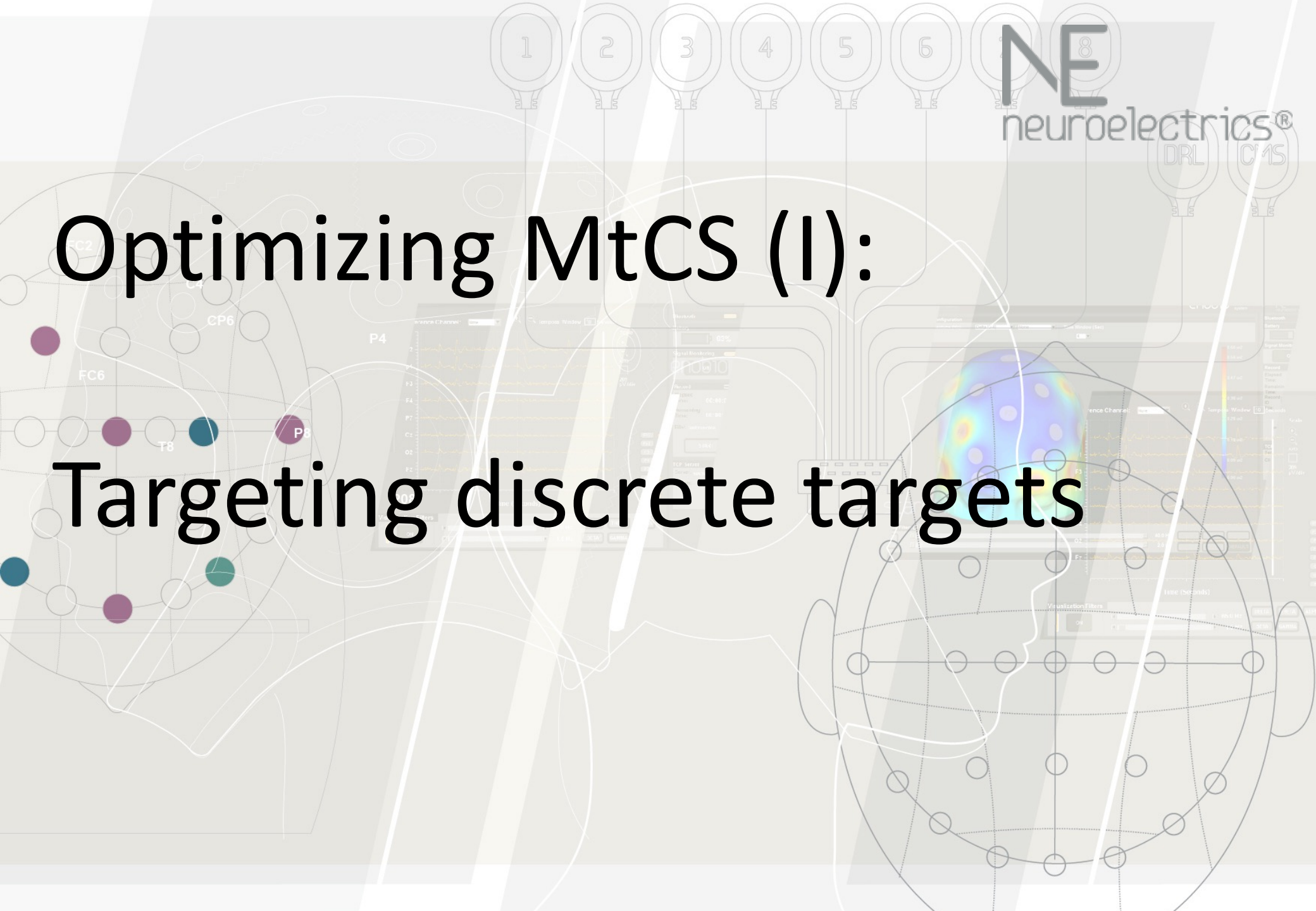






Optimizing MtCS (I):

Targeting discrete targets



The laplacian electrode in EEG (1975)

B. Hjorth, "An on-line transformation of EEG scalp potentials into orthogonal source derivations," *Electroenceph. Clin. Neurophysiol.*, vol. 39, pp. 526–530, 1975.

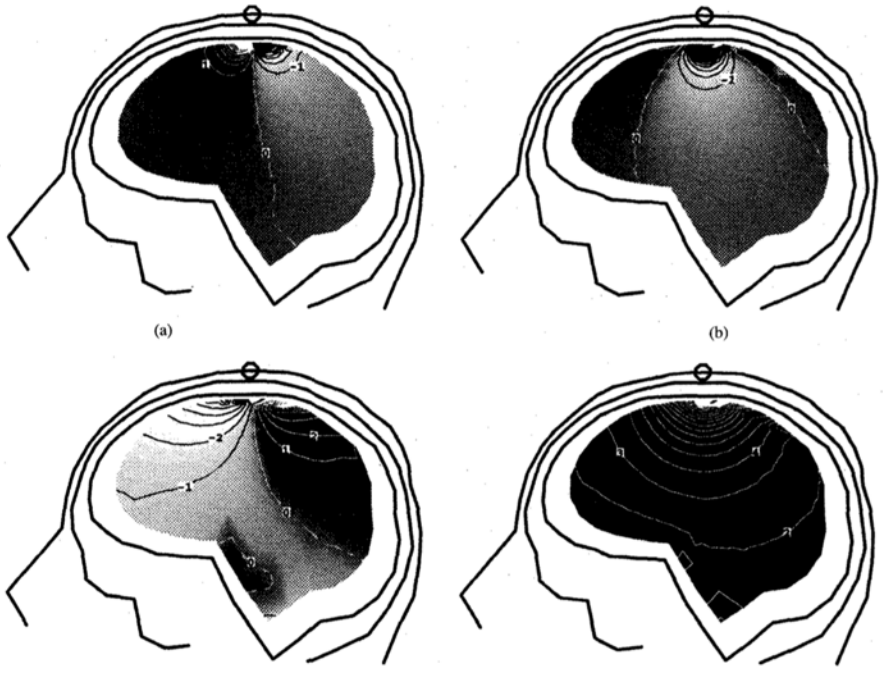


Fig. 3. Laplacian sensitivities for (a) horizontal and (b) vertical dipoles and potential sensitivities for (c) horizontal and (d) vertical dipoles in a cross section of the human head. The observation point is marked by a circle. Isofunction lines are drawn at linear intervals of $1\ V \cdot A^{-1} \cdot cm^{-3}$ and $1\ V \cdot A^{-1} \cdot cm^{-1}$, respectively. Positive isofunction lines are drawn in white, and negative ones in black. The zero-isofunction line is drawn as a dashed white line.

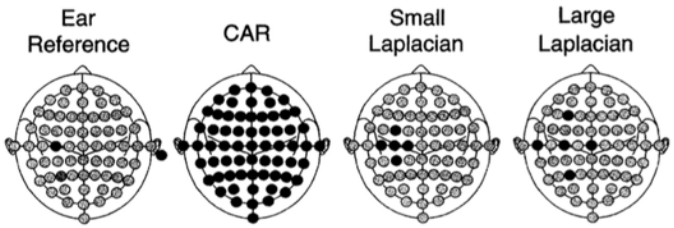


Fig. 1. Electrode locations used in the application of each spatial filter method to the activity recorded from C3 (red). During data acquisition, all elect
are referred to the ear reference. For the CAR and Laplacian methods, the activity at the green electrodes is averaged and subtracted from the activity

The surface Laplacian cannot be measured directly. In EEG, Hjorth [1] estimated the local values of the time-course of the surface Laplacian from potential recordings at the standard 10–20-electrode positions on the head. The surface Laplacian was estimated as the difference between the potential at a certain electrode and the average potential at the neighboring electrodes. In ECG work, a similar procedure was used by

Laplacian electrode montages (rings, 4x1)

31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Comparing different electrode configurations using the 10-10 international system in tDCS: a finite element model analysis

Paula Faria, Alberto Leal, Pedro C Miranda

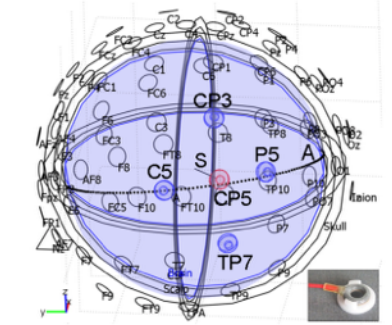
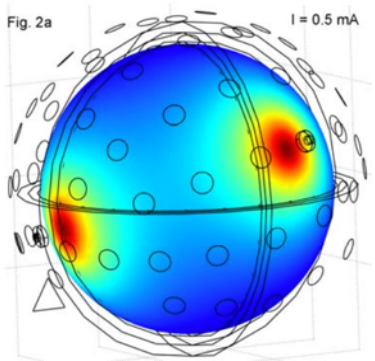


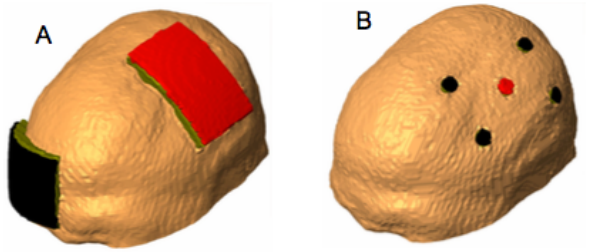
Fig. 1. Representation of the electrode montage M3, where tl cathode is placed on the left hemisphere at CP5 (red electrode) a the four anodes are placed around the cathode at C5, TP7, P5 and Cl (blue electrodes). The radial line (S) in the brain under CP5 and tl arc (A) on the surface of the brain and that passes under C5, CP5 a... P5 are also shown. The 10-10 system electrodes and the anatomic landmarks are also represented. A ring electrode placed on its adaptor is shown in the inset.



31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Bio-heat Transfer Model of Transcranial DC Stimulation: Comparison of Conventional Pad versus Ring Electrode

Abhishek Datta*, *Student Member, IEEE,* Maged Elwassif, and Marom Bikson

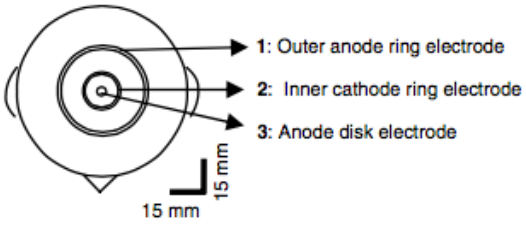


IOP Publishing
J. Neural Eng. 5 (2008) 163–174
Journal of Neural Engineering
doi:10.1088/1741-2560/5/2/007

Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis

Abhishek Datta[1], Maged Elwassif[1], Fortunato Battaglia[2] and Marom Bikson[1,3]

Electrode placement



HD-tDCS and MtCS – the lingo

31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Bio-heat Transfer Model of Transcranial DC Stimulation: Comparison of Conventional Pad versus Ring Electrode

Abhishek Datta*, *Student Member, IEEE,* Maged Elwassif, and Marom Bikson

The spatial focality (targeting) of tDCS has been proposed to increase using a "ring" electrode configuration with electrodes < 11 mm in diameter: 4 X 1 ring [6],[7]. Such stimulation electrodes owing to their proximity and reduced area are referred to as high density (HD) electrodes.

HD - originally a 4x1 concept as in EEG Laplacian electrodes (¼ return currents). *Datta 2009.*

The term HD is now - I believe - more loosely used in a way 100% analogous to MtDCS (general multichannel DC stimulation using small electrodes)

Optimization: two electrodes; 19 fixed electrodes / full caps

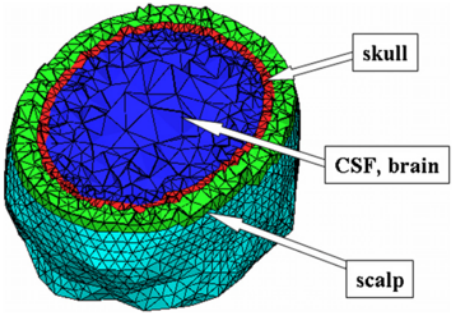
IOP PUBLISHING PHYSICS IN MEDICINE AND BIOLOGY
Phys. Med. Biol. **53** (2008) N219–N225 doi:10.1088/0031-9155/53/11/N03

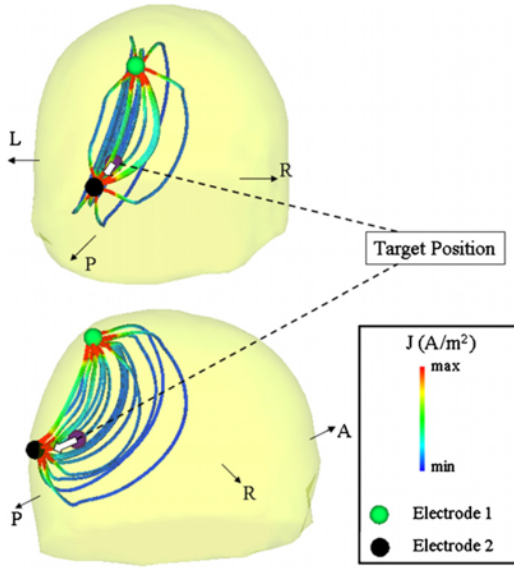
NOTE

Determination of optimal electrode positions for transcranial direct current stimulation (tDCS)

Chang-Hwan Im[1], Hui-Hun Jung[1], Jung-Do Choi[1], Soo Yeol Lee[2] and Ki-Young Jung[3]

[1] Department of Biomedical Engineering, Yonsei University, Wonju, 220-710, Korea





Optimized Multi-Electrode Stimulation Increases Focality and Intensity at Target

Jacek P. Dmochowski, Abhishek Datta, Marom Bikson, Yuzhuo Su, and Lucas C. Parra

Department of Biomedical Engineering, City College of New York–City University of New York, New York NY, 10031

E-mail: jdmochowski@ccny.cuny.edu

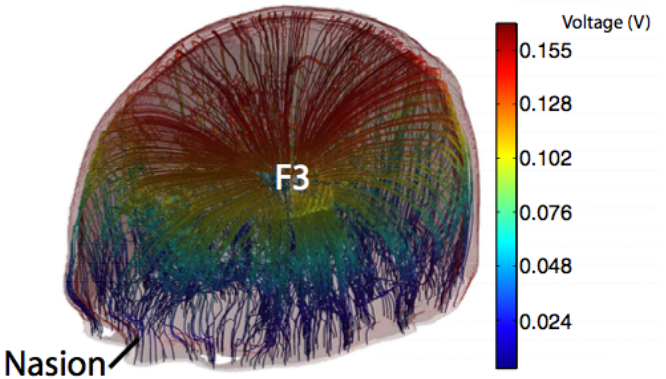
ORIGINAL RESEARCH ARTICLE
published: 17 October 2012
doi: 10.3389/fpsyt.2012.00090

