Asilomar, June 2nd 2016

Principles of tCS (transcranial current stimulation)

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

Overview

- **Intro to tCS (Part 1)**
  - Mechanisms: the electric field
  - Modeling the electric fields in the brain
  - Limitations of classic montages
- **MtCS technology: modeling and optimizing (Part 2)**
  - 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 expanding **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

Back in 2008 … we set to develop this:

neuroelectrics®

Starlab®

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)

In 2010 we did it and created a company

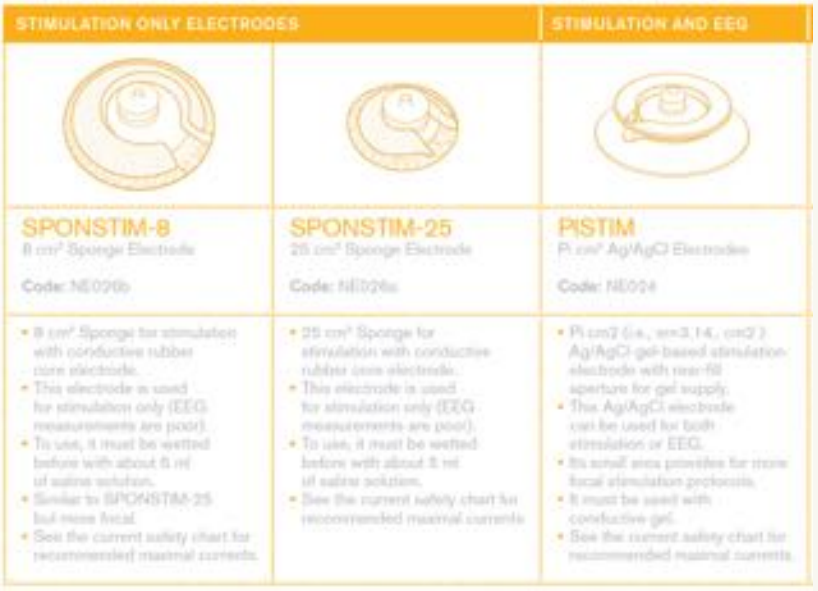
Multi-channel, wireless and programmable tCS
- Stimulate using up to **8 electrodes (now 32)**
- Current-controlled tDCS, tACS, tRNS, Sham
- Allows flexible electrode placement based on the EEG 10-10 system
- Independent current control at each electrode

Dual-use electrodes for stimulation and EEG monitoring
- Stimulate and record at the same site using the same electrodes
- Monitor EEG during tDCS – stimulator circuit is very quiet

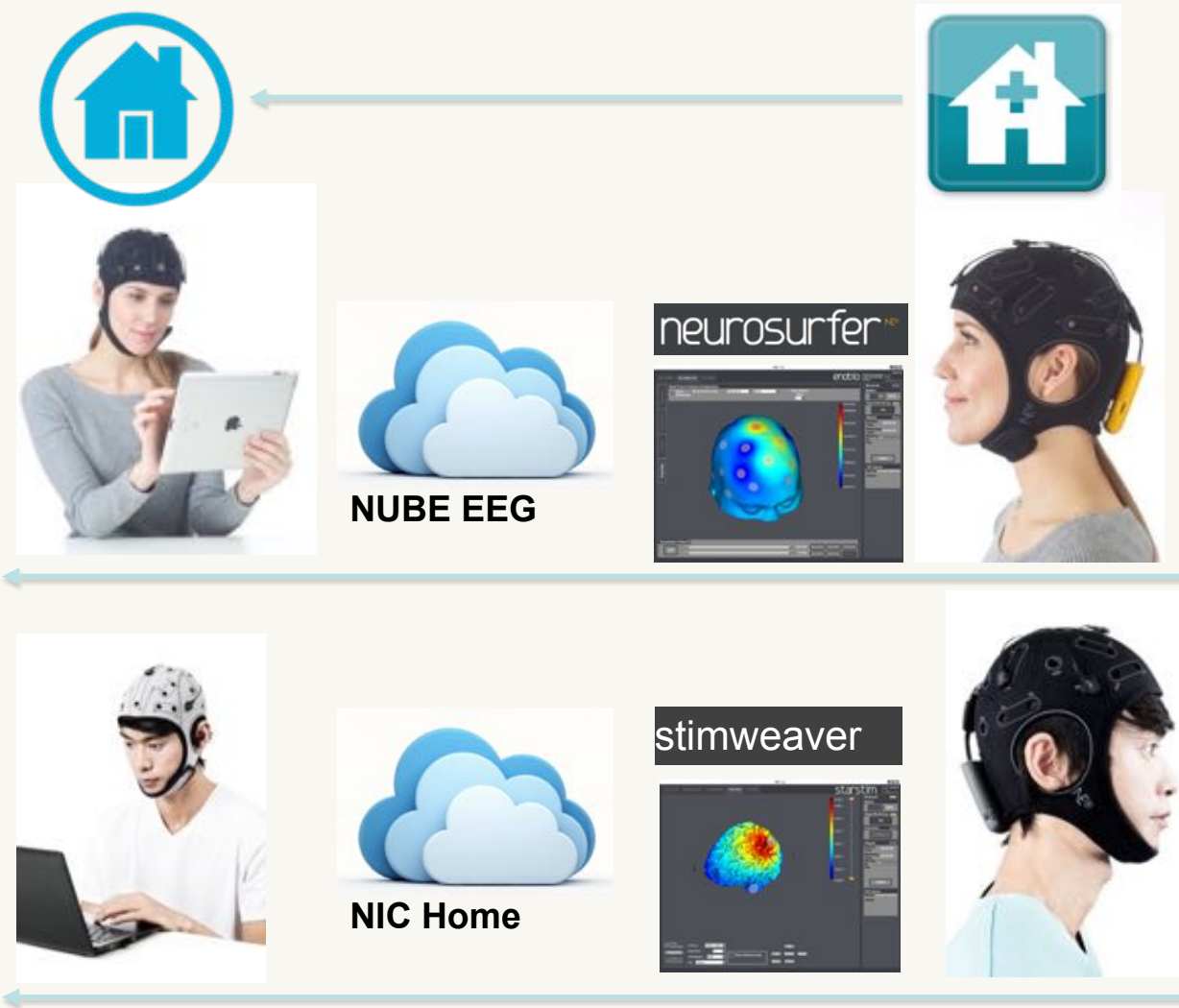
A wireless wearable concept for fast and easy setup
- Mobile stimulation and recording away from the clinic or lab
- Quick setup
- 3D accelerometer + SD card
- USB rechargeable Li-Ion battery

Intuitive user application
- User friendly protocol programming and sequencing
- Provide on-line visualization of EEG features
- Simulate generated electric fields associated with tCS
- Cloud connected / home use
- Programmatic control with Matlab API

EEG 10-10 cap for precise positioning of electrodes



Our vision: from hospital to the home for effective treatment



EEG Monitoring

enobio

ROBUST
PRECISE
WIRELESS
EEG

8, 20 & 32 channel versions

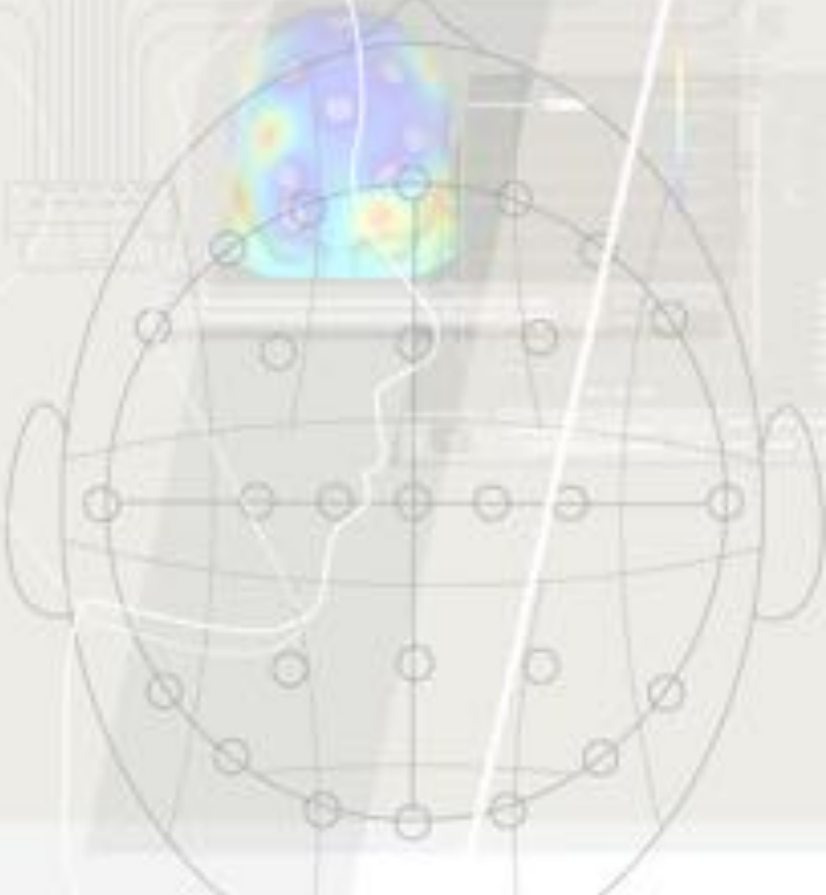
tCS Stimulation+EEG

starstim

NONINVASIVE
WIRELESS tCS
NEUROSTIMULATOR

tCS research, clinic and home research versions
8 Channels tCS/EEG

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 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.

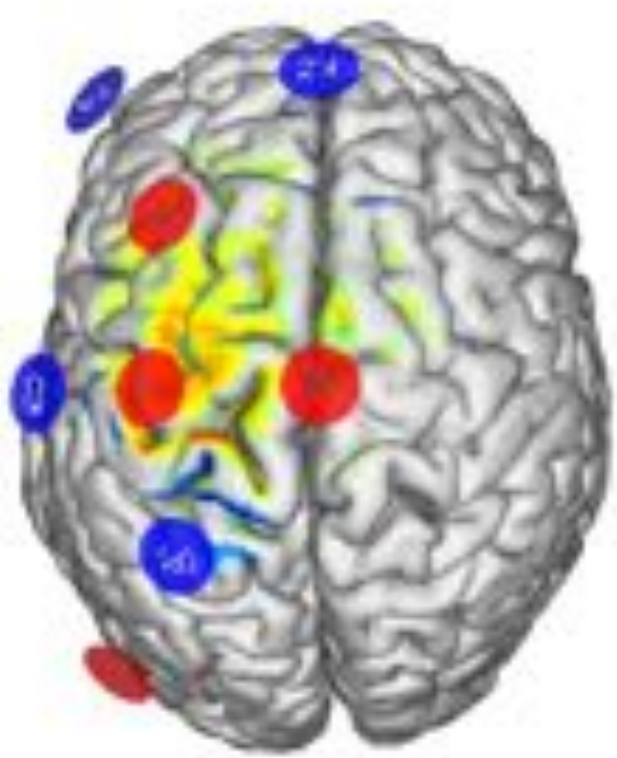
I use the term tCS (transcranial current stimulation) to emphasize that current is what is controlled … other used terms include tES. "MtCS" sometimes used to highlight the use of more than 2 (small)electrodes.

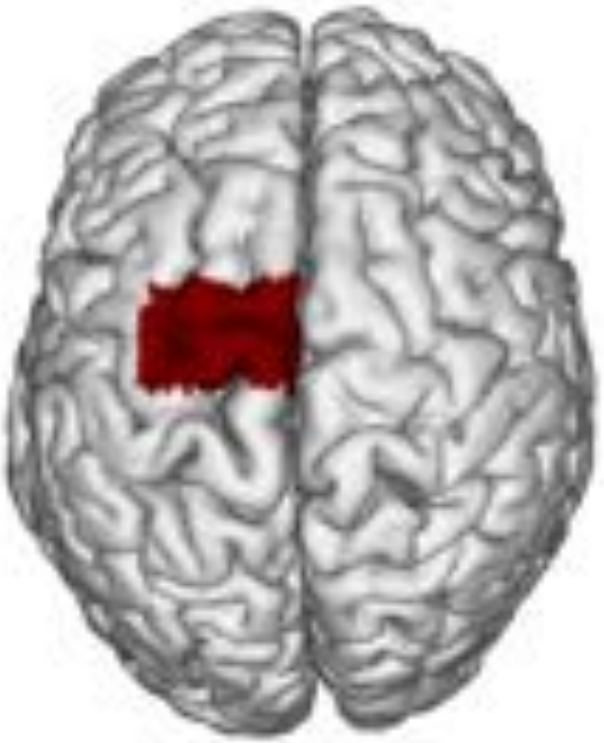
transcranial Current Stimulation (tCS)

- 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 but < 4 mA) 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**. [For ref, the FCC sets 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.** Some of the applications are: neuropathic chronic pain, major depression, stroke rehabilitation, addictive disorders and epilepsy - many others being explored.
- tDCS is most common form. Can also be Alternating Current - **tACS** - random - **tRNS** - , others.
- Known 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!