PSYCHIATRY

Target optimization in transcranial direct current stimulation

Rosalind J. Sadleir[1,2]*, Tracy D. Vannorsdall[3], David J. Schretlen[3,4] and Barry Gordon[5,6]

[1] *J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL, USA*
[2] *Department of Biomedical Engineering, Kyung Hee University, Seoul, South Korea*
[3] *Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[4] *Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[5] *Department of Neurology, Cognitive Neurology/Neuropsychology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[6] *Department of Cognitive Science, The Johns Hopkins University, Baltimore, MD, USA*



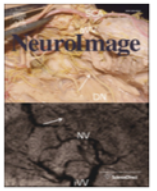
General Optimization / StimWeaver

NeuroImage 89 (2014) 216–225

Contents lists available at ScienceDirect

NeuroImage

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



Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields

Giulio Ruffini [a,b,*], Michael D. Fox [c,d], Oscar Ripolles [b], Pedro Cavaleiro Miranda [b,e], Alvaro Pascual-Leone [d,f]

[a] Starlab Barcelona, C. Teodor Roviralta 45, 08022 Barcelona, Spain
[b] Neuroelectrics Barcelona, C. Teodor Roviralta 45, 08022 Barcelona, Spain
[c] Massachusetts General Hospital, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[d] Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[e] Instituto de Biofísica e Engenharia Biomédica, Faculdade de Ciências da Universidade de Lisboa, 1749-016 Lisbon, Portugal
[f] Institut Guttmann, Hospital de Neurorehabilitació, Institut Universitari adscrit a la Universitat Autònoma de Barcelona, Barcelona, Spain

ARTICLE INFO

Article history:
Accepted 3 December 2013
Available online 15 December 2013

Keywords:
tCS
tDCS
tACS
Transcranial direct current stimulation
Transcranial alternating current stimulation
Electric fields
Targeted stimulation
Multifocal stimulation
Human head model
TES
NIBS
fMRI
PET
rs-fcMRI

ABSTRACT

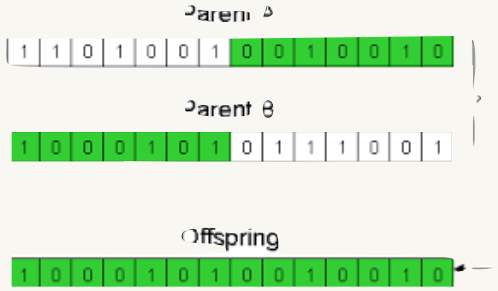
Recently, multifocal transcranial current stimulation (tCS) devices using several relatively small electrodes have been used to achieve more focal stimulation of specific cortical targets. However, it is becoming increasingly recognized that many behavioral manifestations of neurological and psychiatric disease are not solely the result of abnormality in one isolated brain region but represent alterations in brain networks. In this paper we describe a method for optimizing the configuration of multifocal tCS for stimulation of brain networks, represented by spatially extended cortical targets. We show how, based on fMRI, PET, EEG or other data specifying a target map on the cortical surface for excitatory, inhibitory or neutral stimulation and a constraint on the maximal number of electrodes, a solution can be produced with the optimal currents and locations of the electrodes. The method described here relies on a fast calculation of multifocal tCS electric fields (including components normal and tangential to the cortical boundaries) using a five layer finite element model of a realistic head. Based on the hypothesis that the effects of current stimulation are to first order due to the interaction of electric fields with populations of elongated cortical neurons, it is argued that the optimization problem for tCS stimulation can be defined in terms of the component of the electric field normal to the cortical surface. Solutions are found using constrained least squares to optimize current intensities, while electrode number and their locations are selected using a genetic algorithm. For direct current tCS (tDCS) applications, we provide some examples of this technique using an available tCS system providing 8 small Ag/AgCl stimulation electrodes. We demonstrate the approach both for localized and spatially extended targets defined using rs-fcMRI and PET data, with clinical applications in stroke and depression. Finally, we extend these ideas to more general stimulation protocols, such as alternating current tCS (tACS).

Based on our realistic head fast electric field generator,

1. Define target and weight map
2. Search in the space of electrode configurations for the best match to desired target

Specific aspects in Stimweaver algorithm

- Working with extended, weighted targets from neuroimaging, or discrete targets (e.g., BA or AAL)
- Optimizing using normal and tangential components of E fields on cortical surface
- Use of genetic algorithms to work with electrode subsets
- Developed for Starstim, with up to ~70 electrode positions in the 10-10 system using Pi electrodes (3 cm2)

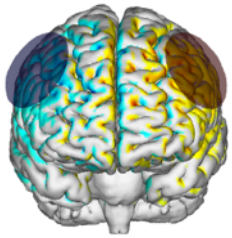


Example: Targeting the DLPFC

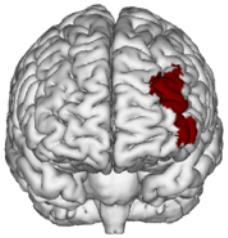
- **Stimulation type:** tDCS
- **Target:** Left dorsolateral prefrontal cortex (BA46)
- **Electric field in target area:** 0.25 V/m excitatory
- **Electrode type:** PITRODE (π cm^2Ag/AgCl/gel electrode)
- **Max current any electrode:** 1 and 2 mA
- **Max total injected current:** 4 mA
- **Max number of electrodes:** 8
- **Other:** 10-10 cap