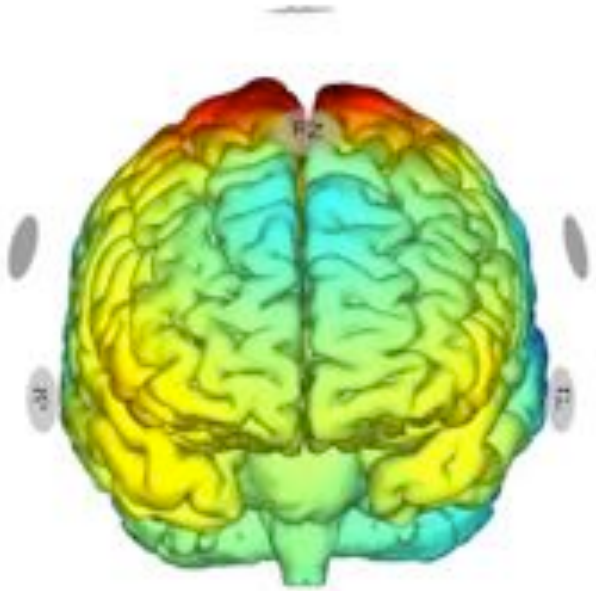
Targeting the Sup MC: 8 “Pi” electrodes





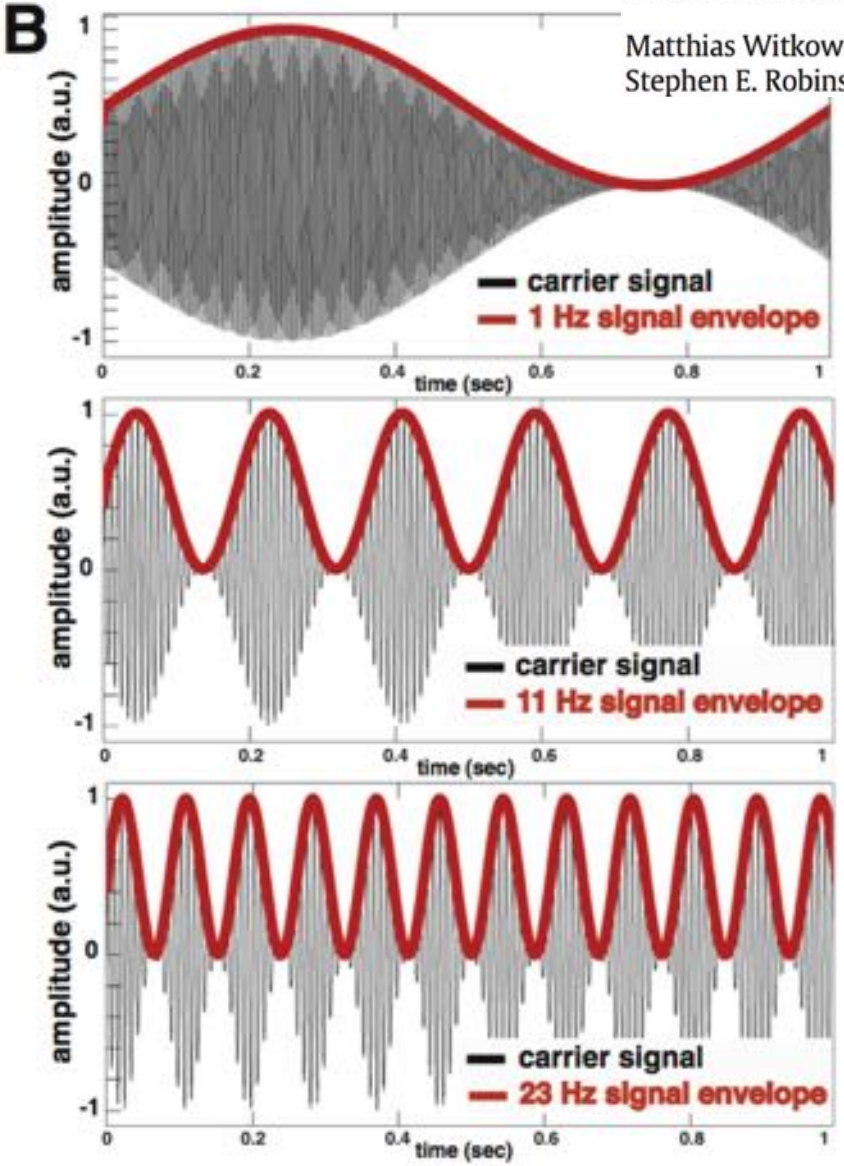
Multielectrode tDCS using small electrodes

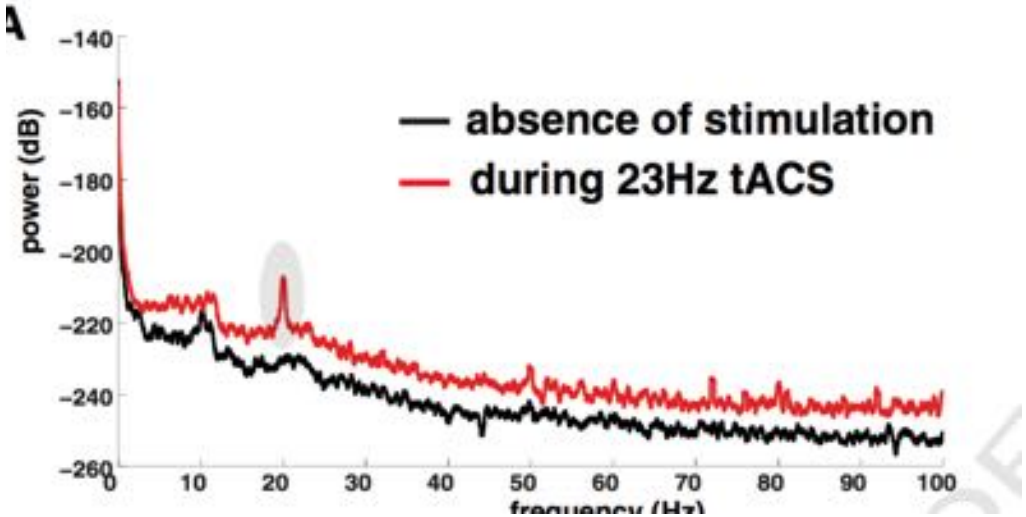
Multielectrode indepedent configuration



Mapping entrained brain oscillations during transcranial alternating current stimulation (tACS)

Matthias Witkowski [a,1], Eliana Garcia Cossio [a,b,c,1], Bankim S. Chander [a], Christoph Braun [d,e], Niels Birbaumer [b], Stephen E. Robinson [f], Surjo R. Soekadar [a,b,*]