Targeting the DLPFC: 2 channels

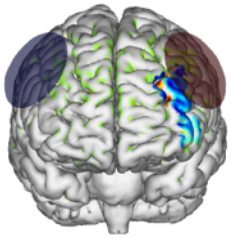
classical sponges



E field

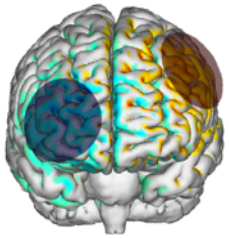


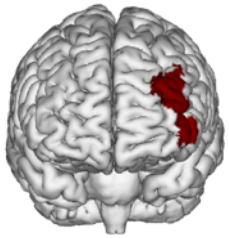
target

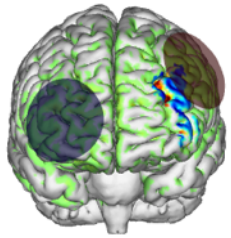


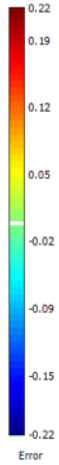
error

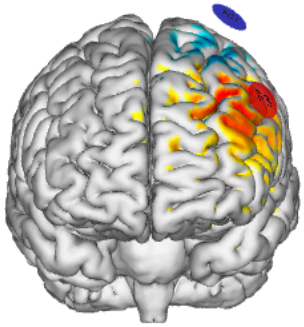
classical sponges

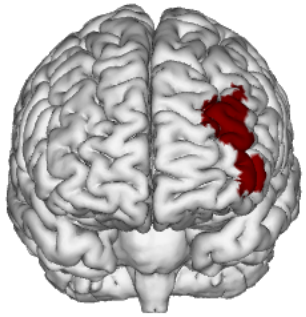


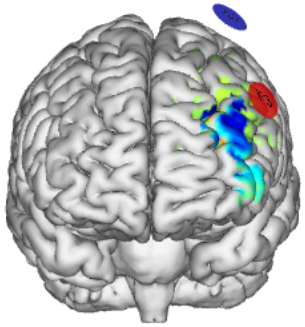


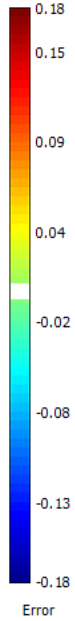








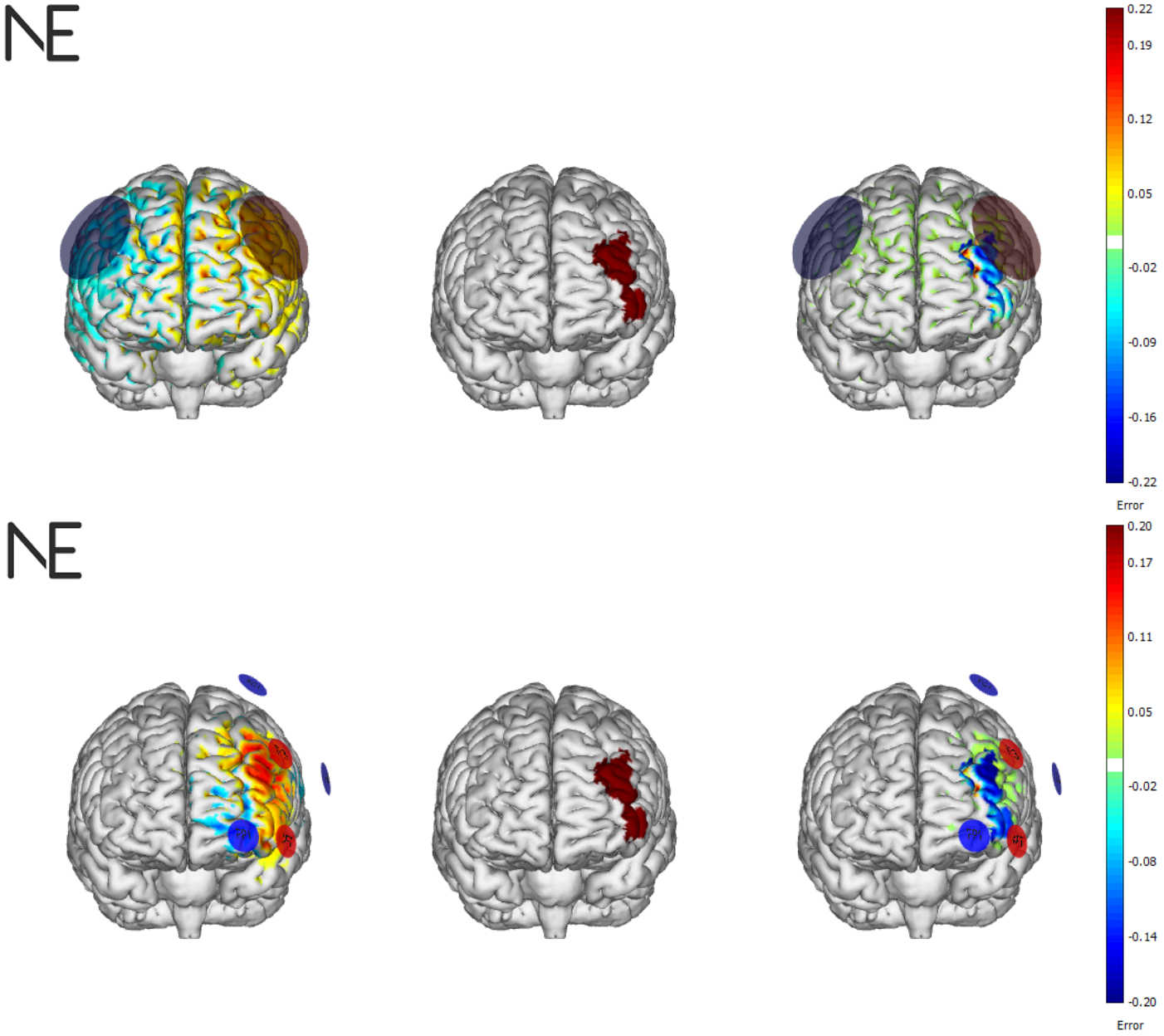




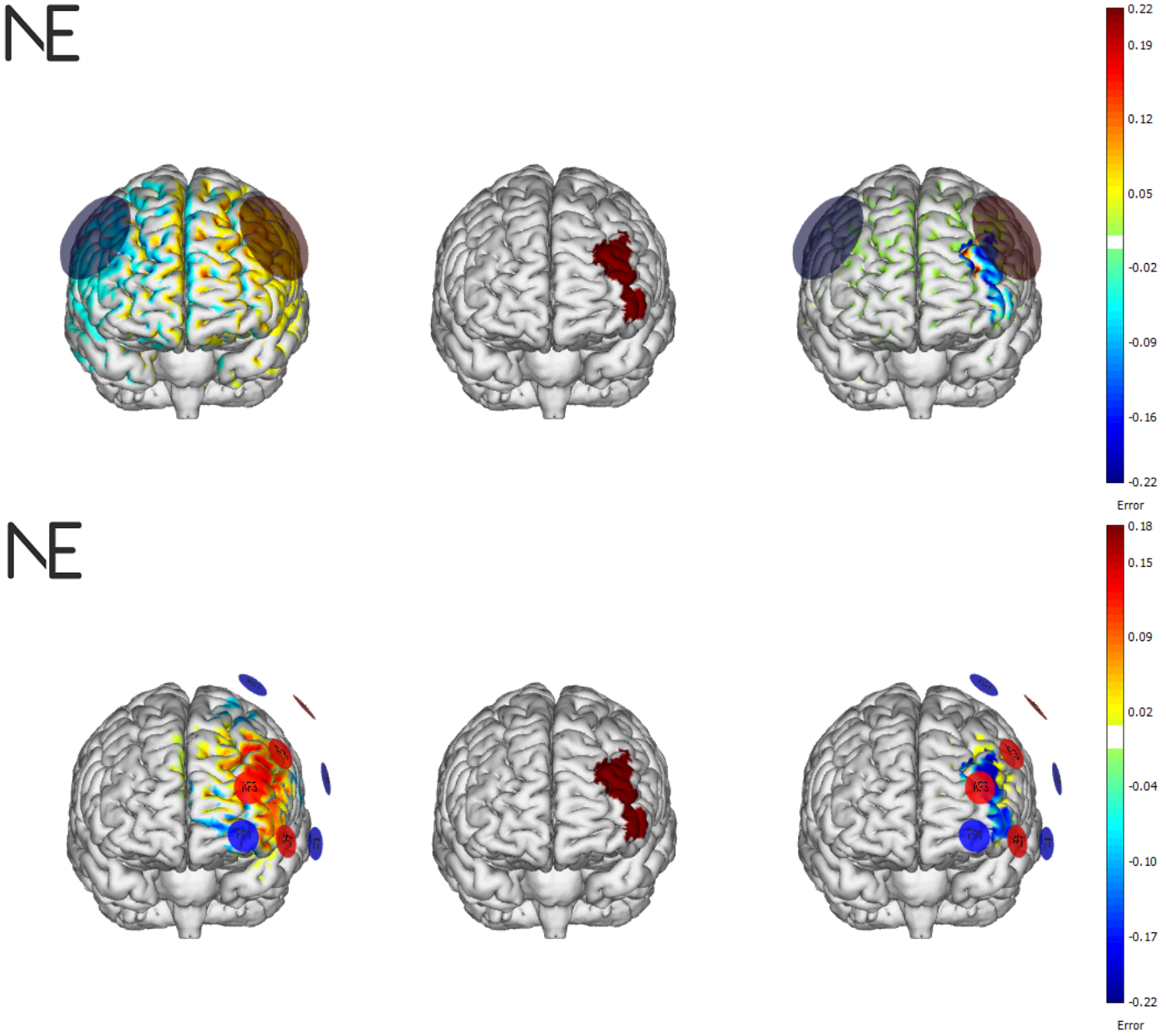
Ruffini 2015, in preparation

2 optimized Pi electrodes

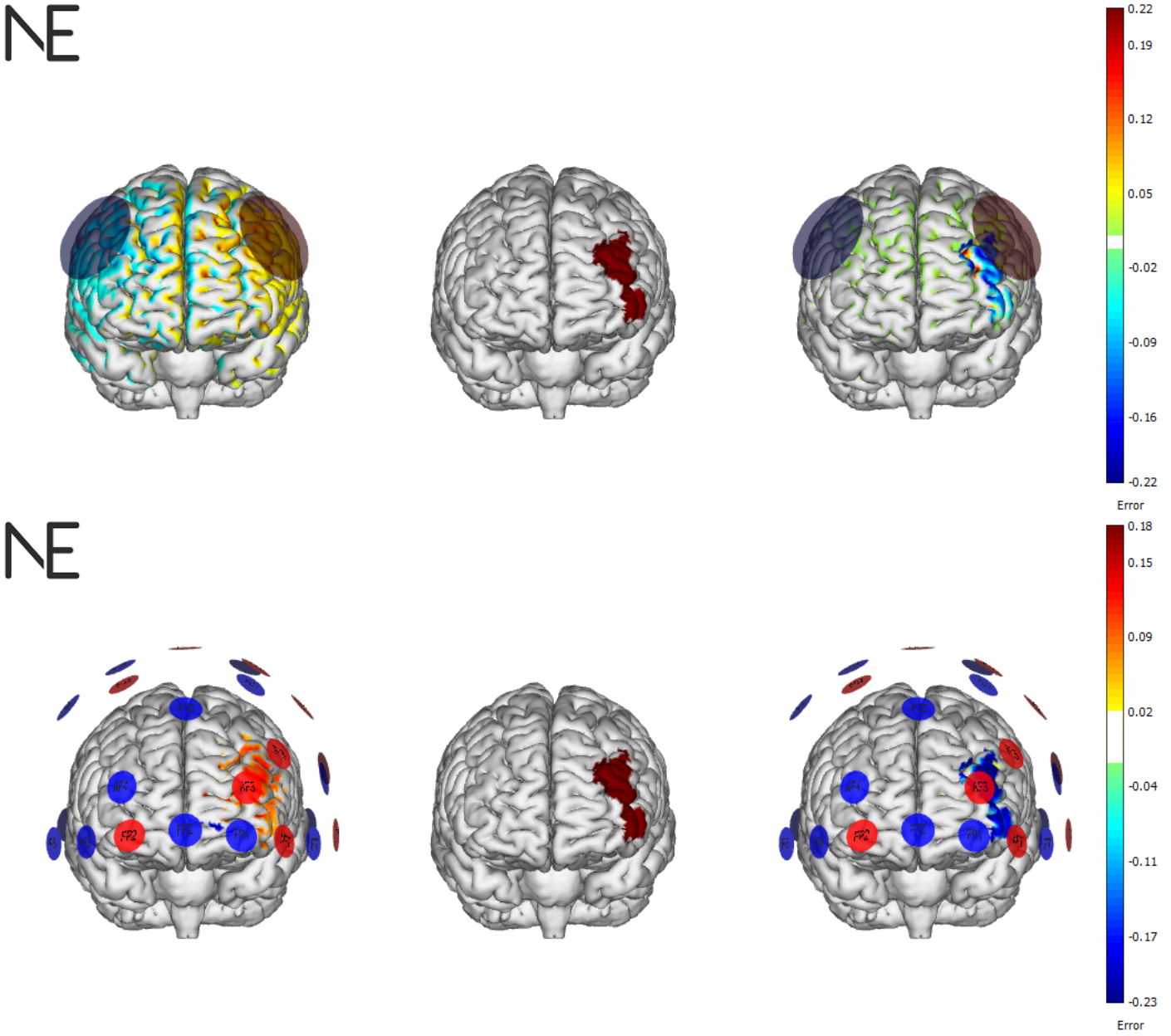
Targeting the DLPFC: 2 sponges vs 5 channels



Targeting the DLPFC: 2 sponges vs 8 channels



Targeting the DLPFC: 2 sponges vs. 39 channels



Targeting the DLPFC

11 Annex: Bipolar Montages

Solution	WCC	Average En on target	Average En on non-target
2CH 1mA	0.338	0.033	-0.00004
2CH 2mA	0.338	0.033	-0.00004
5CH 1mA	0.505	0.058	-0.00015
5CH 2mA	0.520	0.059	-0.00013
8CH 1mA	0.534	0.061	0.00012
8CH 2mA	0.552	0.071	-0.00016
39CH 1mA	0.545	0.066	-0.00013
39CH 2mA	0.560	0.071	-0.00009
F3-Fp2 1mA	0.232	0.047	-0.00023
F3-F4 1mA	0.228	0.049	-0.00027

Table 1 – Analysis of multipolar and bipolar solutions.

Optimized Multifocal transcranial Current Stimulation: DLPFC and MC solutions

wiki.neuroelectrics.com

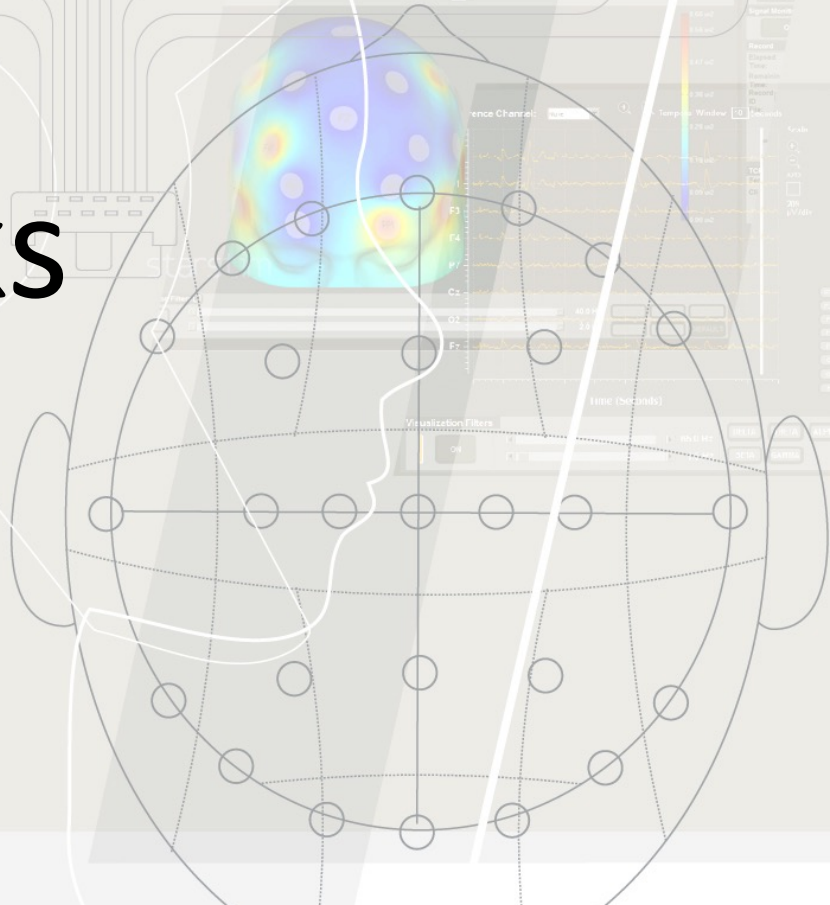
Neuroelectrics White Paper WP201503

Author: G. Ruffini (PhD), O. Ripolles (PhD), L. Dubreuil Vall

Released: May 27th 2015

Optimizing MtCS (II):

Targeting networks



Targeting a network: example with DBS Depression seed

- Use a DBS target in depression therapy as a seed in rs-fcMRI
- Use the resulting correlation map on the cortex as target
- Optimize using weighted least squares with normal component of electric field
- For excitation of deep target, seek to excite positive correlated regions and inhibit negatively correlated ones (or viceversa)
- Statistical significance of correlation used for weighting
- This approach can be used with other imaging techniques.

Fox et al 2012

ARCHIVAL REPORT

Efficacy of Transcranial Magnetic Stimulation Targets for Depression Is Related to Intrinsic Functional Connectivity with the Subgenual Cingulate

Michael D. Fox, Randy L. Buckner, Matthew P. White, Michael D. Greicius, and Alvaro Pascual-Leone

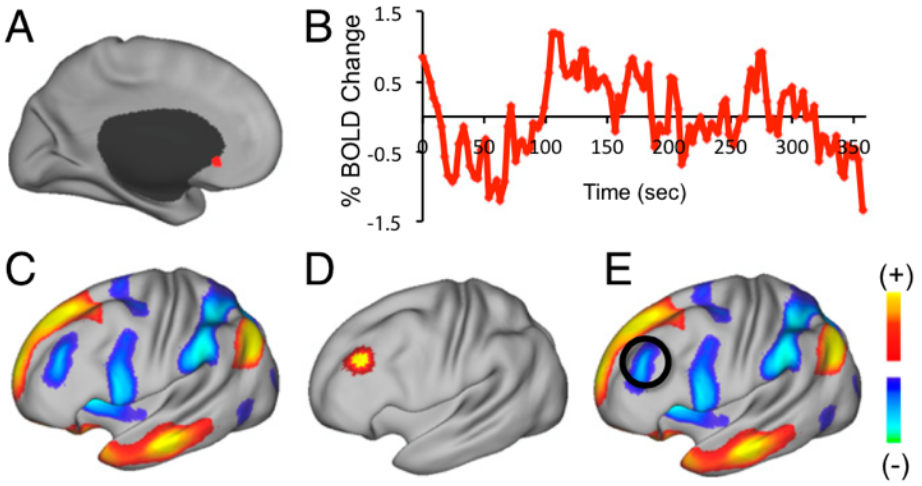


Fig. 1. Methodological approach for linking sites for invasive and non-invasive brain stimulation. (*A*) An ROI is created at a DBS site with reported efficacy for a given disease, in this case the subgenual cingulate for depression. (*B*) For each of 1,000 normal subjects, spontaneous modulations in the fMRI signal are extracted from this DBS ROI. (*C*) This time course is correlated with all other brain voxels and then averaged across subjects to create a DBS correlation map. (*D*) An ROI is created at the site where noninvasive stimulation is reported effective in the given disease, in this case the left DLPFC. (*E*) The site of noninvasive brain stimulation is illustrated on the DBS correlation map using a circle centered over the site.

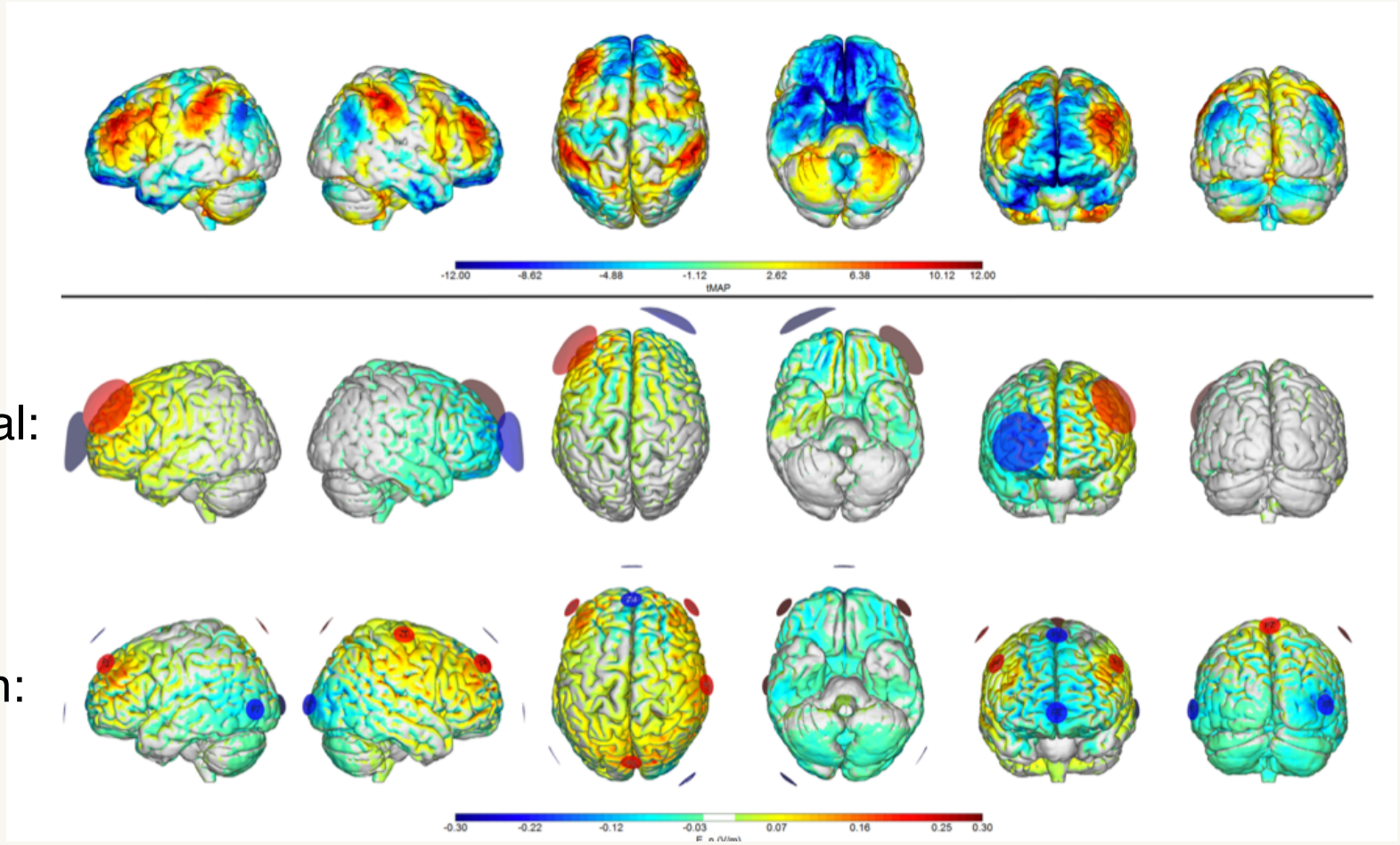
1. Select seed
2. Compute rs-fcMRI from healthy subjects
3. Use resulting t-map as target

Distributed target map (depression SG seed /8Ch)

neuroelectrics®

Classical:

Modern:



rs-fcMRI SG seed map	Traditional	0.11
	8 Channel	0.29
	27 Channel	0.31

Ruffini et al 2014

Table 1: Montage comparisons for the four target maps discussed in the text. Weighted correlation coefficient, mean weighted error $\chi(I)$, maximal current at any electrode and total injected current are provided for traditional (bipolar), 8 and 27 channel solutions.

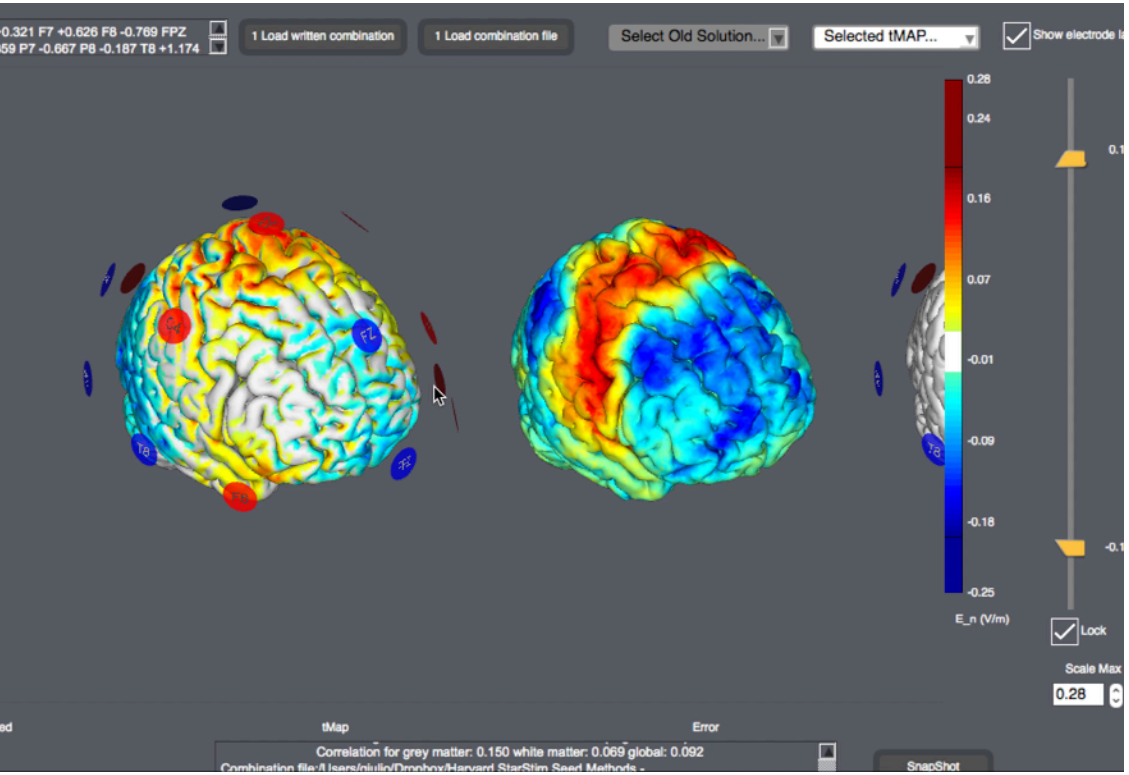
Target	Montage	Weighted CC	$\chi(I)$ (mV^2/m^2)	Max I (μA)	Tot Inj I (μA)
BA4 Left	Traditional	0.02	163	1,000	1,000
	8 Channel	0.31	-8	1,000	1,297
	27 Channel	0.31	-9	1,000	2,146
BA4 Bilateral	Traditional	-0.07	184	1,000	1,000
	8 Channel	0.26	-13	823	1,513
	27 Channel	0.26	-14	854	2,045
rs-fcMRI SG seed map	Traditional	0.11	1	1,000	1,000
	8 Channel	0.29	-214	1,000	3,262
	27 Channel	0.31	-239	1,000	4,000
PET DBS map	Traditional	-0.05	125	1,000	1,000
	8 Channel	0.21	-51	843	2,236
	27 Channel	0.23	-59	1,000	4,000

Fox et al 2014

Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases

Michael D. Fox[a,b,c,1], Randy L. Buckner[c,d,e], Hesheng Liu[c], M. Mallar Chakravarty[f,g], Andres M. Lozano[h,i], and Alvaro Pascual-Leone[a]

Optimized solution: Stimweaver



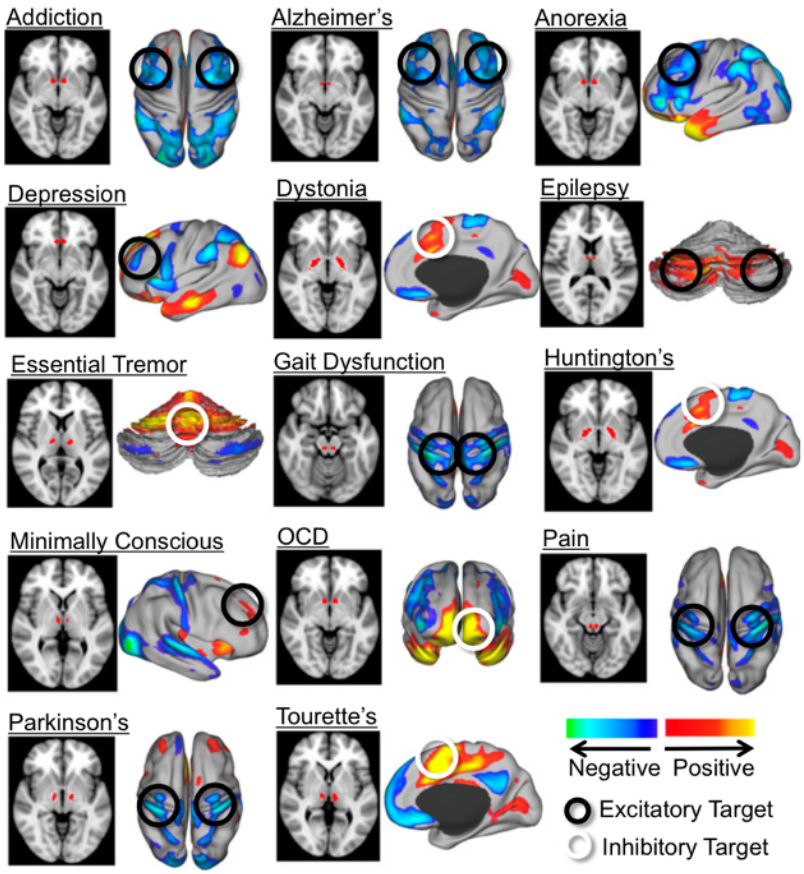
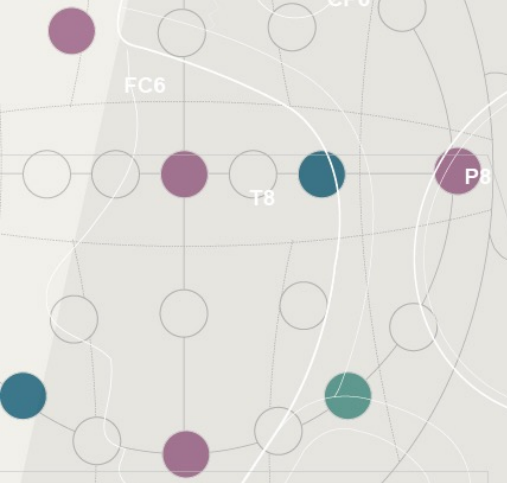


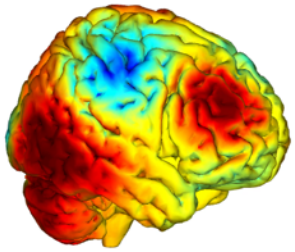
Fig. 2. Sites for invasive and noninvasive brain stimulation with the best evidence of therapeutic efficacy in each disease are functionally connected. For each disease, the site at which DBS is most effective is shown in red. Resting-state functional connectivity with this site is shown along with the correspondence to the site at which noninvasive stimulation is most effective in each disease (circles). Black circles indicate sites at which noninvasive excitatory stimulation (>5 Hz TMS or anodal tDCS) has been reported to be efficacious. White circles indicate sites where inhibitory stimulation (<1 Hz TMS or cathodal tDCS) has been reported to be efficacious.

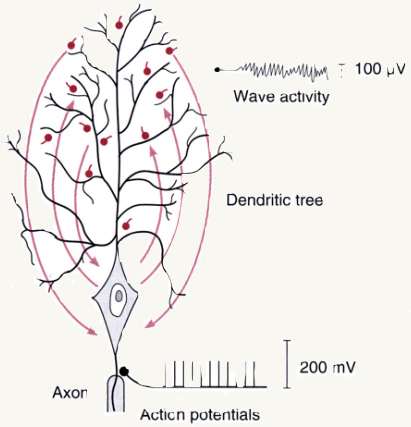
Combining EEG and tCS

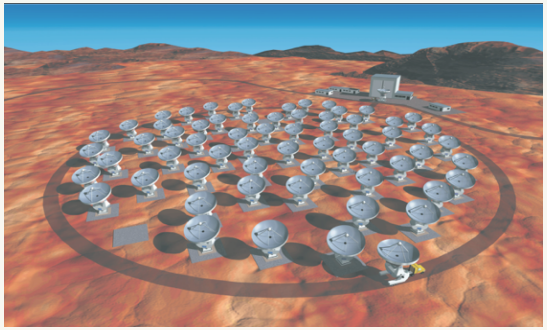


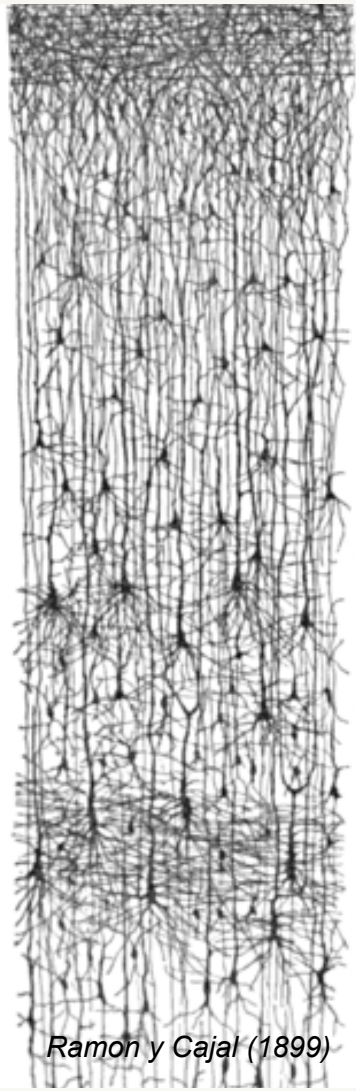
Basics on **EEG** & **tCS**

- Pyramidal neurons in the cortex act coherently to generate cortical currents & electric fields which can be measured by on the scalp by EEG.
- EEG thus provides information on brain function dynamics.
- EEG is intensely used to research brain function, and clinically for sleep and epilepsy, for example.
- In a related manner, electric currents forced from the outside via scalp electrodes generate cortical electrical fields that modulate the activity of cortical neurons.
- The used currents and associated fields in tCS are weak. Coherence in reception is again key.





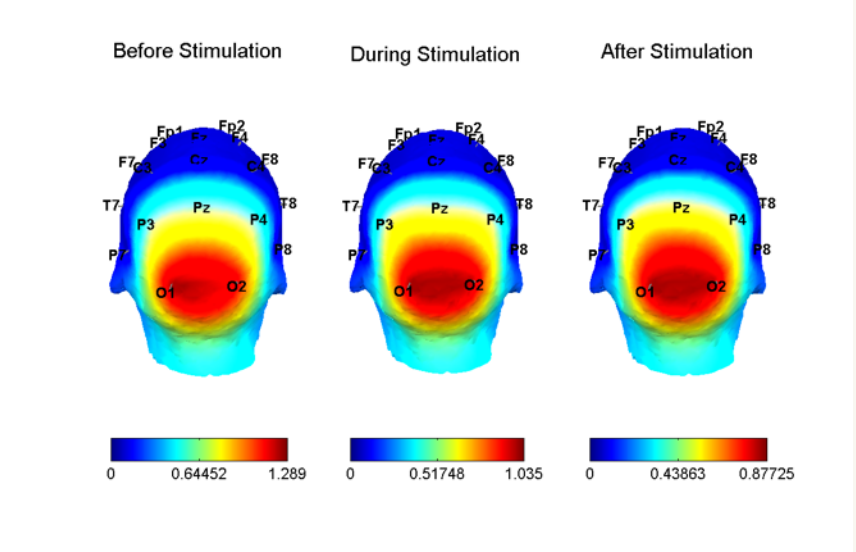




Ramon y Cajal (1899)

Why measure EEG in tCS research?

- Compare before, during, after tCS changes in EEG
  - Explore the impact of tDCS, tACS at different frequencies / entrainment / the interaction with natural oscillations.
  - Work at the level of spontaneous EEG or ERPs
- Explore the impact of TMS after or during tCS using EEG
- Develop dosing strategies
- Develop targeting strategies
- Develop Closed-Loop strategies



Marshall et al 2006

nature Vol 444|30 November 2006|doi:10.1038/nature05278

LETTERS

Boosting slow oscillations during sleep potentiates memory

Lisa Marshall[1], Halla Helgadóttir[1], Matthias Mölle[1] & Jan Born[1]

Marshall et al, 2006: An oscillating current applied at 0.75 Hz during sleep **entrains** cortical oscillations, boosts slow-wave sleep and frontal spindles, and improves memory

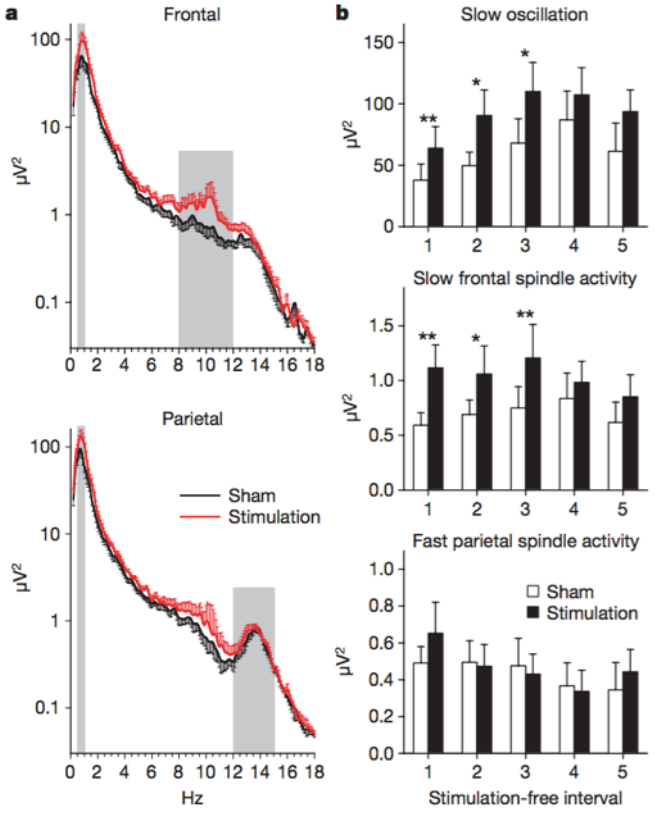


Figure 3 | EEG activity during the 1-min intervals between periods of slow oscillation stimulation and between corresponding periods of sham stimulation. **a,** Average power spectrum (across first three stimulation-free intervals) at the midline frontal and parietal sites. Shaded areas indicate frequency bands for slow oscillations (0.5–1 Hz), slow frontal spindle activity (upper panel, 8–12 Hz), and fast parietal spindle activity (lower panel, 12–15 Hz). **b,** Time course of power in the five stimulation-free intervals for slow oscillations, slow frontal spindle activity and fast parietal spindle activity. Slow frontal spindle activity is to some extent also visible over the parietal cortex, reflecting the more widespread neuronal synchrony underlying this spindle class[30]. Stimulation enhances slow oscillation and slow spindle activity at the frontal location, but not fast spindle activity at the parietal location. Asterisks indicate statistical significance (**$P < 0.01$, *$P < 0.05$) for pairwise comparison. Data are the means ± s.e.m.