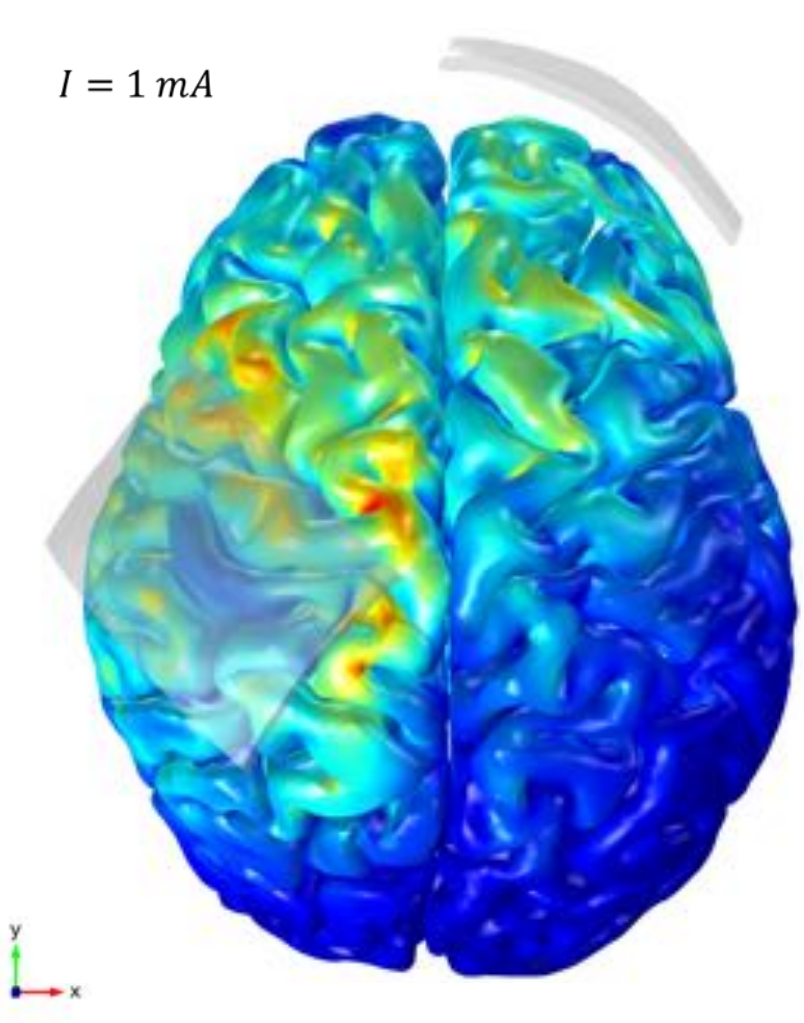




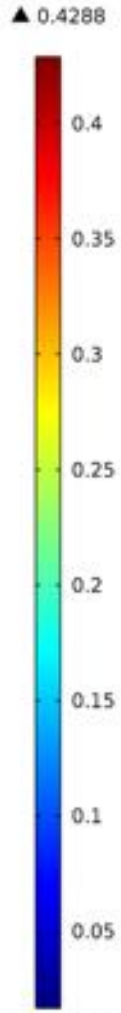
Stimulation with amplitude modulation

E-field distribution - tDCS

Ricardo Salvador & Pedro Miranda 2015, in prep

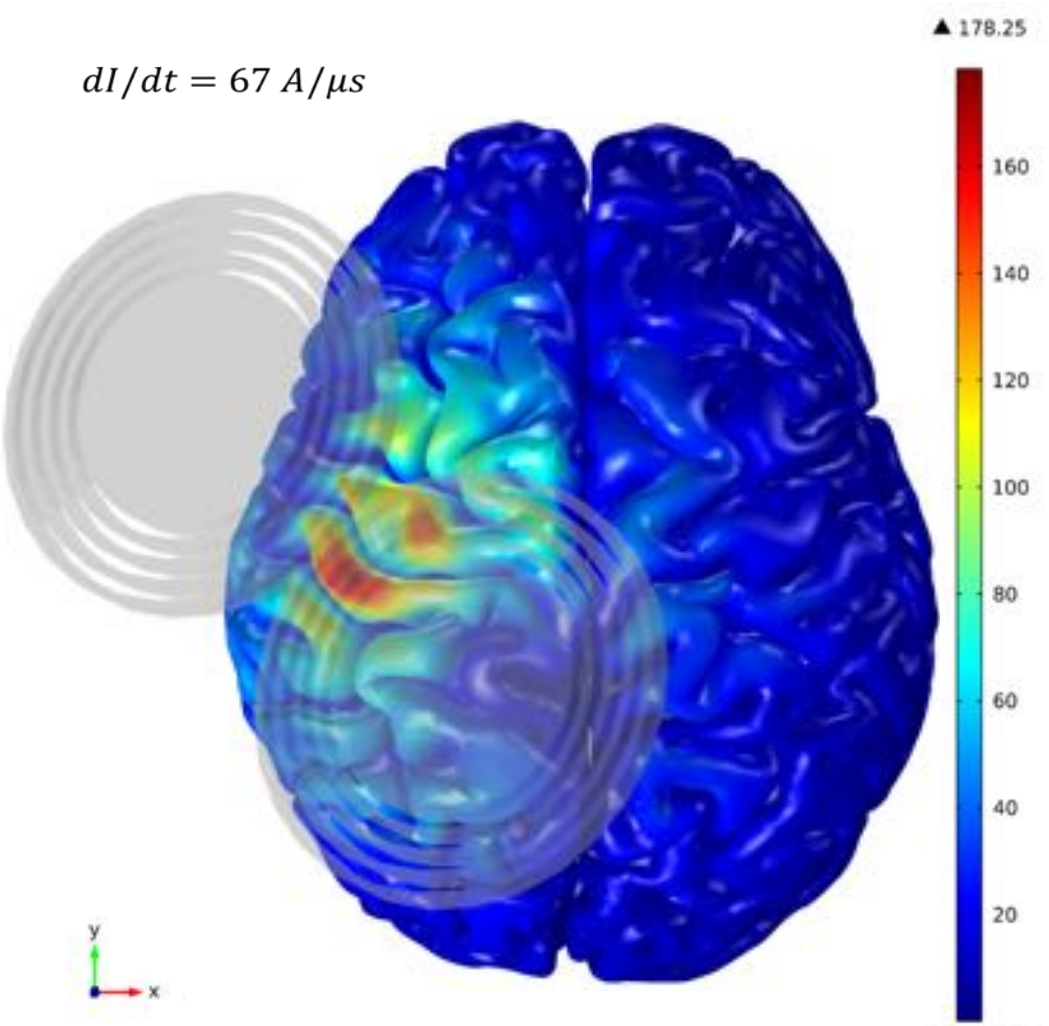


E-field's mag (V/m)



E-field distribution - TMS

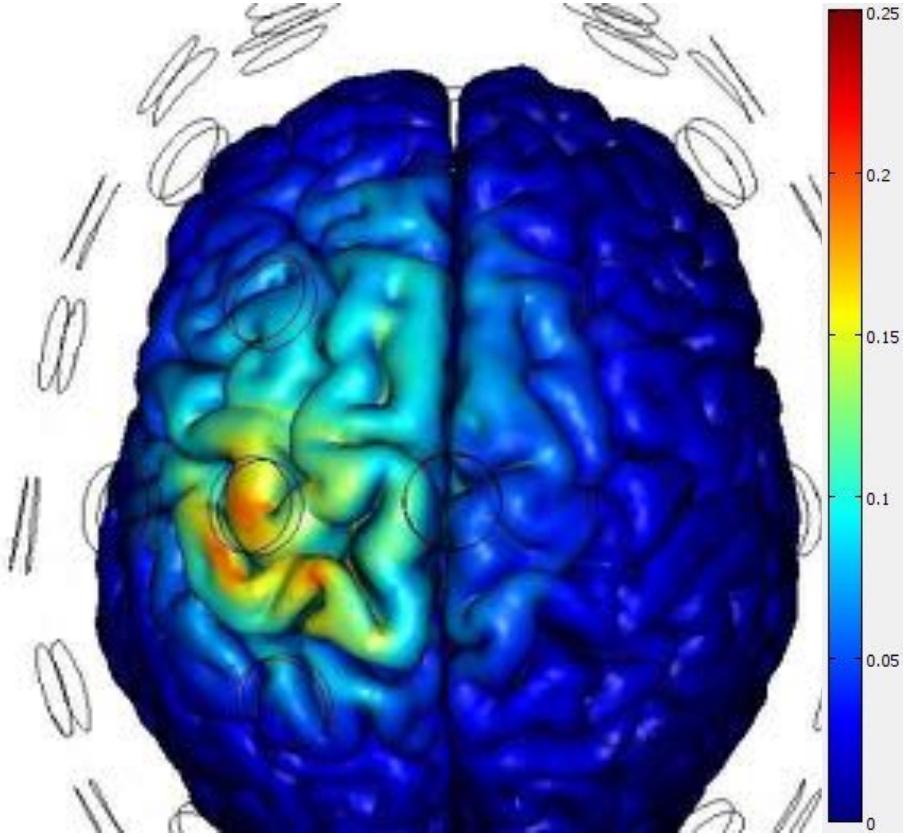
E-field mag (V/m)



- On the other hand, long application: session of rTMS using 3000 TMS pulses of say 0.2 ms pulse width sum to ~1 second of effective stimulation (compare to 1800 s in a 30 minute tDCS session).

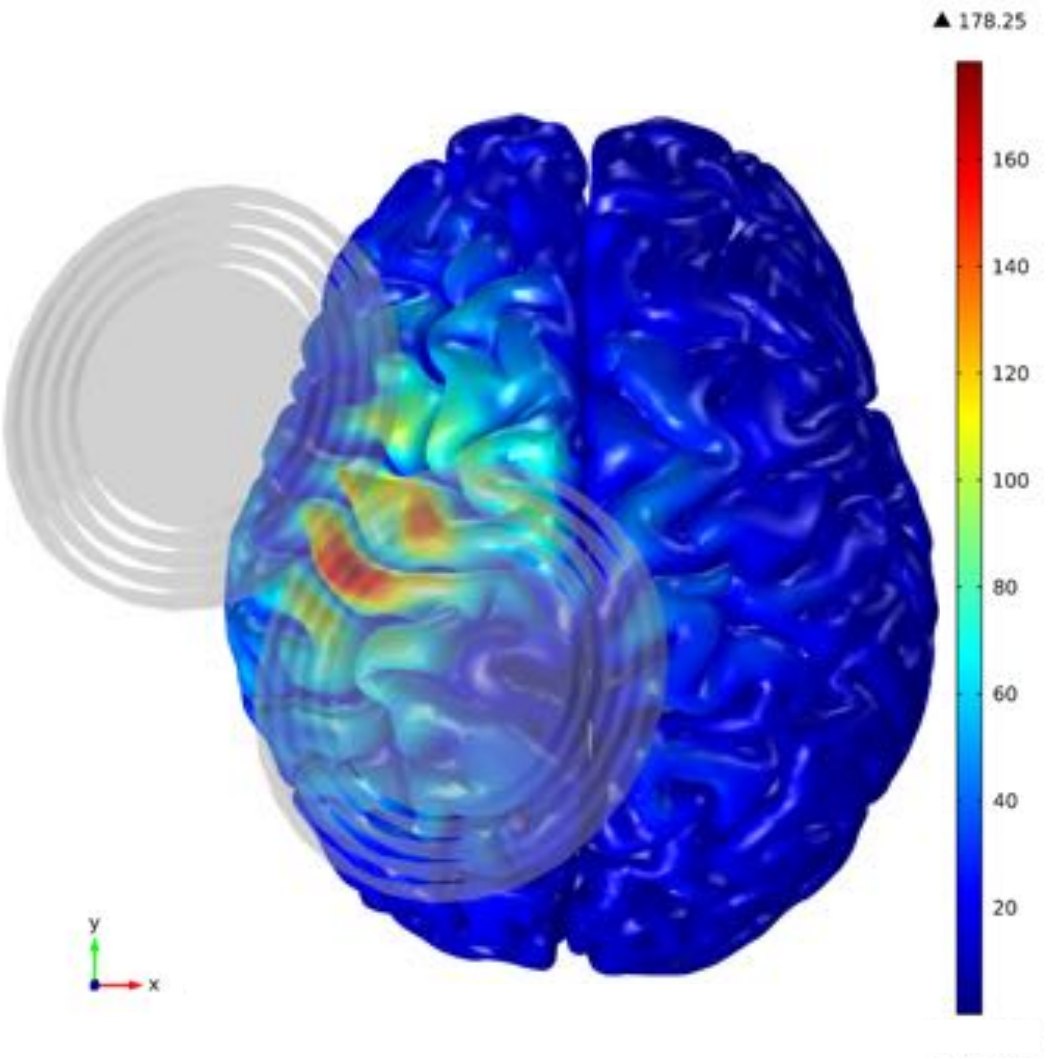
E-field distribution - MtDCS

E-field's mag (V/m)



E-field distribution - TMS

E-field mag (V/m)



R. Salvador & P. Miranda, G. Ruffini 2015, in prep

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).

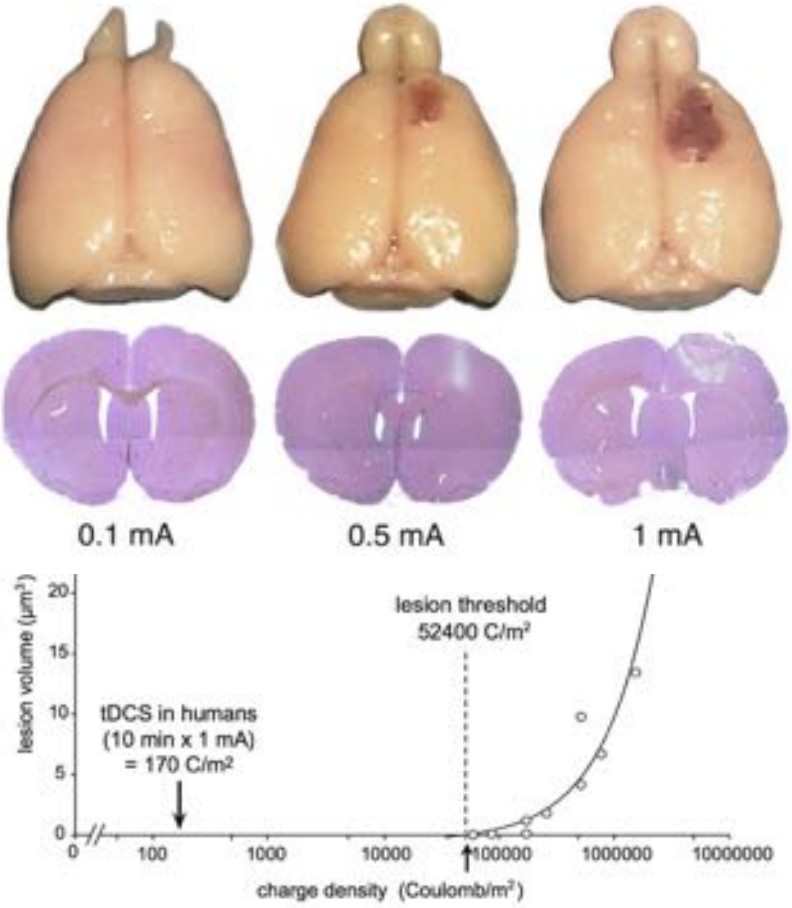
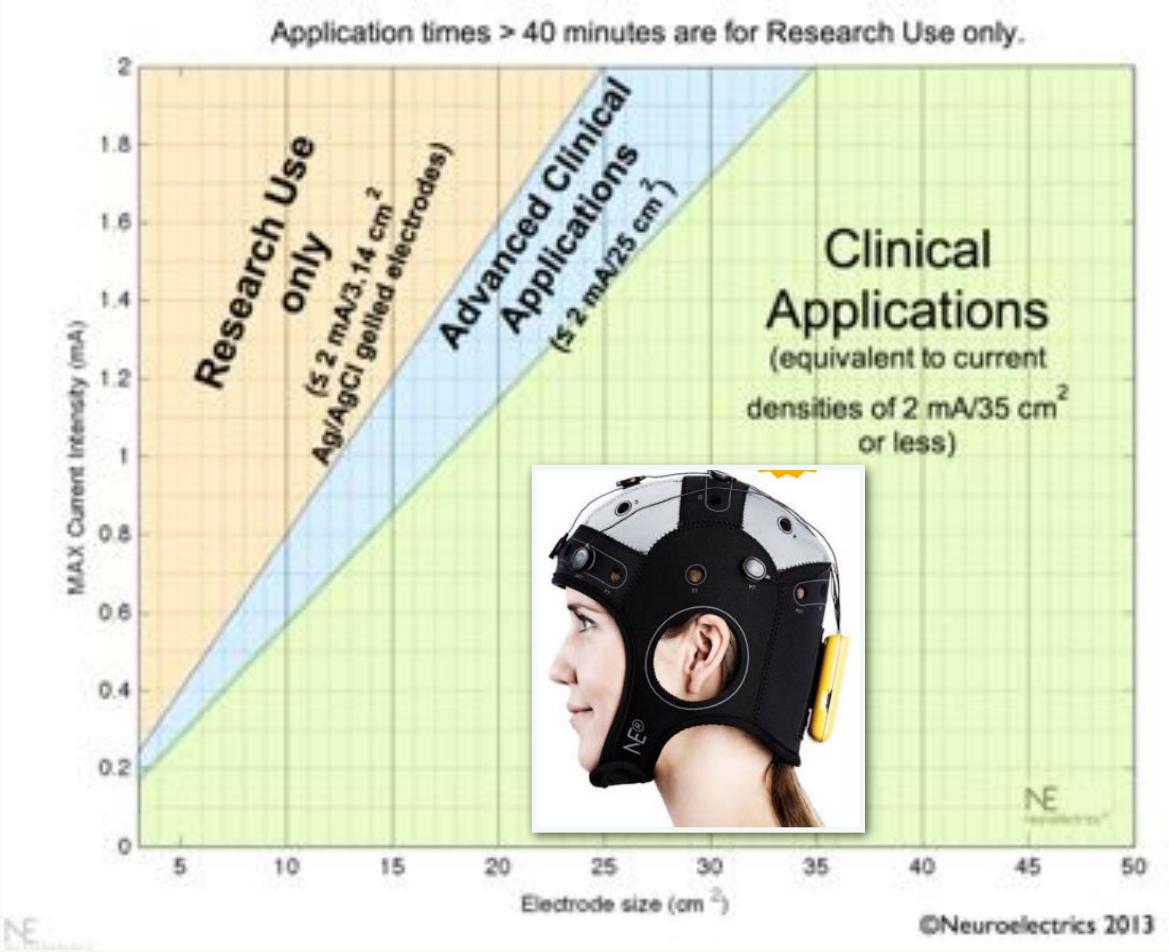