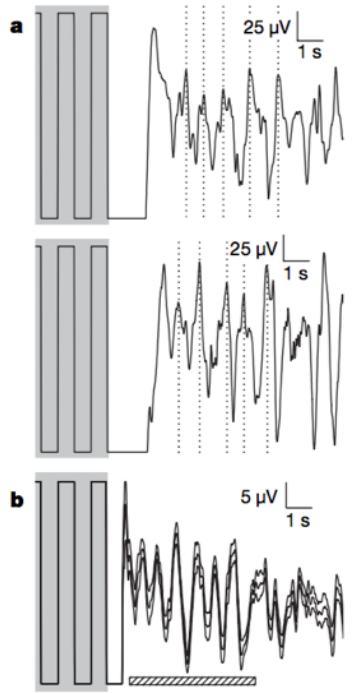


Figure 2 | Synchronization of slow oscillatory EEG activity. **a,** EEG recordings during the last seconds of a 5-min stimulation period (shaded areas) and first few seconds of a stimulation-free interval of two individua at prefrontal sites (Fz). **b,** Corresponding mean ±s.e.m. across all subject and stimulation periods over the parietal cortex (where the EEG is least contaminated by the ceasing stimulation artefact). Positivity upward. No entrainment of the slow oscillatory EEG activity to the slow oscillatory rhythmic stimulation. Hatched bar indicates time interval of stimulation-induced phase changes in the 0.78–0.98-Hz and 1.37–1.56-Hz bins of the EEG signal.

tDCS and connectivity measured by EEG

Modulating Functional Connectivity Patterns and Topological Functional Organization of the Human Brain with Transcranial Direct Current Stimulation

Rafael Polanía*, **Michael A. Nitsche, and Walter Paulus**

Department of Clinical Neurophysiology, Georg-August University of Göttingen, 37075 Göttingen, Germany

Abstract: Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that alters cortical excitability and activity in a polarity-dependent way. Stimulation for few minutes has been shown to induce plastic alterations of cortical excitability and to improve cognitive performance. These effects might be caused by stimulation-induced alterations of functional cortical network connectivity. We aimed to investigate the impact of tDCS on cortical network function through functional connectivity and graph theoretical analysis. Single recordings in healthy volunteers with 62 electroencephalography channels were acquired before and after 10 min of facilitatory anodal tDCS over the primary motor cortex (M1), combined with inhibitory cathodal tDCS of the contralateral frontopolar cortex, in resting state and during voluntary hand movements. Correlation matrices containing all 62 pairwise electrode combinations were calculated with the synchronization likelihood (SL) method and thresholded to construct undirected graphs for the θ, α, β, low-γ and high-γ frequency bands. SL matrices and undirected graphs were compared before and after tDCS. Functional connectivity patterns significantly increased within premotor, motor, and sensorimotor areas of the stimulated hemisphere during motor activity in the 60–90 Hz frequency range. Additionally, tDCS-induced significant intrahemispheric and interhemispheric connectivity changes in all the studied frequency bands. In summary, we show for the first time evidence for tDCS-induced changes in brain synchronization and topological functional organization. *Hum Brain Mapp 00:000–000, 2010.*

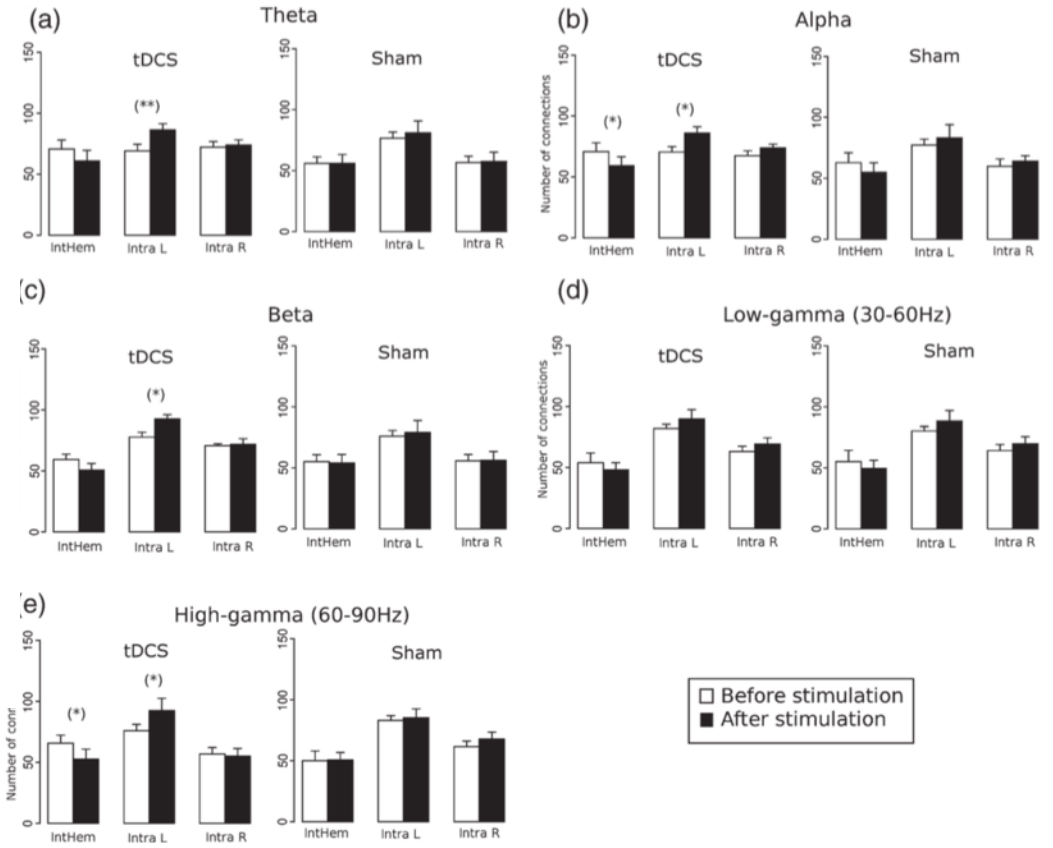


Figure 7.

Number of inter- (intHem) and intra-hemispheric [intra-hemispheric left (intra L) and right (intra R)] connections before (white) and after (black) real tDCS and sham stimulation during the performance of the motor task when setting the mean connectivity degree threshold $K = 10$ in the θ (**a**), α (**b**), β (**c**), low-γ, (**d**) and high-γ (**e**) frequency bands (mean ± SEM). Black asterisk indicates where the difference between the two groups is significant (paired *t*-test: (*) $P < 0.05$; (**) $P < 0.01$).

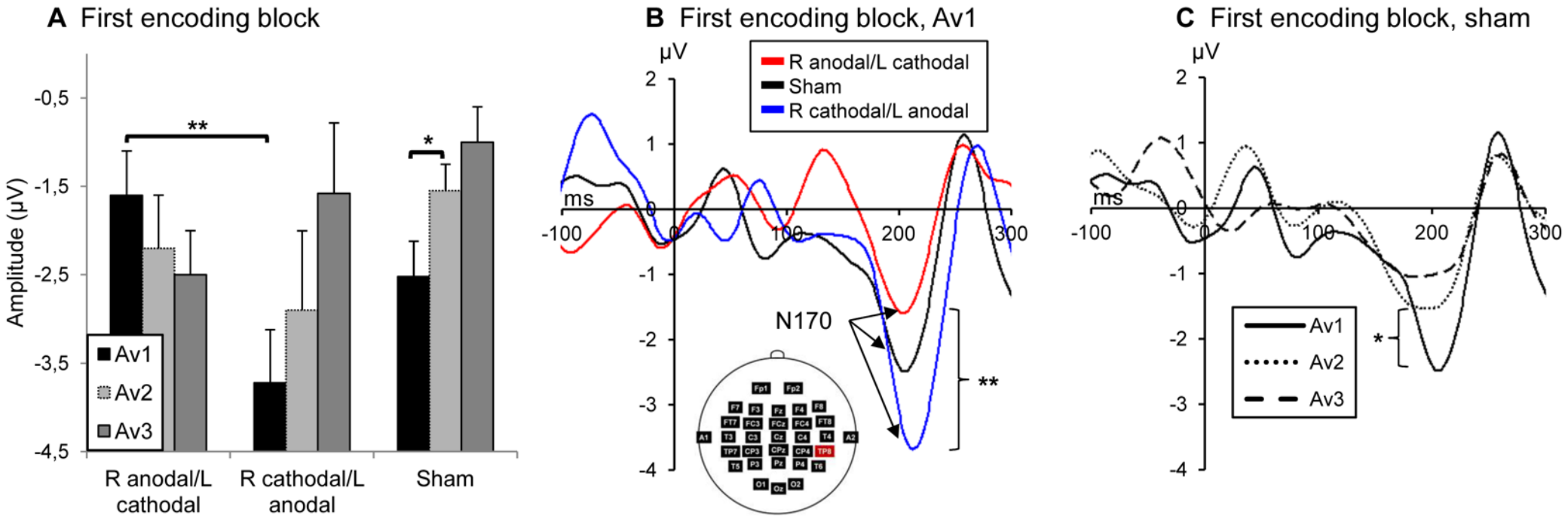
tDCS and ERP's

neuroelectrics®

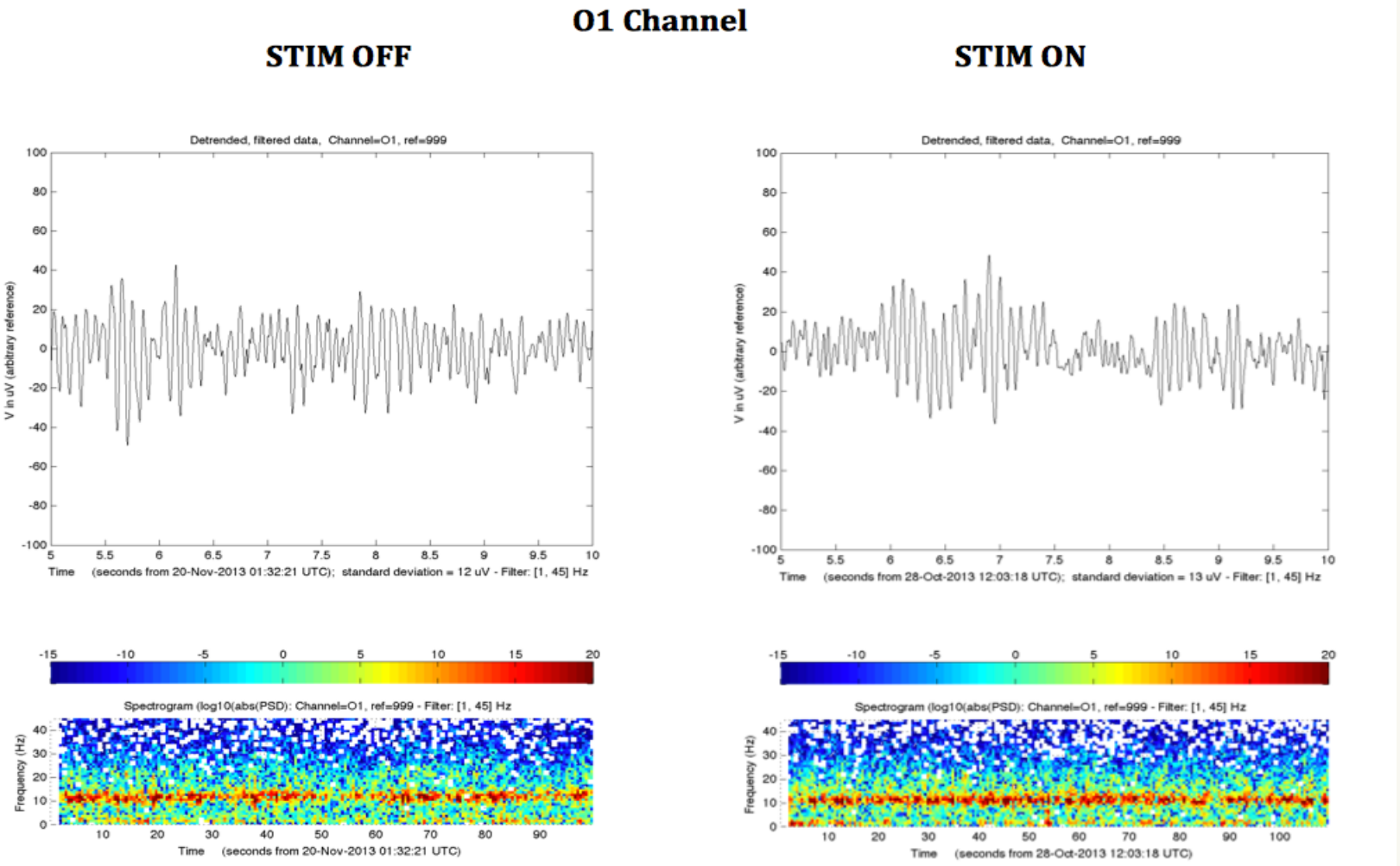
Transcranial Direct Current Stimulation of the Dorsolateral Prefrontal Cortex Modulates Repetition Suppression to Unfamiliar Faces: An ERP Study

Marc Philippe Lafontaine, Hugo Théoret, Frédéric Gosselin, Sarah Lippé

Published: December 4, 2013 • DOI: 10.1371/journal.pone.0081721



Measuring EEG during tDCS using Pi electrodes

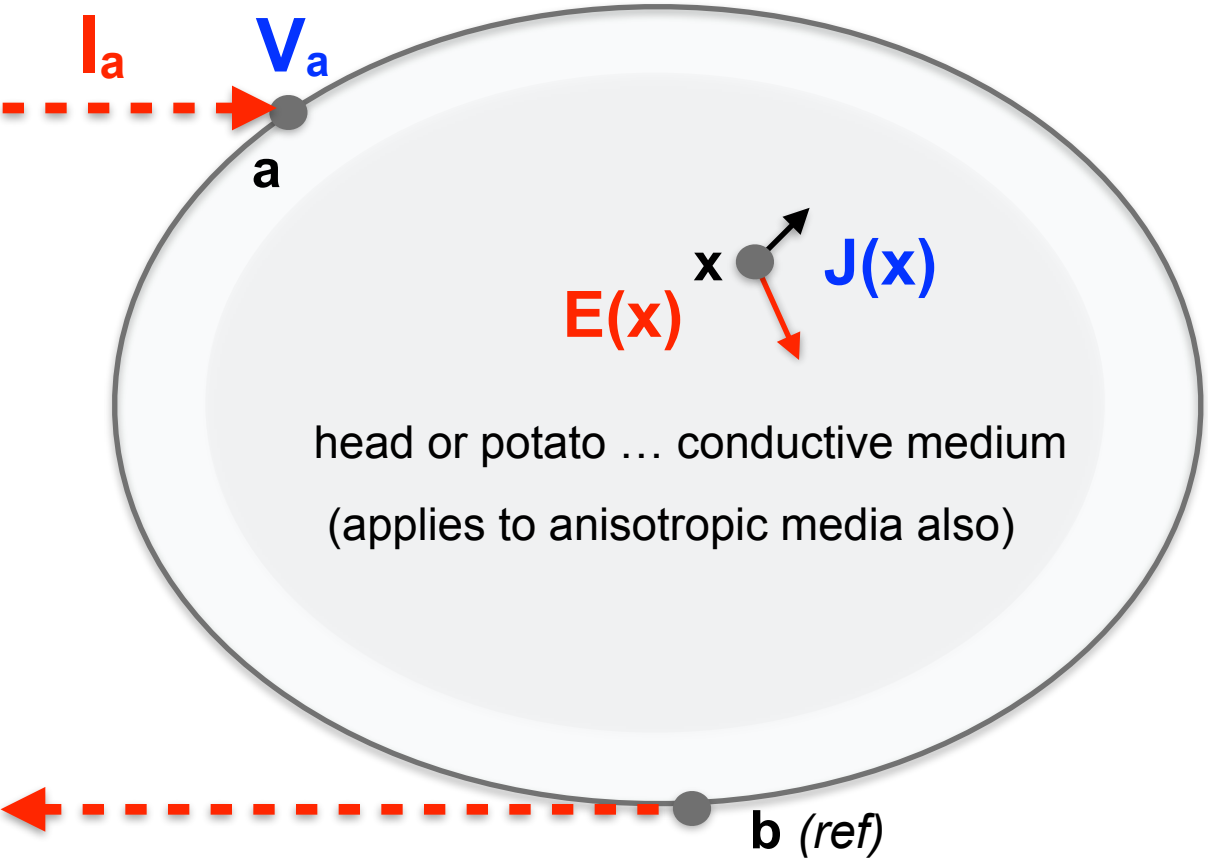


Neuroelectrics White Paper (WP201307)

Reciprocity theorem (Hemholtz 1853)

1) **EEG**: Dipole generates scalp potential: J(x) → V_a
2) **tCS**: Current generates E field: I_a → E(x)

$$V_a I_a = -\vec{J}(x) \cdot \vec{E}(x) \delta V$$



RECIPROCITY

The reciprocity theorem was first introduced into biophysical areas in 1853 by Helmholtz [5], and its modern usage in electrocardiography is due to the vision of Dr. Frank Wilson. As a result of the latter's interest, important papers on this subject were published by his colleagues McFee and Johnston [6] and by Brody and Romans [7]. Subsequently, the theory was developed in considerably more detail by Brody, Bradshaw, and Evans [8] and by Plonsey [9].

IEEE TRANSACTIONS ON BIO-MEDICAL ENGINEERING, VOL. BME-16, NO. 1, JANUARY 1969

EEG Electrode Sensitivity—An Application of Reciprocity

STANLEY RUSH, SENIOR MEMBER, IEEE, AND DANIEL A. DRISCOLL, STUDENT MEMBER, IEE

Generalization to multiple sources and electrodes

Using the reciprocity theorem it is possible to show (Ruffini 2015) that given multiple scalp entry/measurement points {a} and EEG sources J(x),

$$\sum_a V_a \, I_a = - \int dx \, \vec{J}(x) \cdot \vec{E}(x)$$

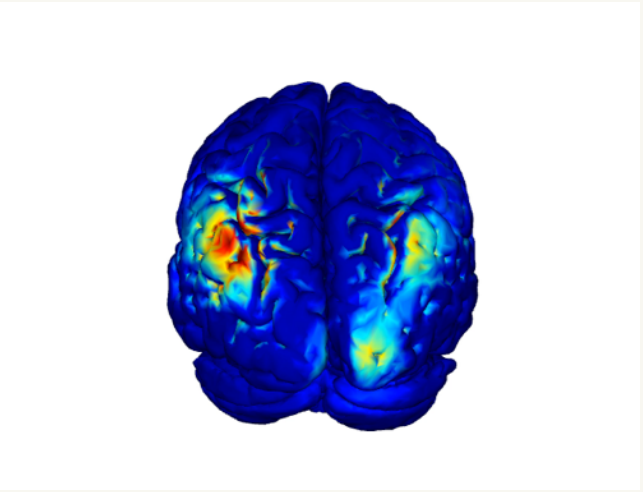
Here E(x) are the electric fields generated by I_a currents, and V_a the scalp potentials generated by the EEG sources J(x).

This beautiful equation says that if you want generated electric fields and EEG sources to be correlated, currents and potentials have to be anti-correlated. This gives a simple way to determine optimal stimulation currents given scalp potential. Make currents and potentials to be parallel. E.g., maximize $|I_a V_a|$ subject to some constraints (maximal current, etc).

A limitation is that you will not really know what size electric fields you are generating, cannot add a weight map to work with weighted correlation, etc. But still, give some constraints on currents it provides a recipe to optimize currents to EEG sources. This can be especially useful in close-loop applications.

Applications of generalized reciprocity

1. Online optimization of MtCS from EEG
2. Closed-loop applications from EEG: Listen to EEG, create stimulation waveform (e.g., I=c V) to amplify or reduce EEG
3. “Playing back” EEG using MtCS currents (I ~ V) may actually make sense! Soon possible with Starstim 2 (2016)
4. Theoretical analysis (e.g., number of electrodes?)



Entrainment

Studying the interaction of oscillatory systems

Weak E-field Entrainment

There are several interesting results already in the literature on the topic of neural activity entrainment by weak oscillating electric fields.

These include:

- **Marshall 2006:** slow tACS increases power in EEG during sleep slow frequencies and also in the alpha band
- **Kanai 2008:** showed frequency sensitivity with tACS phosphene perception in humans (central montage)
- **Deans 2007:** demonstrated entrainment in vitro in rat hippocampus with weak AC fields
- **Frohlich 2010:** demonstrated entrainment in vitro in ferret cortical slices; followed by **Schmidt 2014** and **Ali 2013** with models and in vivo
- **Merlet 2013:** modeling of EEG as influenced by tCS

Remarkably, the used electric fields are similar in magnitude and frequency to endogenously generated ones (ephaptic interaction hypothesis).

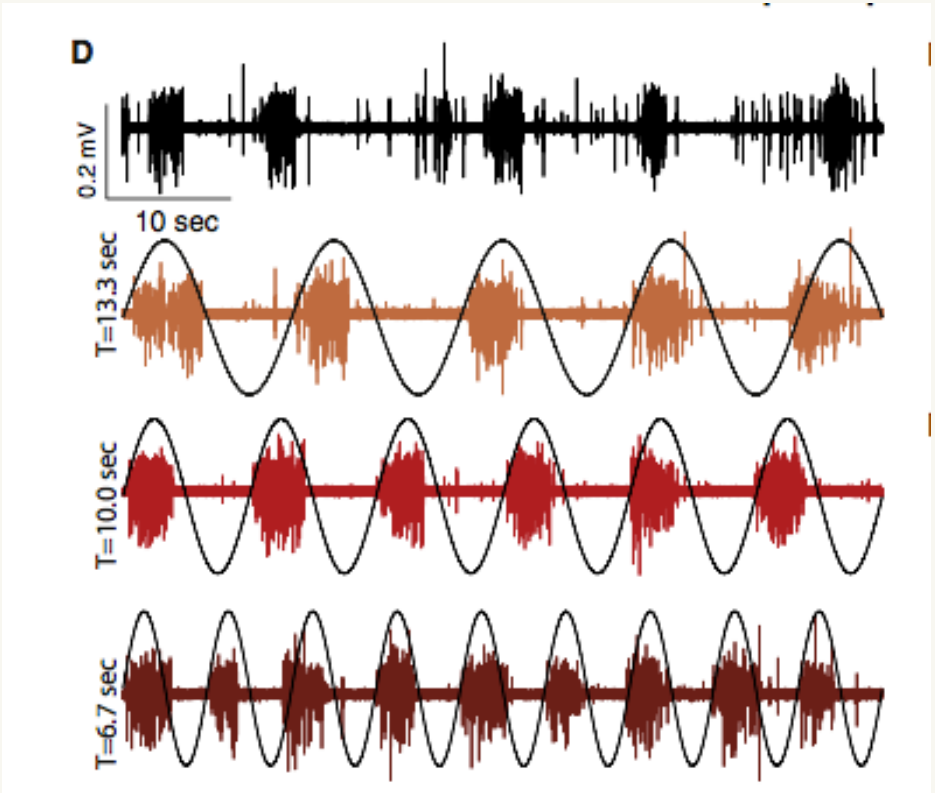
Frohlich and McCormick 2010 (in vitro)

Endogenous Electric Fields May Guide Neocortical Network Activity, Neuron 67, 2010

External applied fields similar in magnitude to endogenous ones (i.e., weak) can entrain in-vitro oscillations in cortical slices in the ferret brain.

Resonance effects also seen.

Endogenous field “virtual replicas” also active



Zaehle 2010 (humans + EEG)

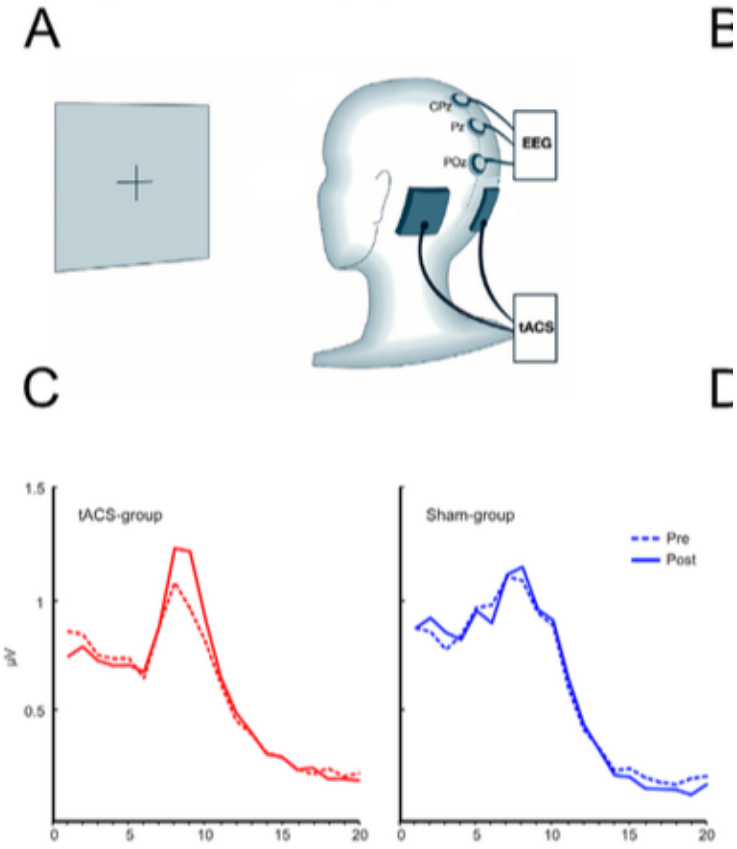
Transcranial Alternating Current Stimulation Enhances Individual Alpha Activity in Human EEG

Tino Zaehle[1,2], Stefan Rach[3], Christoph S. Herrmann[3]*

1 Department of Neurology, Otto-von-Guericke University, Magdeburg, Germany, 2 German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany, 3 Experimental Psychology Lab, Carl von Ossietzky Universität, Oldenburg, Germany

Abstract

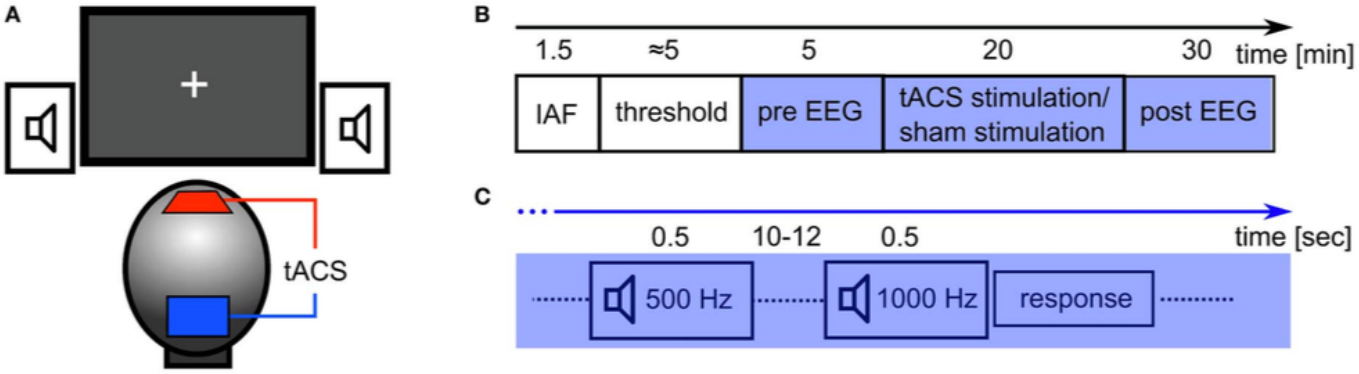
Non-invasive electrical stimulation of the human cortex by means of transcranial direct current stimulation (tDCS) has been instrumental in a number of important discoveries in the field of human cortical function and has become a well-established method for evaluating brain function in healthy human participants. Recently, transcranial *alternating* current stimulation (tACS) has been introduced to directly modulate the ongoing rhythmic brain activity by the application of oscillatory currents on the human scalp. Until now the efficiency of tACS in modulating rhythmic brain activity has been indicated only by inference from perceptual and behavioural consequences of electrical stimulation. No direct electrophysiological evidence of tACS has been reported. We delivered tACS over the occipital cortex of 10 healthy participants to entrain the neuronal oscillatory activity in their individual alpha frequency range and compared results with those from a separate group of participants receiving sham stimulation. The tACS but not the sham stimulation elevated the endogenous alpha power in parieto-central electrodes of the electroencephalogram. Additionally, in a network of spiking neurons, we simulated how tACS can be affected even after the end of stimulation. The results show that spike-timing-dependent plasticity (STDP) selectively modulates synapses depending on the resonance frequencies of the neural circuits that they belong to. Thus, tACS influences STDP which in turn results in aftereffects upon neural activity. The present findings are the first direct electrophysiological evidence of an interaction of tACS and ongoing oscillatory activity in the human cortex. The data demonstrate the ability of tACS to specifically modulate oscillatory brain activity and show its potential both at fostering knowledge on the functional significance of brain oscillations and for therapeutic application.