Fig. 4. Threshold estimation from the relation of charge density and lesion size at current intensities of 500–1000 μA. The results of all above-threshold experiments (n = 12) are depicted with respect to the charge density (C/m^2) and the size of the DC-induced brain lesion (μm^3). For better overview, 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

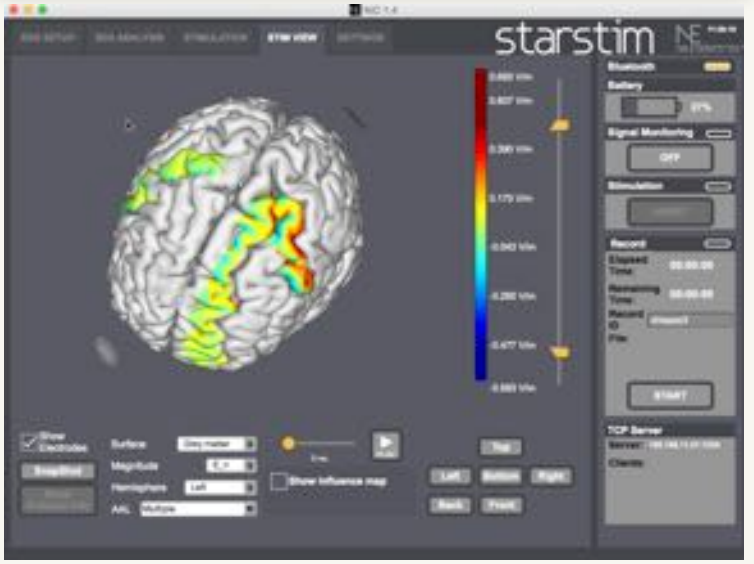
- After thousands of hours of stimulation, short term ill effects associated to tCS in <u>controlled</u> settings remain scarce and minor
- Devices need to implement safety measures
- Starstim designed for safety:
  - –Current at electrode < 4 mA
  - –Max injected current < 8 mA
  - –Programmed durations < 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 of tCS and EEG** 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!)

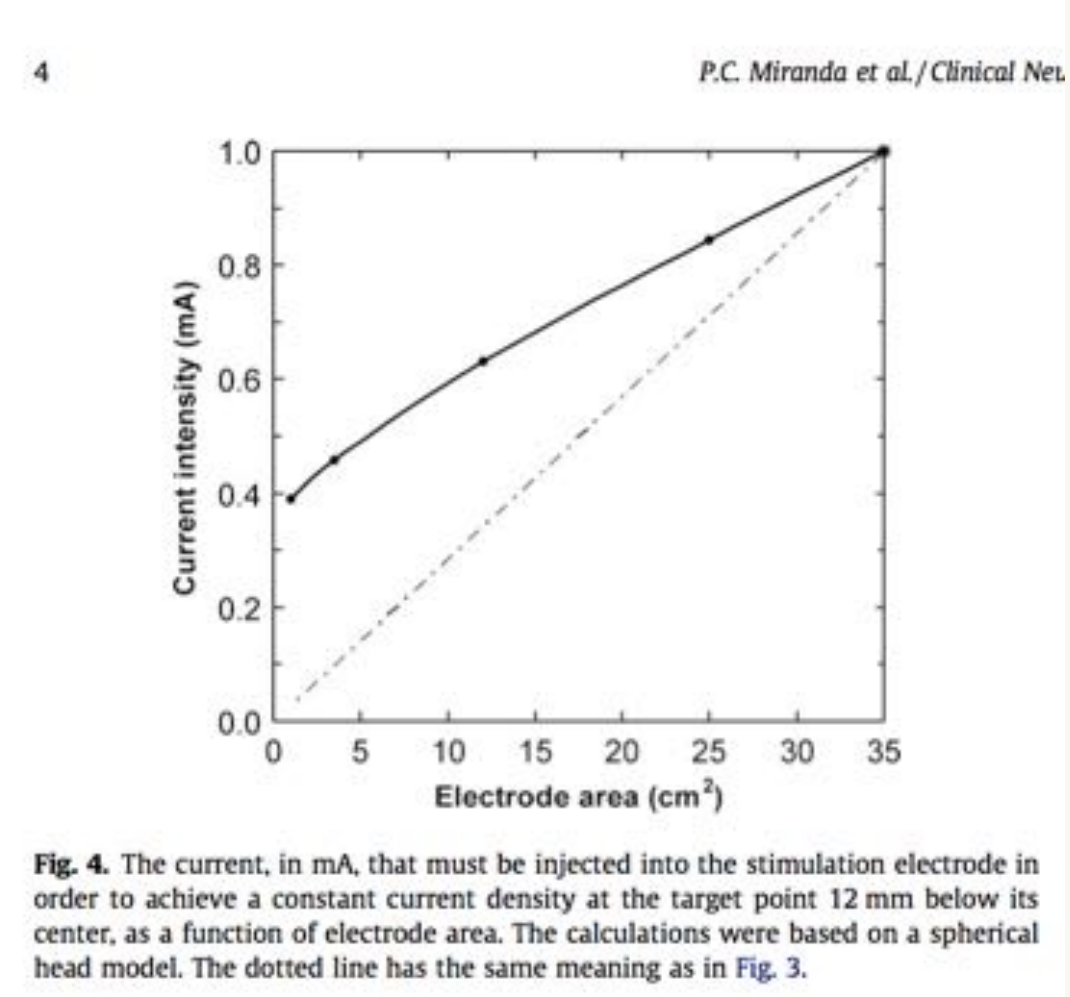
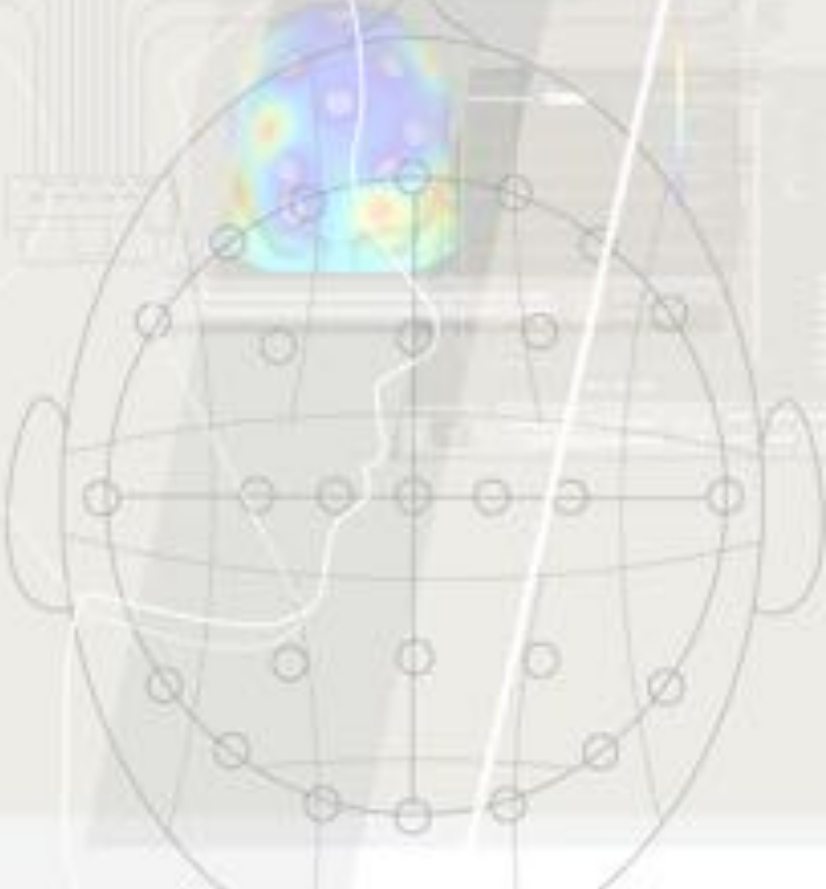


Fig. 4. The current, in mA, that must be injected into the stimulation electrode in order to achieve a constant current density at the target point 12 mm below its center, as a function of electrode area. The calculations were based on a spherical head model. The dotted line has the same meaning as in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

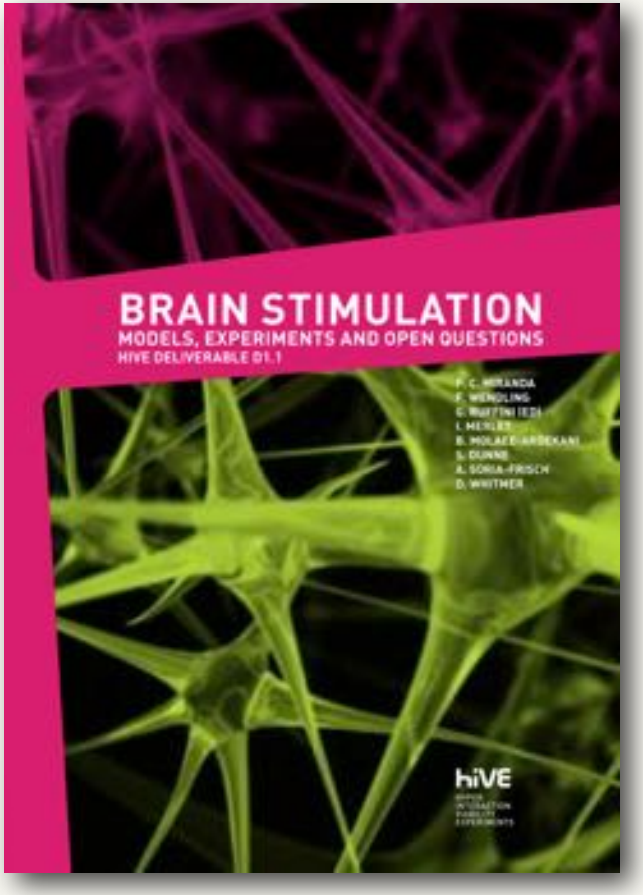
Mechanisms matter

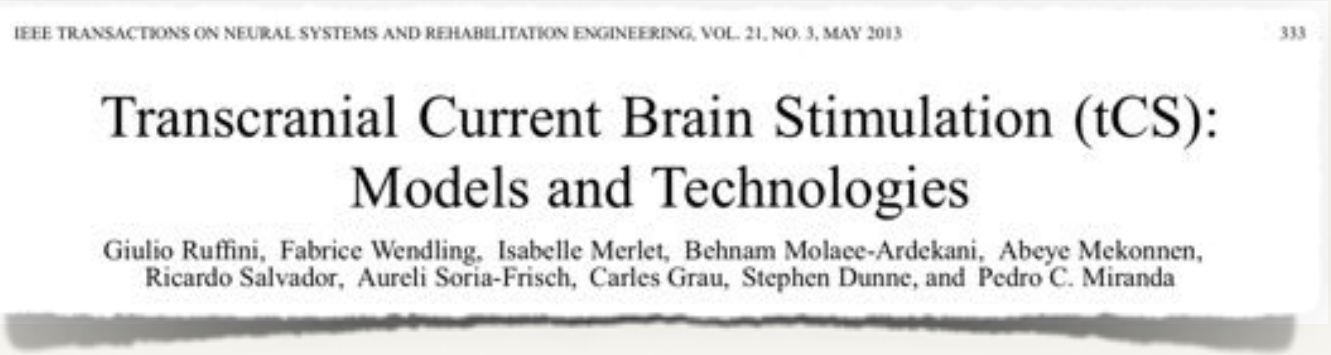


The concurrent and aftereffects of tCS

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 is altered (plasticity)





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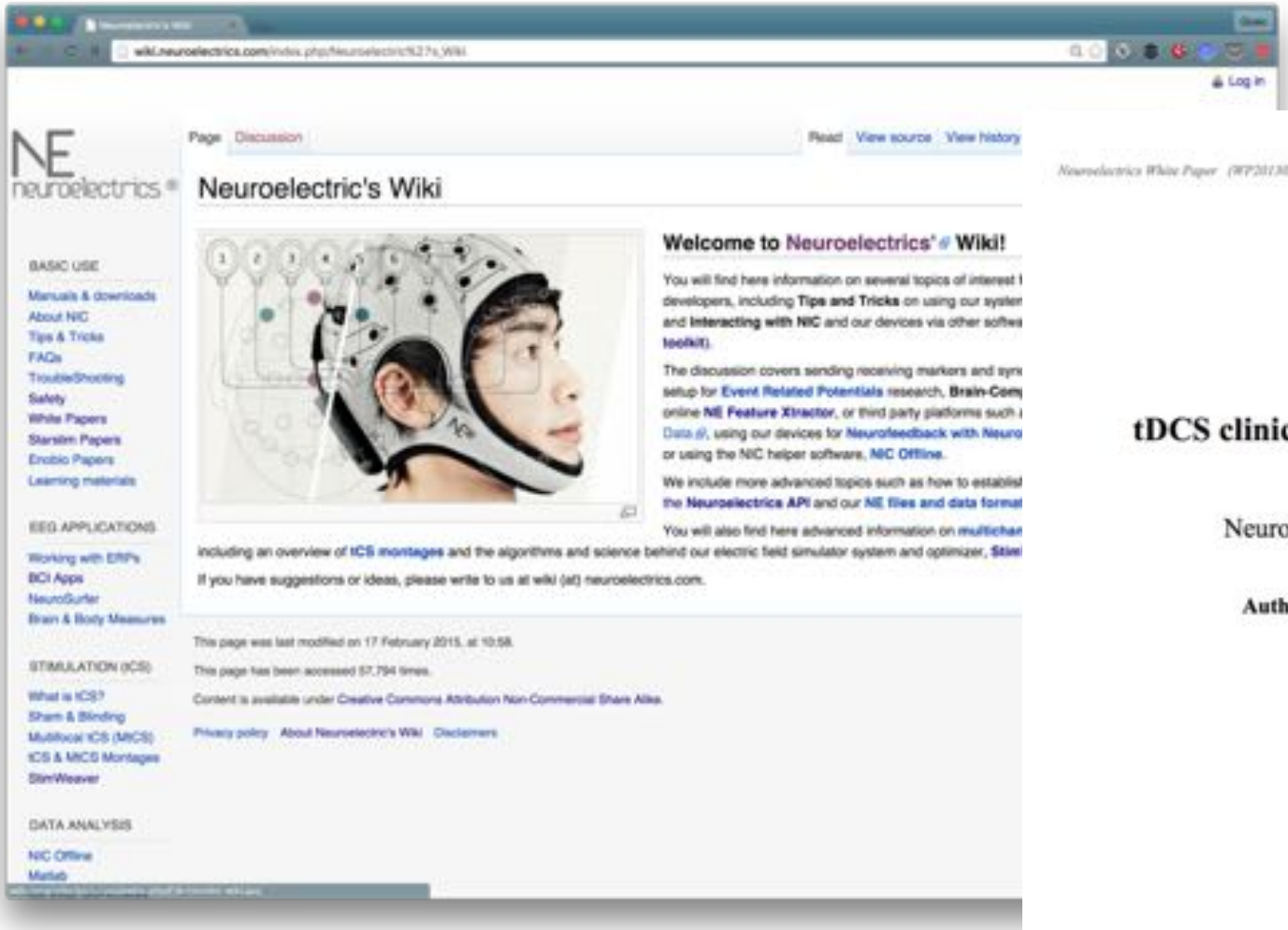
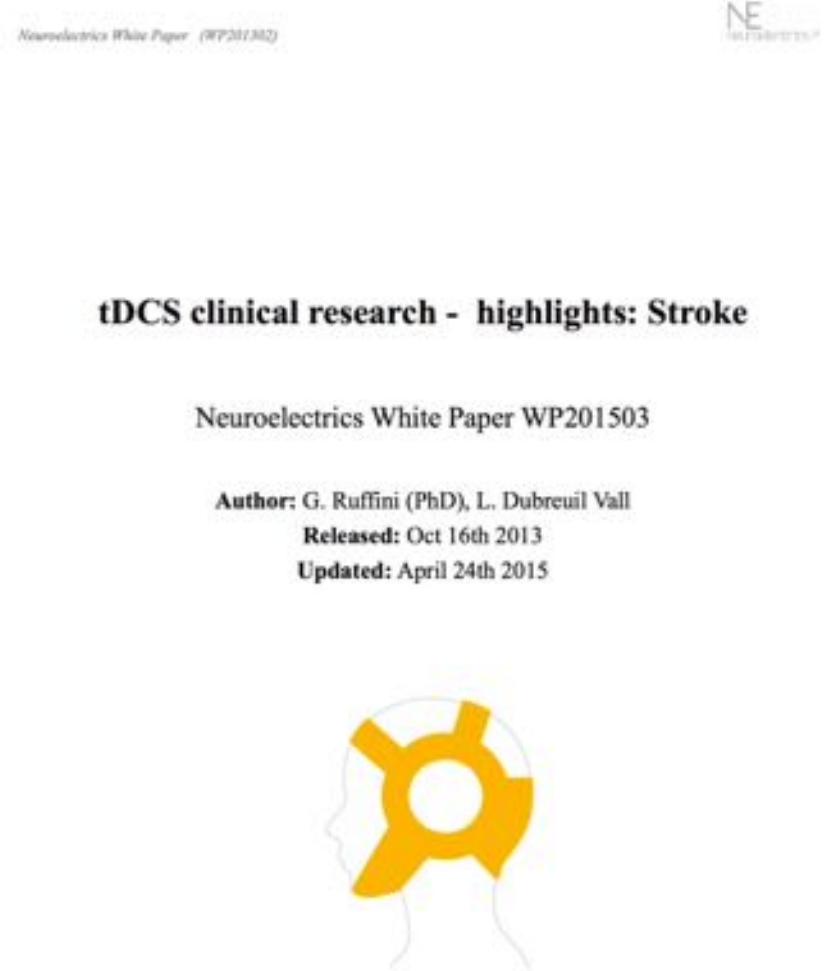




Neuroelectrics White Paper (WP201302)

tDCS clinical research - highlights: Stroke

Neuroelectrics White Paper WP201503

Author: G. Ruffini (PhD), L. Dubreuil Vall
Released: Oct 16th 2013
Updated: April 24th 2015

Concurrent effects

Effects on firing rates. Linear dependence of firing rates on fields ~ 1 V/m

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[1-21] 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 (1 V/m) seen to modulate ongo but cannot start it

Orientation-dependence observed

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[3]

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

Received October 23, 1961; and January 30, 1962

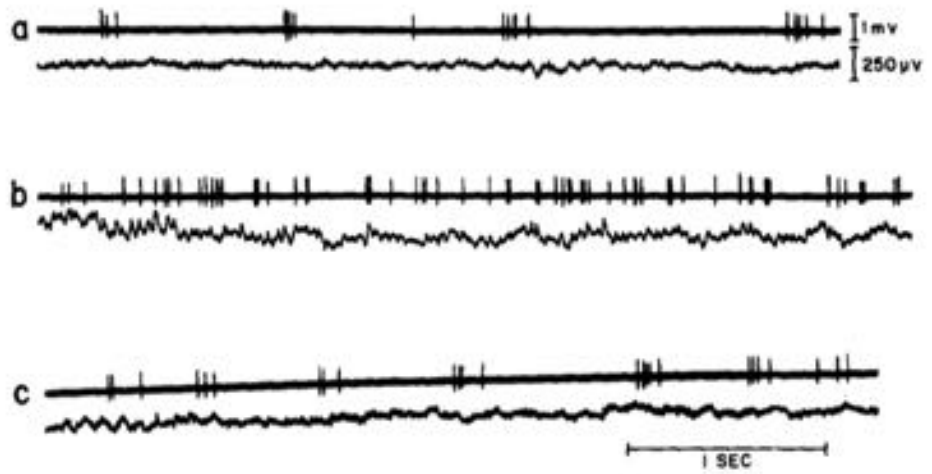
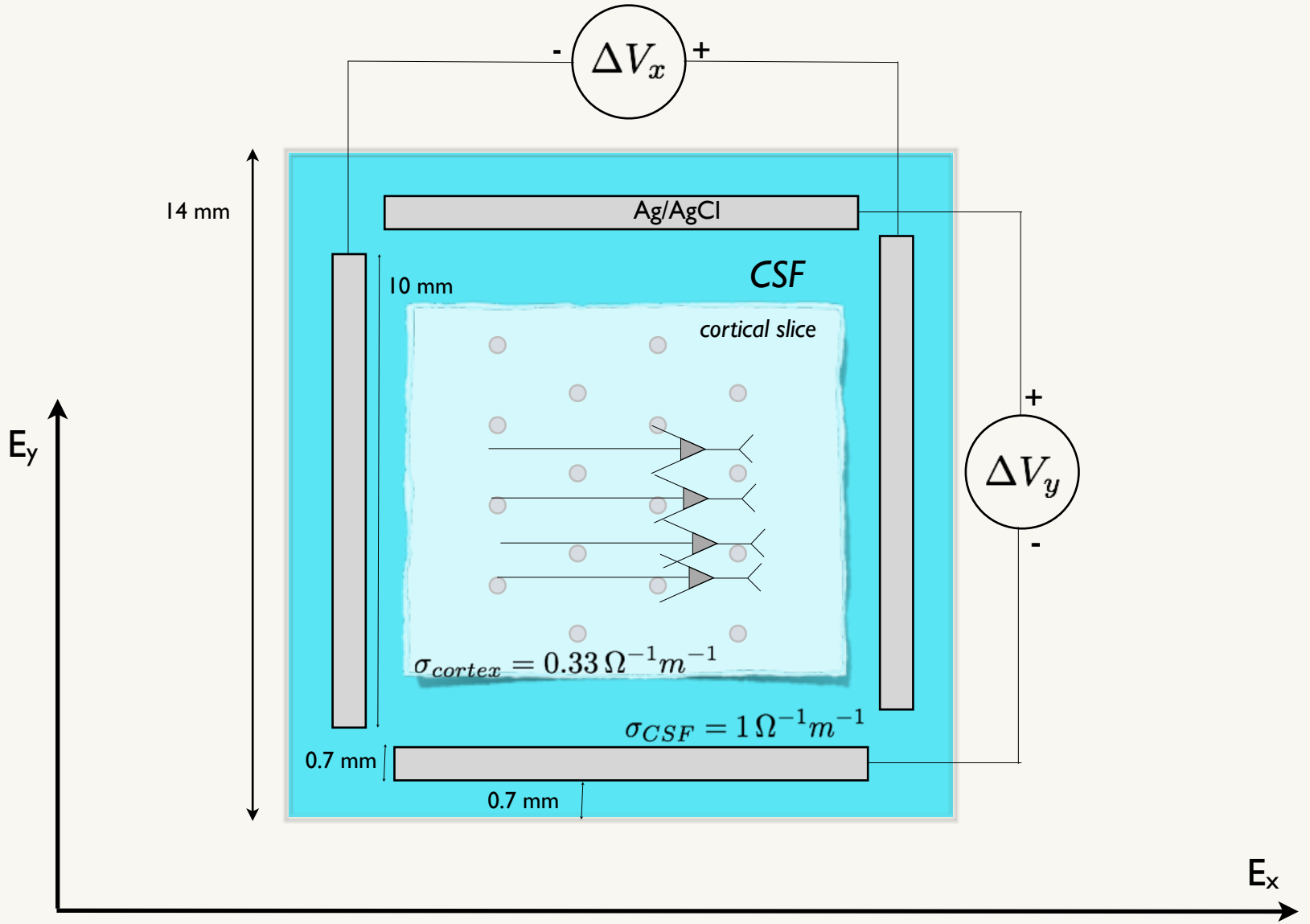


FIG. 1. Effect of transcortical d-c current on spontaneous neuron activity and EEG in the motor cortex; *a*, control; *b*, 1,000 μa inward (surface-positive); *c*, control, 20 sec after *b*.