PRE + POST Eyes Closed
DURing: Eyes Open

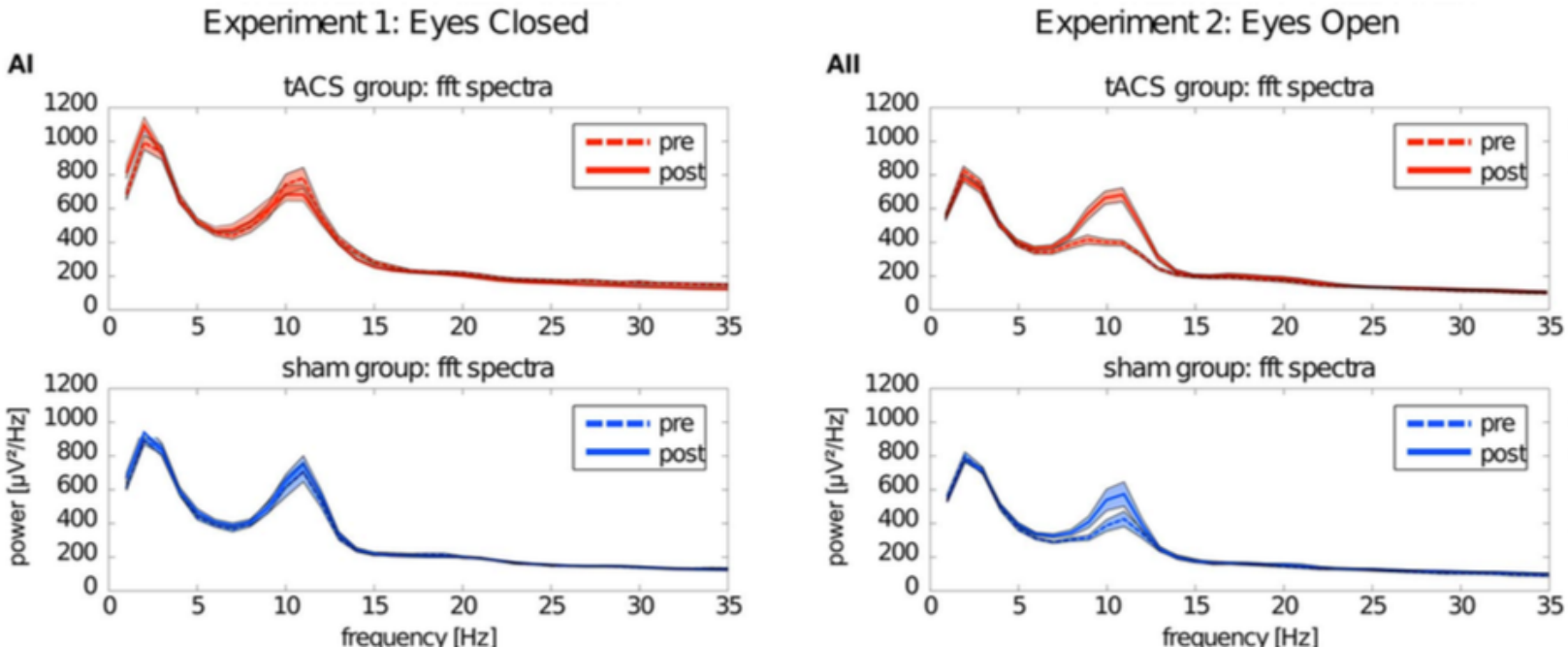
Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states

Toralf Neuling[1], Stefan Rach[1,2] and Christoph S. Herrmann[1,2]*



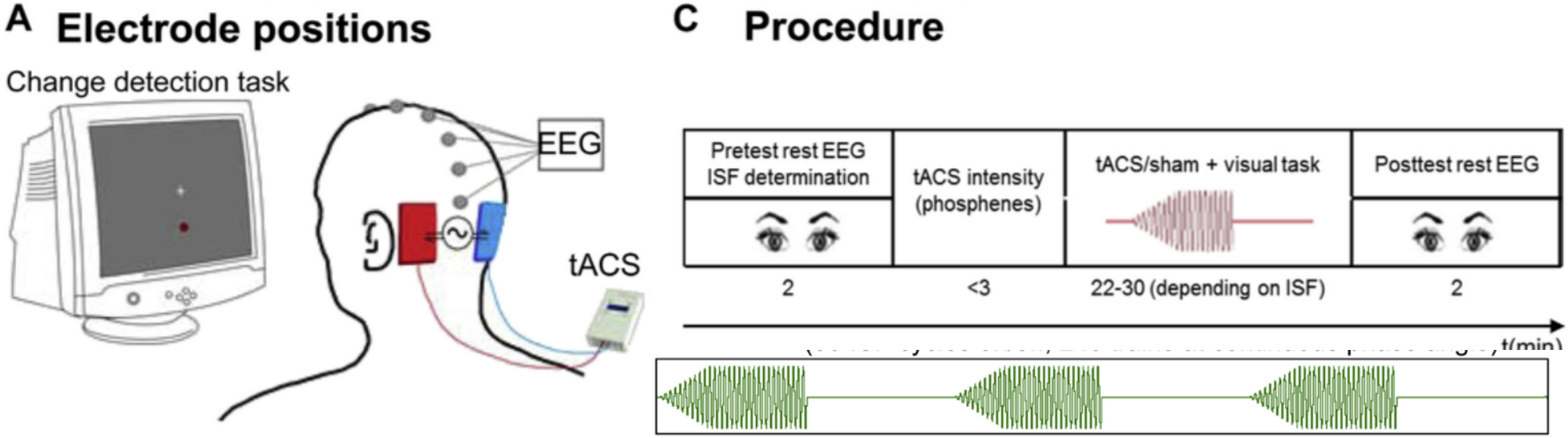
PAF Power up
with PAF (IAF) tACS in EO

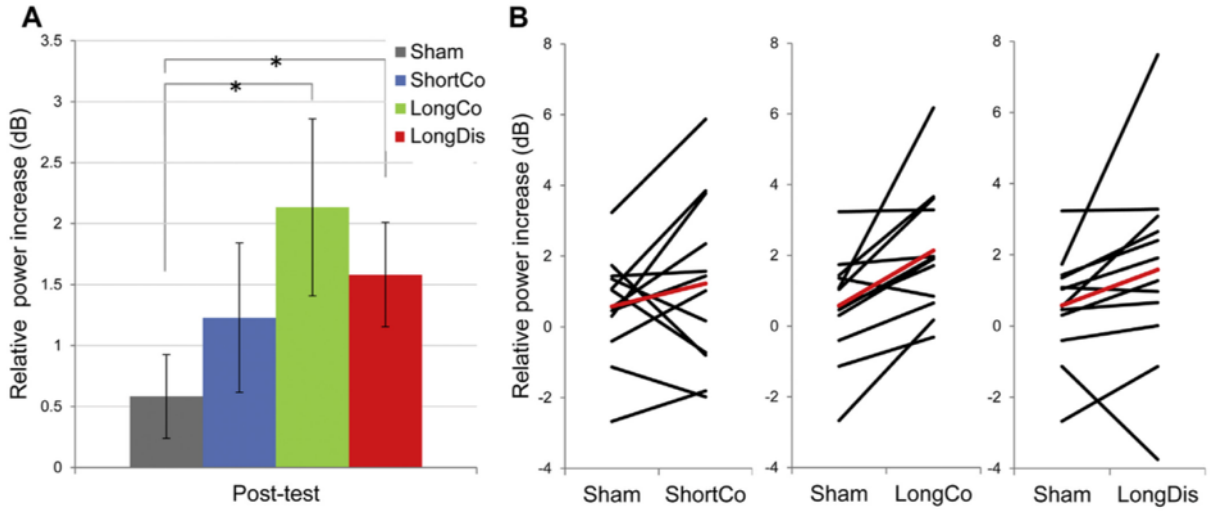
Coherence up in EC



Alpha Power Increase After Transcranial Alternating Current Stimulation at Alpha Frequency (α-tACS) Reflects Plastic Changes Rather Than Entrainment 2015

Alexandra Vossen [a,*], Joachim Gross [b], Gregor Thut [b,**]

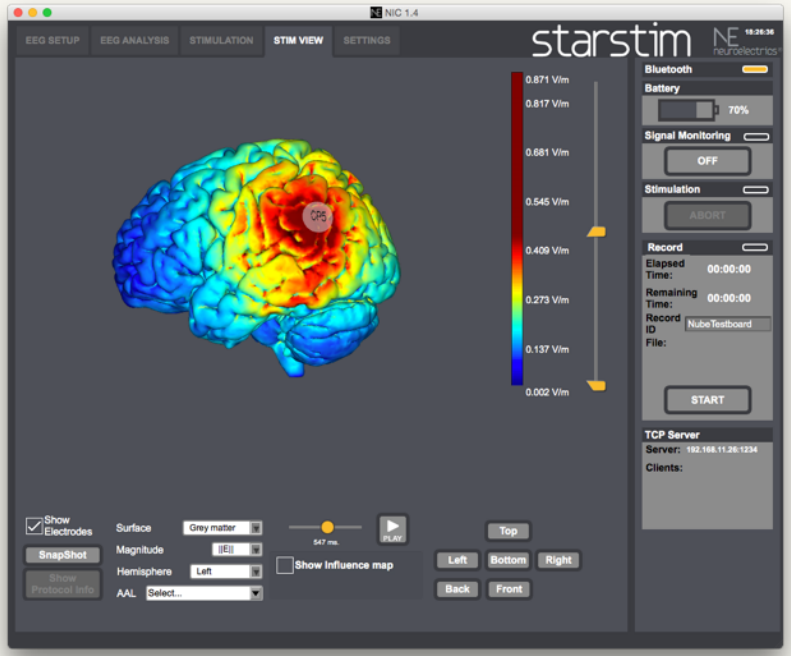


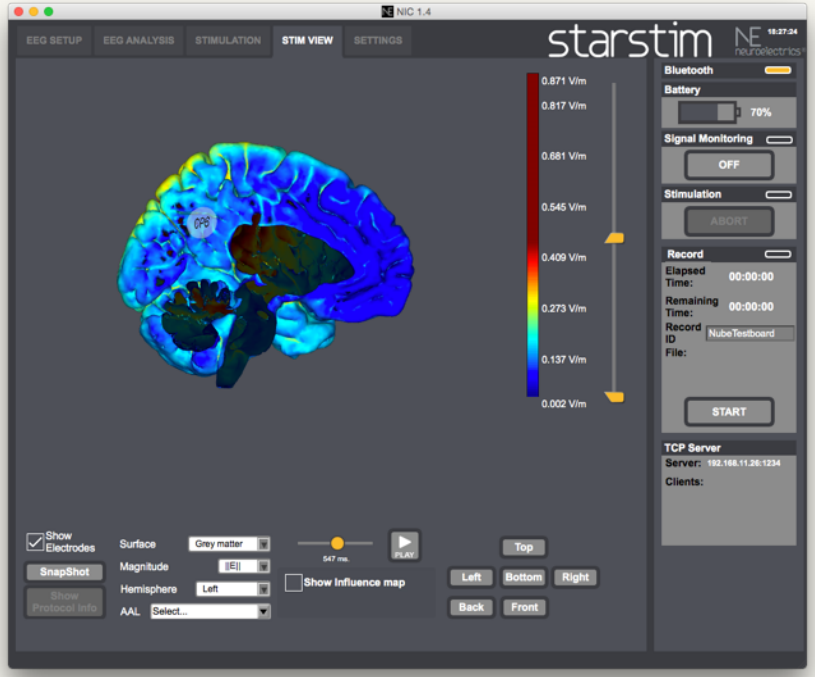


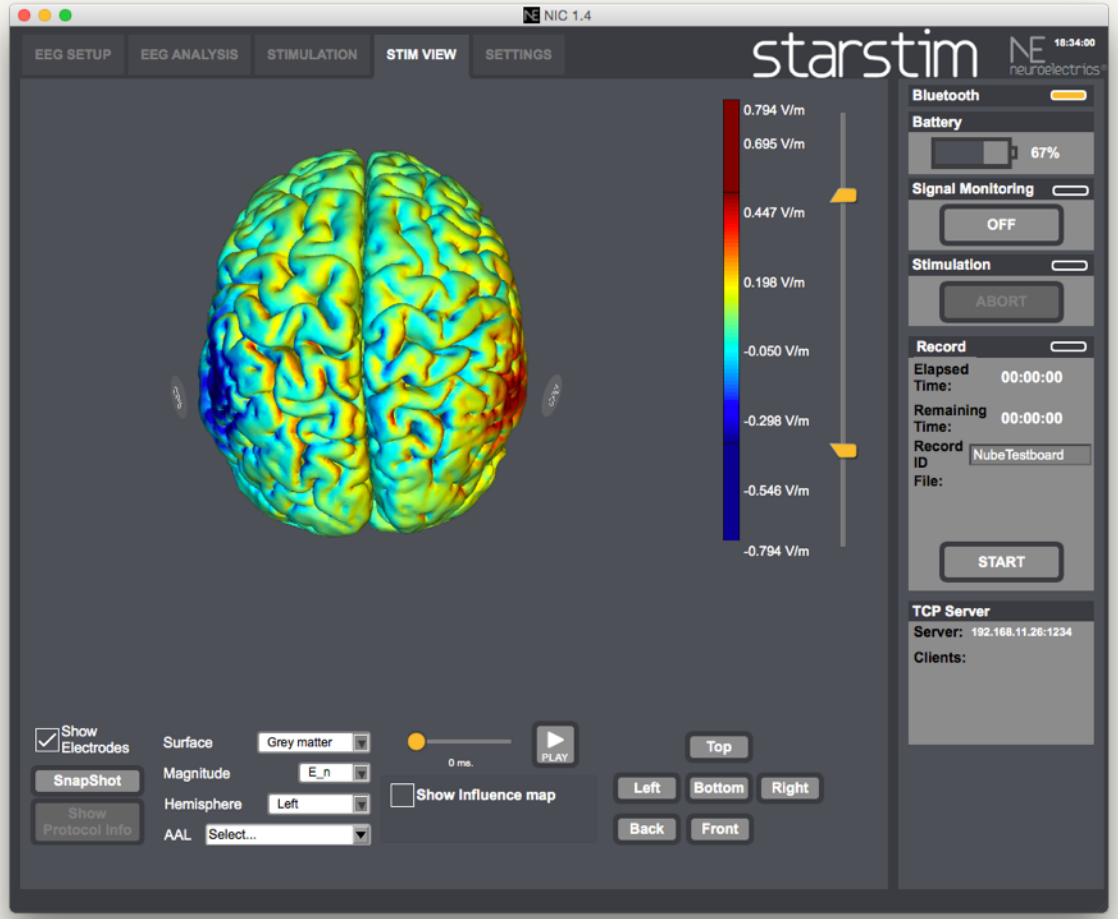
PAF Power up with PAF tACS in EO (long stim sequences)