Fields and neurons in flatland



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

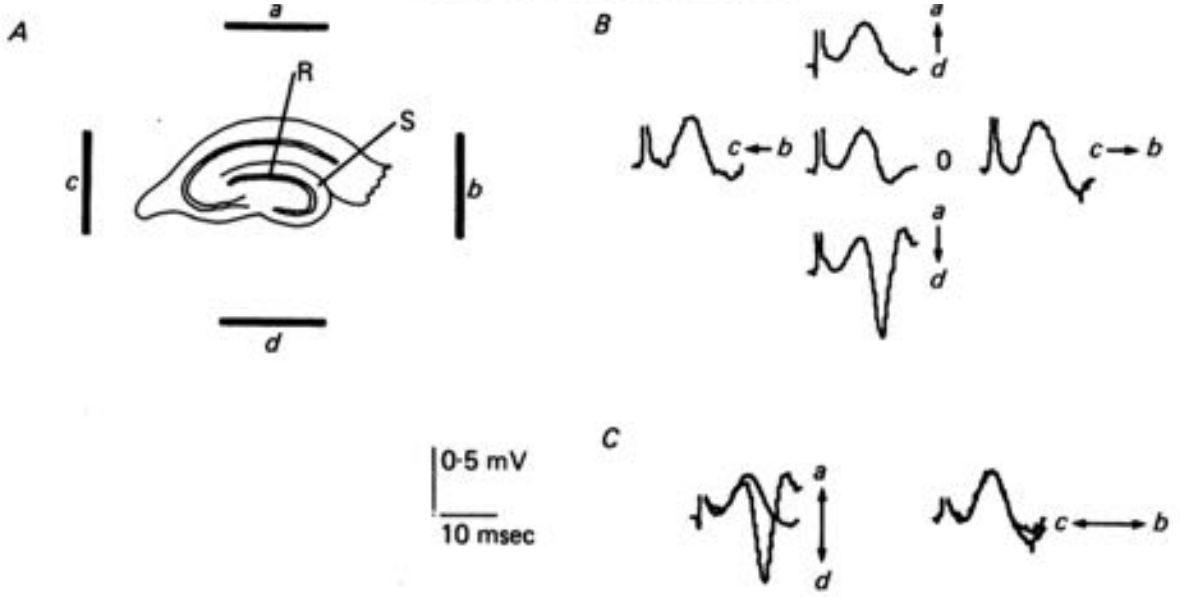
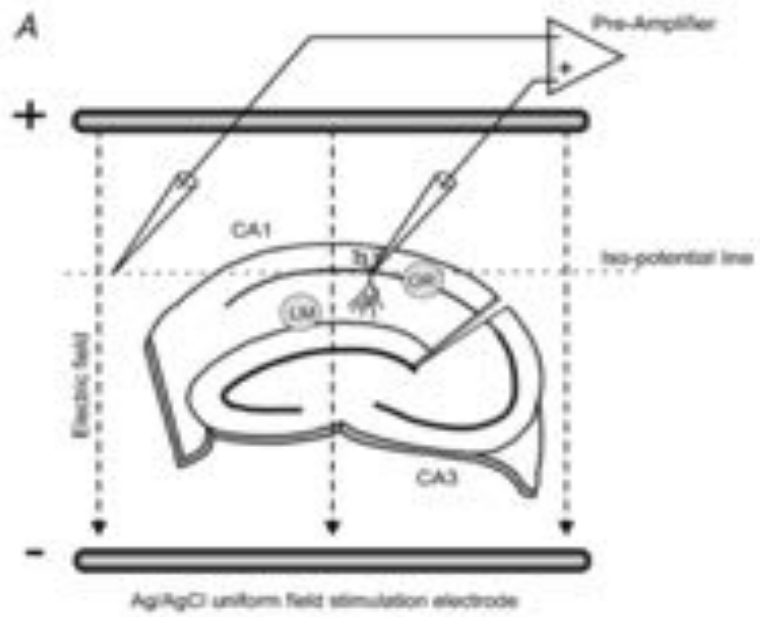
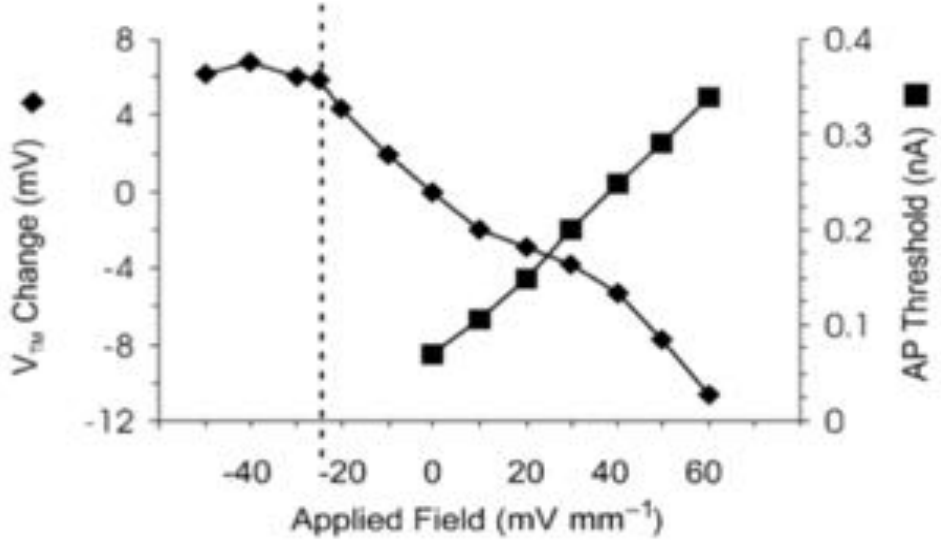


Fig. 1. Effect of direction of polarizing current. *A*, polarization currents were passed across a transverse slice, between gross electrodes positioned in the artificial c.s.f. at sites *a* and *d* or *b* and *c* (S, stimulus, site; R, recording site). The polarization potential gradient was 17 mV/mm, 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.

The E-field and the transmembrane potential (linearity)



Rat hippocampal slices

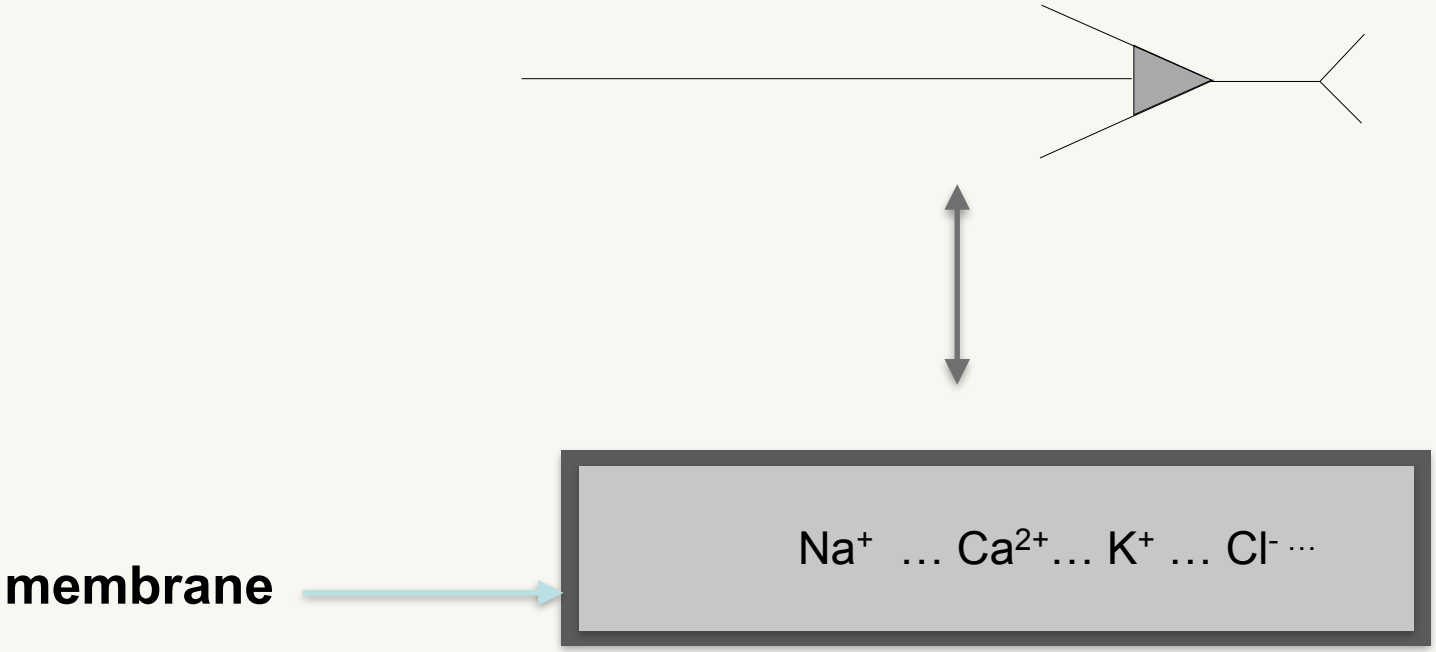


J Physiol 557.1 (2004) pp 175–190

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

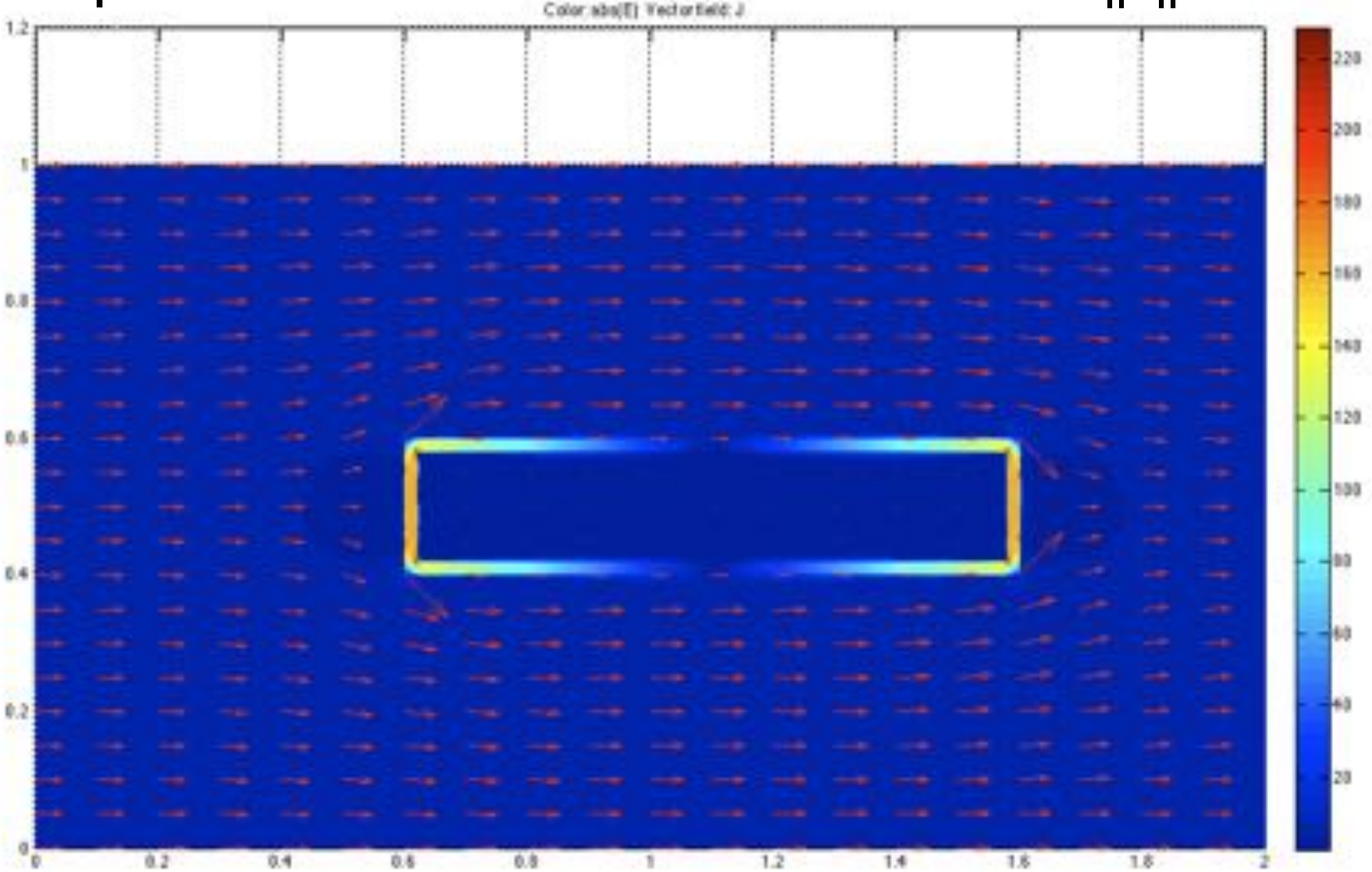
Marom Bikson[1], Masashi Inoue[2], Hiroki Akiyama[2], Jackie K. Deans[1], John E. Fox[1], Hiroyoshi Miyakawa[2] and John G. R. Jefferys[1]

A simple (very simple) model!

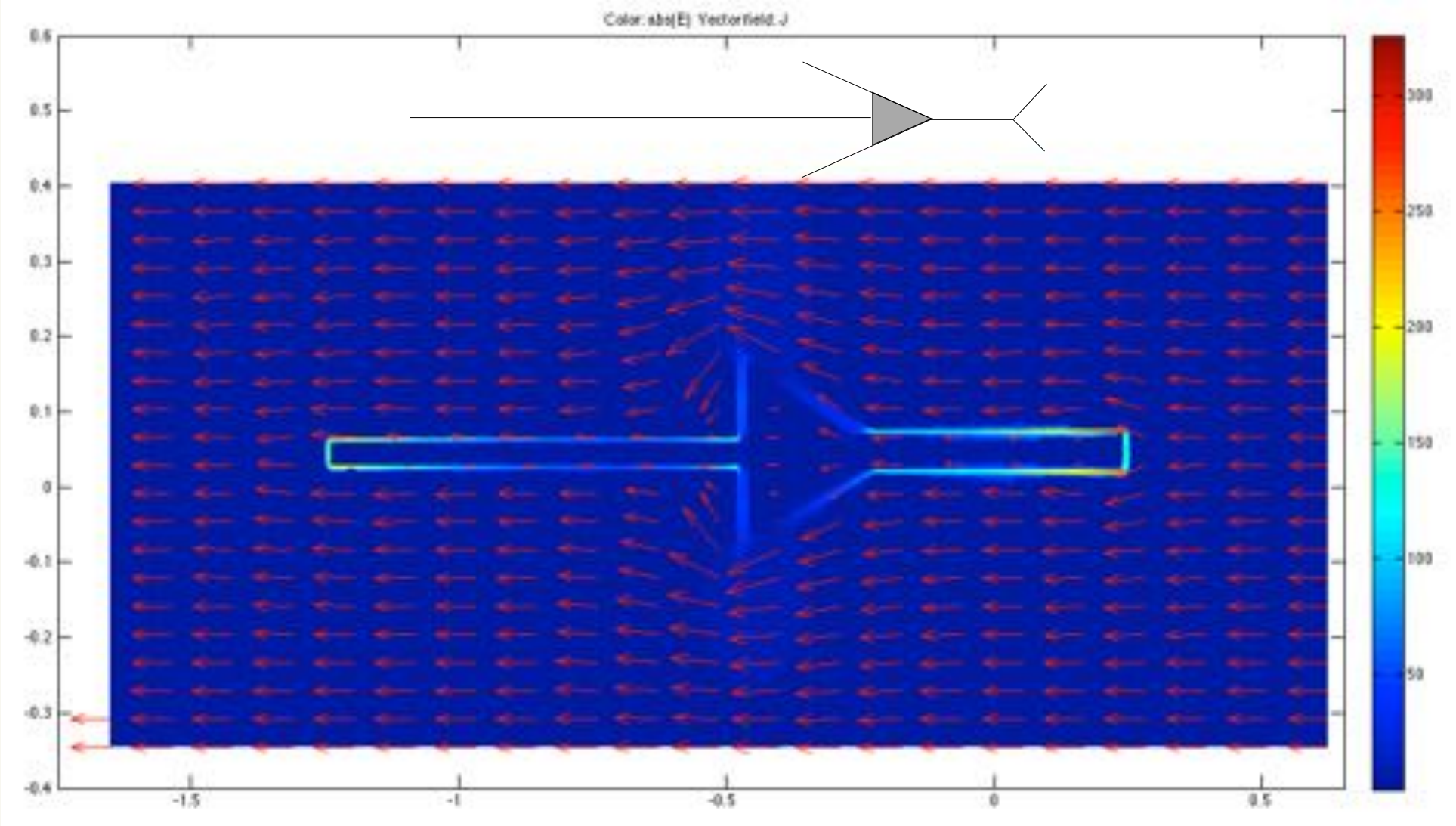


Simple neuron model: a sealed (ok, somewhat leaky) box with a membrane

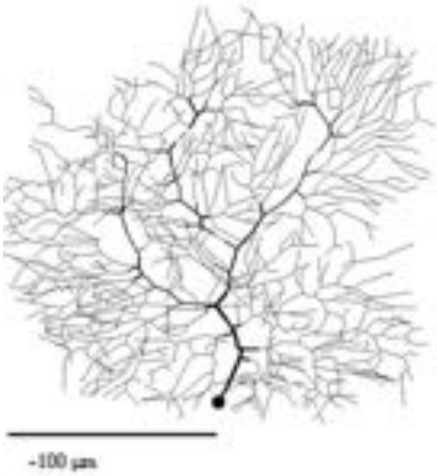
Simple neuron model: a sealed box with a membrane ||E||



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

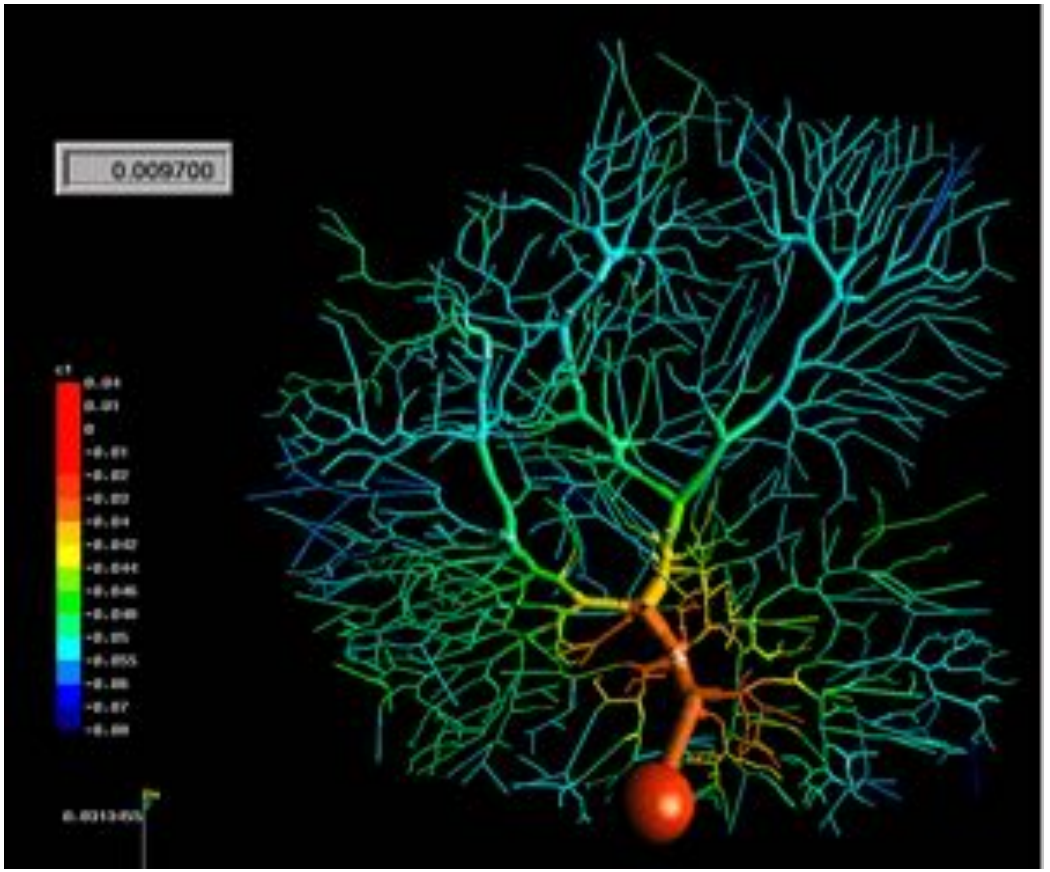


Going beyond…is hard. But needed.



Purkinje cell		DCN neuron	
surface area	261,000 µm²	• surface area	11,056 µm²
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

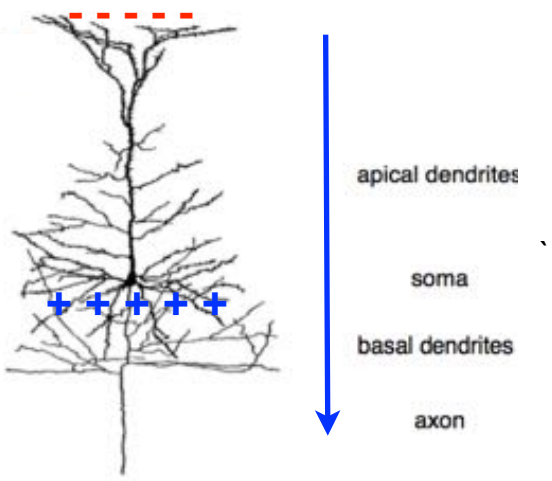


http://www.brains-minds-media.org/archive/222

tCS physiology and mechanism of action

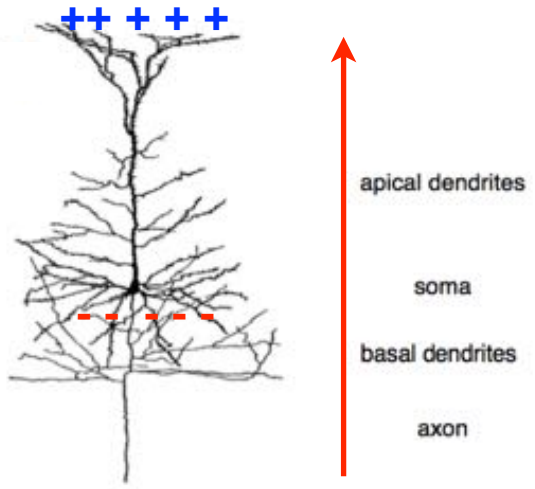
The suggested primary mechanism is alteration of transmembrane potentials and neuronal excitability in pyramidal neurons. Secondary effects include after-effects (plasticity) and effects in brain regions distal to the site of stimulation. Roles of other neurons yet unclear.