Figure 2. Alpha-aftereffects across protocols. A) Mean relative increase (dB) in individual alpha band power from pre-test to post-test. Both long protocols are followed by a significantly higher alpha-increase compared to sham. Asterisks reflect significant pairwise comparisons using Wilcoxon Signed Rank Tests ($\alpha = 0.05$). Only the respective com-

CP5 vs. CP6 (2 mA)







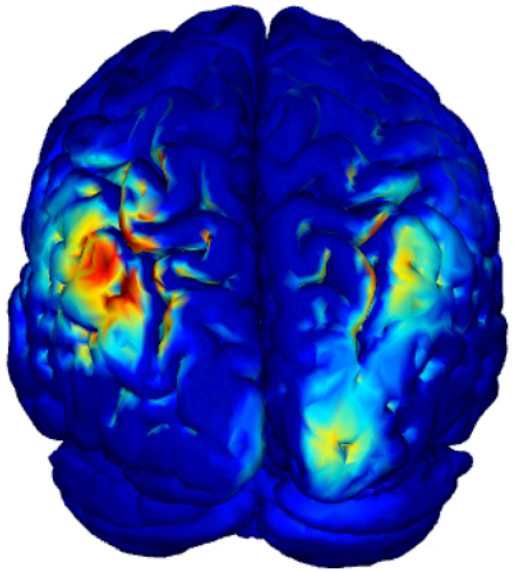
Challenges

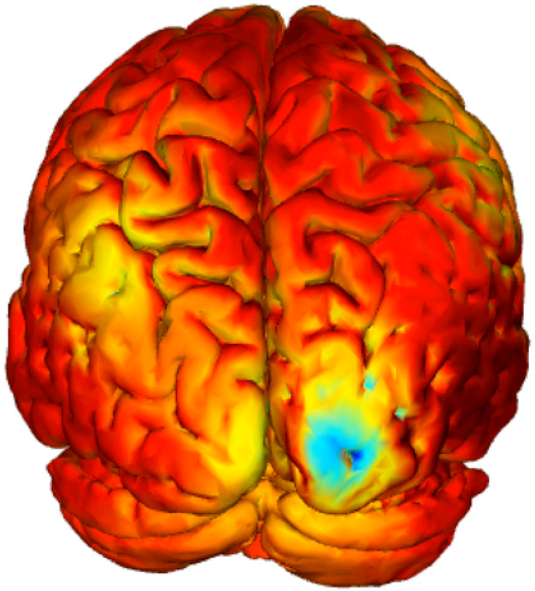
Alpha frequency and distribution is quite subject-dependent.

May need to adjust not only frequency but also montage (use Reciprocity!).

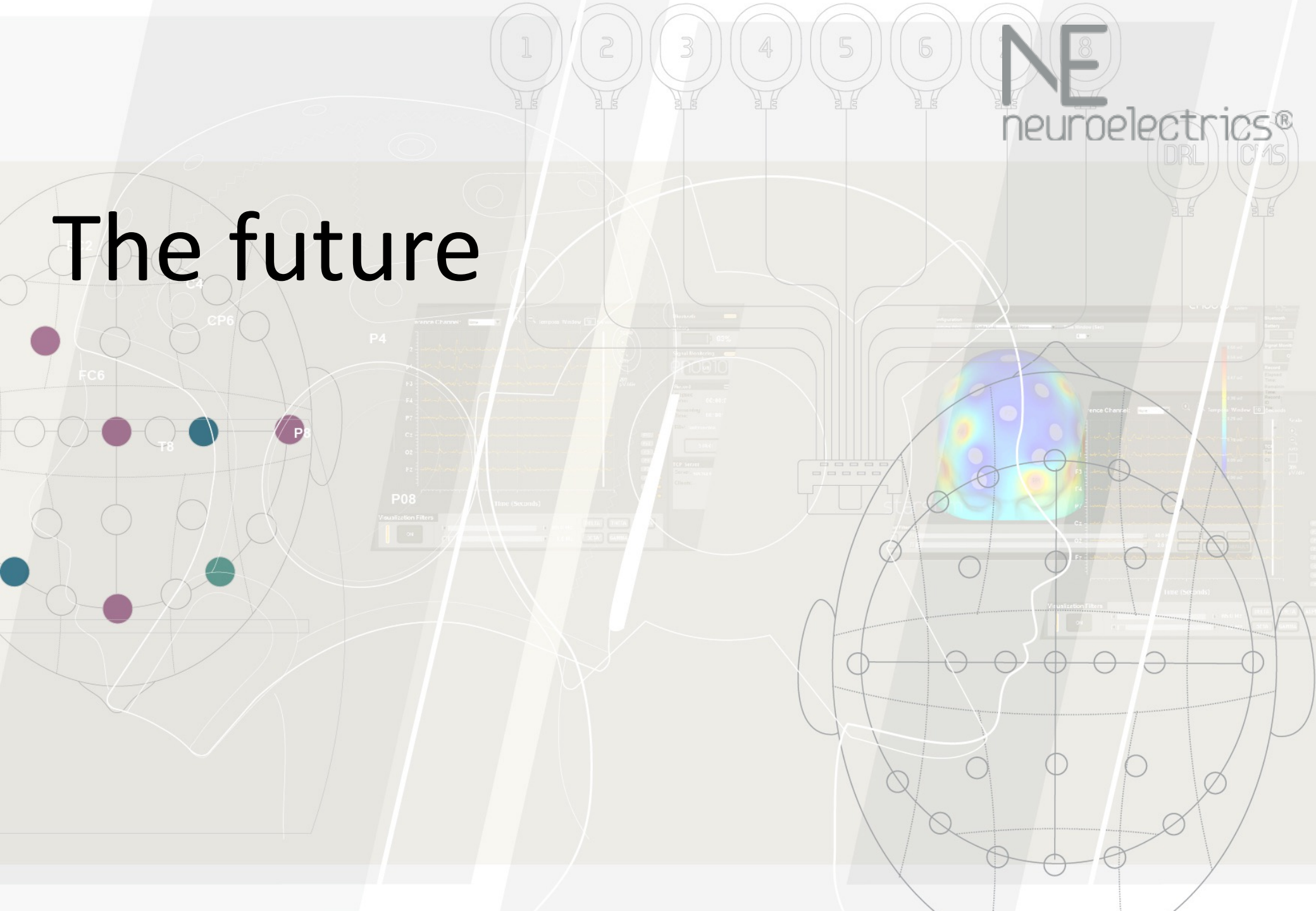
Here is an example of alpha dipole activity.

S8T1T1C1000F9-8_Pre (first IC and full alpha band)





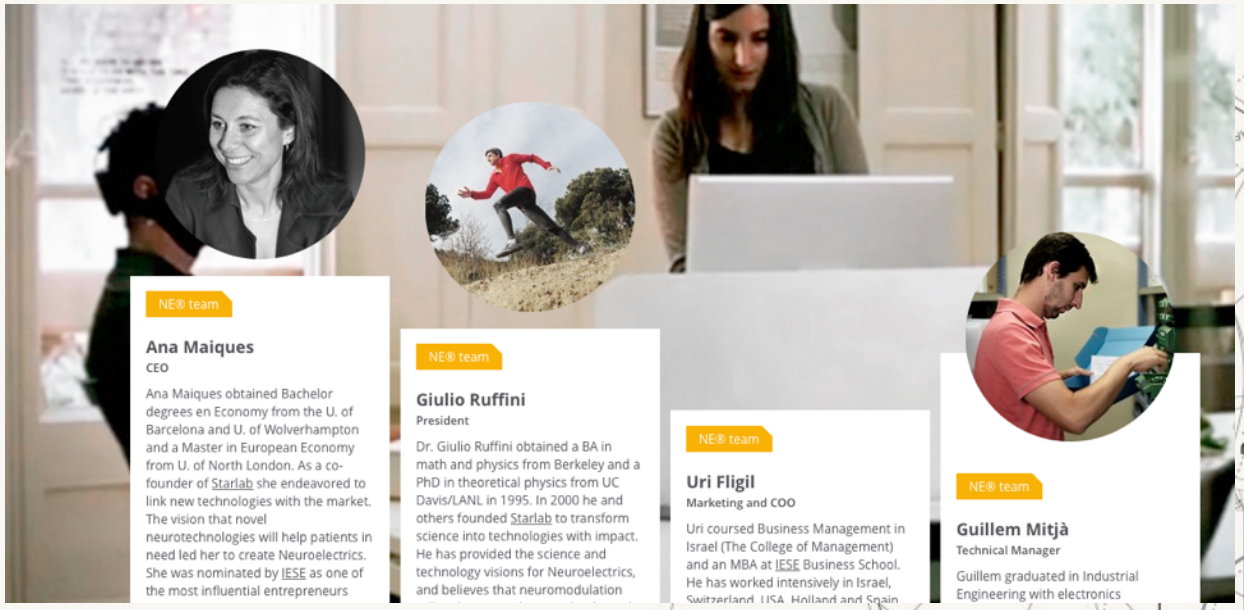
The future



The Future

- Models represent the state of the art in our understanding what tCS produces physically. Not perfect but much better than nothing, and they will be improved over time using the scientific method.
- Targeted multi-electrode montages using small electrodes offer the opportunity for more precise, meaningful stimulation research.
- Brain function is mediated by networks: let's go after them! Target maps can be defined in various ways: Brodmann Areas or AAL; simple or multiple; rs-fcMRI; rs-fcEEG / ERPs / MEG; PET.
- Technologies now offer the possibility of modeling/optimizing and – crucially – implementing advanced methods.
- The combination of EEG and tCS technologies is natural and powerful.
- Approach is applicable to tACS and tRNS. There are many meaningful questions yet to explore.

And thanks to all the NE team and Advisors



NE® team

Ana Maiques
CEO

Ana Maiques obtained Bachelor degrees en Economy from the U. of Barcelona and U. of Wolverhampton and a Master in European Economy from U. of North London. As a co-founder of Starlab she endeavored to link new technologies with the market. The vision that novel neurotechnologies will help patients in need led her to create Neuroelectrics. She was nominated by IESE as one of the most influential entrepreneurs

NE® team

Giulio Ruffini
President

Dr. Giulio Ruffini obtained a BA in math and physics from Berkeley and a PhD in theoretical physics from UC Davis/LANL in 1995. In 2000 he and others founded Starlab to transform science into technologies with impact. He has provided the science and technology visions for Neuroelectrics, and believes that neuromodulation

NE® team

Uri Fligil
Marketing and COO

Uri coursed Business Management in Israel (The College of Management) and an MBA at IESE Business School. He has worked intensively in Israel, Switzerland, USA, Holland and Spain

NE® team

Guillem Mitjà
Technical Manager

Guillem graduated in Industrial Engineering with electronics

Advisory Board

Alvaro Pascual-Leone, MD, PhD
BIDMC/Harvard Medical School

Born in Spain in 1961, MD and PhD degrees in Neurophysiology from the Albert Ludwigs University in Germany. He also trained at he University of Minnesota and the US National Institutes of Health. Currently he is the Principal Investigator of the Center for Non-Invasive Brain Stimulation and Professor of Neurology at Harvard Medical School and the Beth Israel Deaconess Medical Center (Boston, USA). He is a world leader in the development of brain stimulation technologies (TMS and tDCS).

Advisory Board

Prof. Adam Gazzaley
Neuroscience Imaging Center / UC San Francisco

Dr. Adam Gazzaley obtained an M.D. and a Ph.D. in Neuroscience at the Mount Sinai School of Medicine in New York, completed clinical residency in Neurology at the University of Pennsylvania, and postdoctoral training in cognitive neuroscience at UC Berkeley. He is the founding director of the Neuroscience Imaging Center at the UC San Francisco, an Associate Professor in Neurology, Physiology and Psychiatry, and Principal Investigator of a cognitive neuroscience laboratory.

Advisory Board

Prof. Michael Nitsche
Universitätsmedizin Göttingen

Currently, he is a Professor for Clinical Neurophysiology in the University of Göttingen (Germany). He is a tDCS pioneer and a key opinion leader in the field of non-invasive brain stimulation, neuroplasticity and neuropsychopharmacology, among others.

Advisory Board

Dr. Luis García-Larrea
Neurological Hospital of Lyon/ INSERM

Born in Spain in 1956, MD and PhD degrees from the University of Barcelona. Currently Research Director at the INSERM (French National Agency for Medical Research) and Head of the Inserm Unit U879 "Central Integration of Pain in Humans" (U-879) at the Neurological Hospital of Lyon. Author or co-author of 105 international publications and 40 didactic papers. General Secretary of the European Chapter of Clinical Neurophysiology Societies and President of the French Clinical Neurophysiology Society.

Advisory Board

Prof. Niels Birbaumer
University of Tübingen

Niels Birbaumer is one of the leading figures in the history of brain-computer interfaces (BCI), which are direct communication devices between the brain and a computer. Birbaumer has been dealing with BCIs for as much as forty years. He believes in the power of BCIs, a power that is based on human imagination and is used to treat brain disturbances. The director of the Institute of Medical Psychology and Behavioural Neurology in Tübingen was awarded the prestigious Leibniz Prize in 1995 for his pioneering work on BCIs.

Advisory Board

Prof. Pedro Cavaleiro Miranda
Faculty of Science, University of Lisbon

Pedro Cavaleiro Miranda obtained a BSc and a PhD in Physics from the University of Sussex, UK and an MSc in Computer Science from UCL, UK. He is currently an Associate Professor in the Faculty of Science of the University of Lisbon, where he teaches Biomedical Engineering, and a researcher at the Institute of Biophysics and Biomedical Engineering, in the same University. His expertise lies in the calculation of the electric field induced by non-invasive brain stimulation techniques, based on realistic models of the human head.

Advisory Board

Prof. Roi Cohen Kadosh
Kadosh Lab, U. of Oxford

Wellcome RCD Fellow and University Research Lecturer at the University of Oxford, Prof. Kadosh is a leader in the study of the neuropsychological mechanisms of numerical and magnitude processing using advanced techniques such as tCS/tES. His main research focuses on the psychological and biological factors that shape learning and cognitive achievements. Understanding and enhancing learning and cognition have significant implications to different fields including psychology, neuroscience, education, and medicine, and have a translational impact for cognitive enhancement for clinical and non-clinical populations.