- In particular, it appears that tDCS is able to alter spontaneous neuronal firing rates without producing action potentials during stimulation (too weak!).
- In vitro and animal studies have shown that weak electric fields induced by tCS can respectively increase and decrease spontaneous neuronal firing.



Electric field: Excitatory

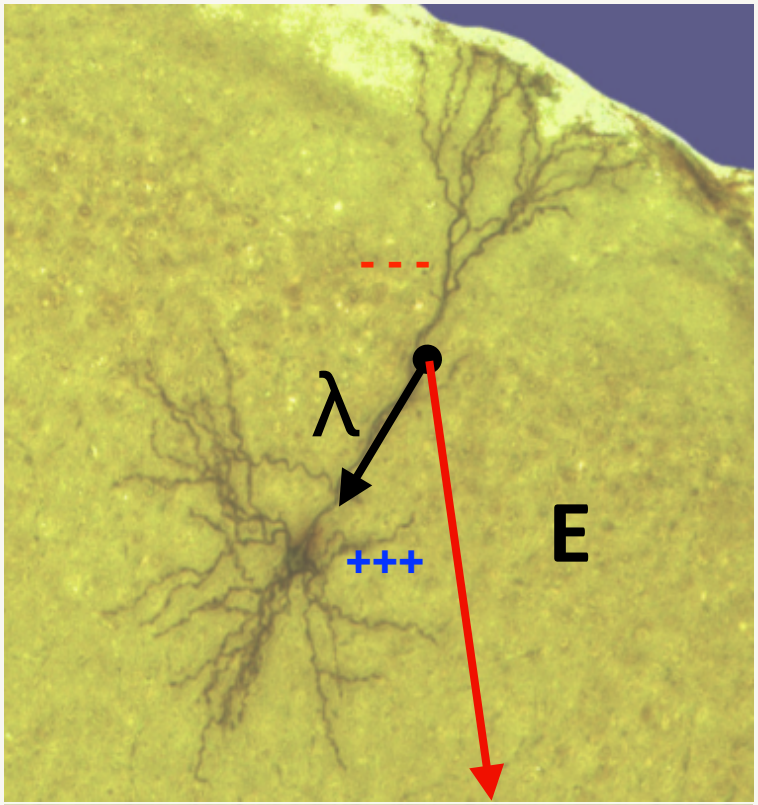
Figure 5: Pyramidal cell structure (from [Bower:2003aa]). The outer cortical boundary is on top.



Electric field: Inhibitory

Figure 5: Pyramidal cell structure (from [Bower:2003aa]). The outer cortical boundary is on top.

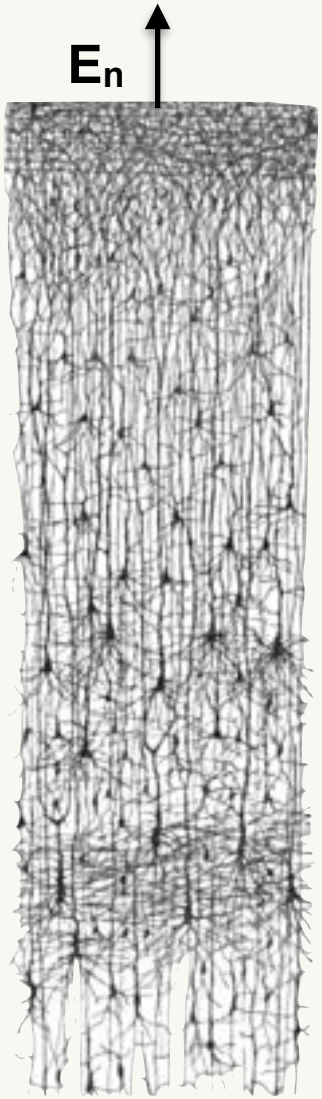
A linear, orientation dependent model

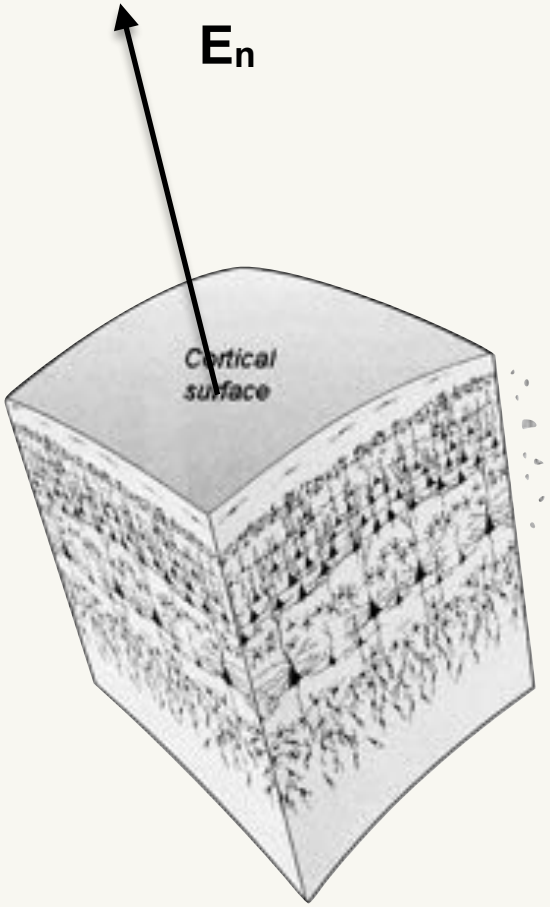


- **λ** points from tree to axon termination
- First order effect from dot product of E and λ
- Units of $\delta\Phi = E \cdot \lambda$ are Volts

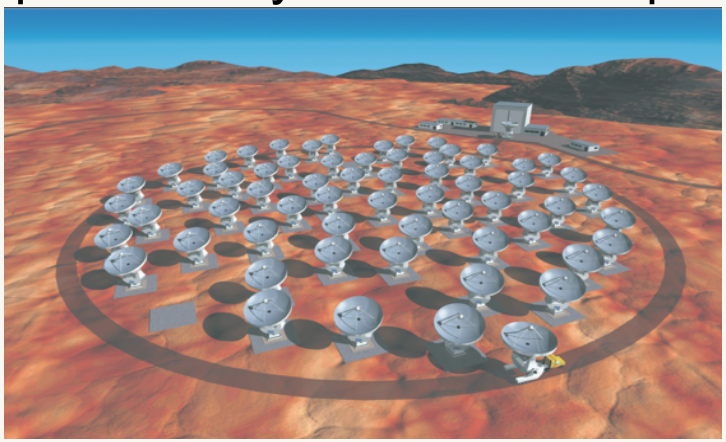
$$\delta\Phi = \lambda \cdot E$$

Spatio-temporal coherence enhances everything

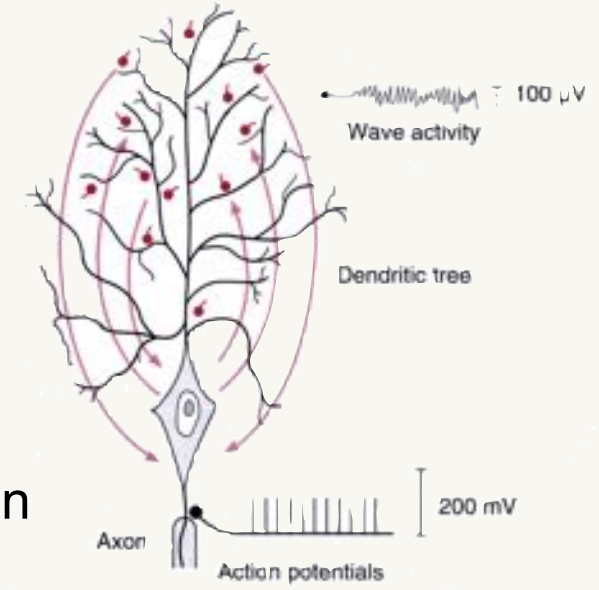




phase array - radio telescope



EEG generation



Effects of transcranial Direct Current Stimulation (tDCS) on cortical activity: A computational modeling study

Behnam Molaee-Ardekani[a,b], Javier Márquez-Ruiz[c], Isabelle Merlet[a,b], Rocio Leal-Campanario[c], Agnès Gruart[c], Raudel Sánchez-Campusano[c], Gwenael Birot[a,b], Giulio Ruffini[d], José-Maria Delgado-García[c], Fabrice Wendling[a,b,*]

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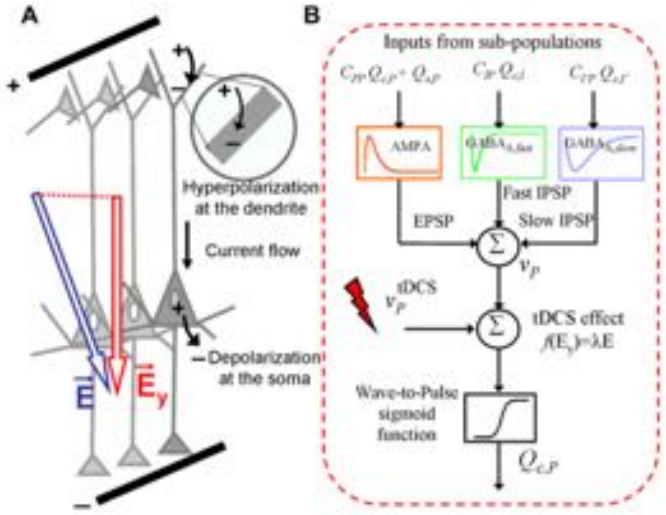
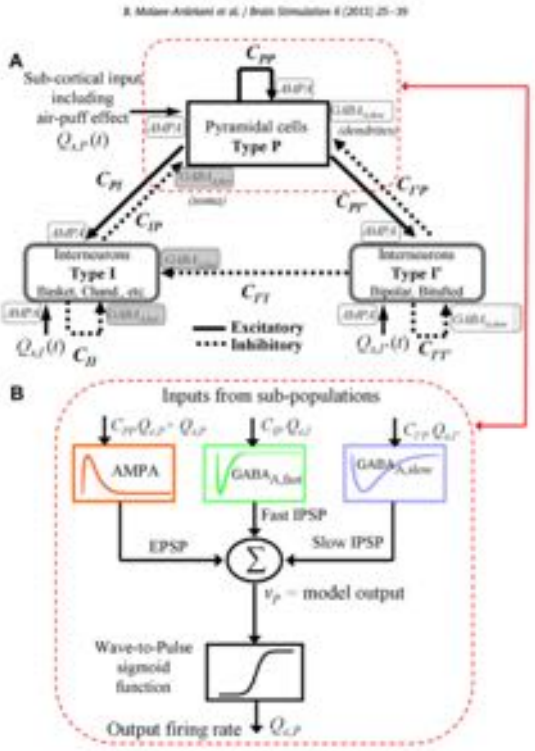
Pyramidal cells
Interneurons

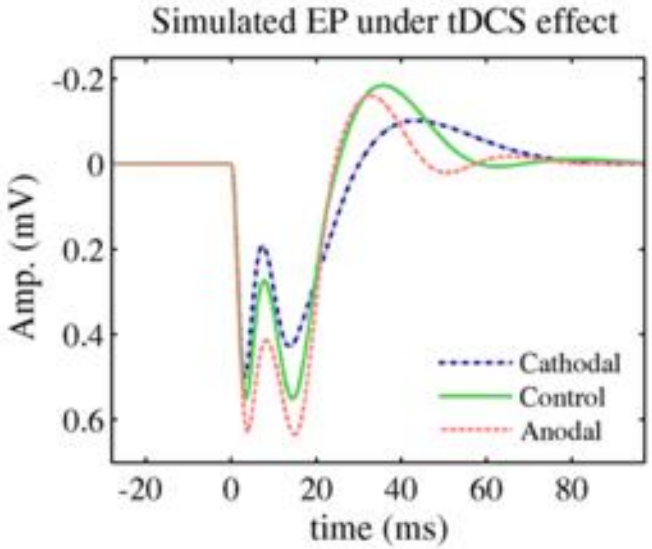
ABSTRACT

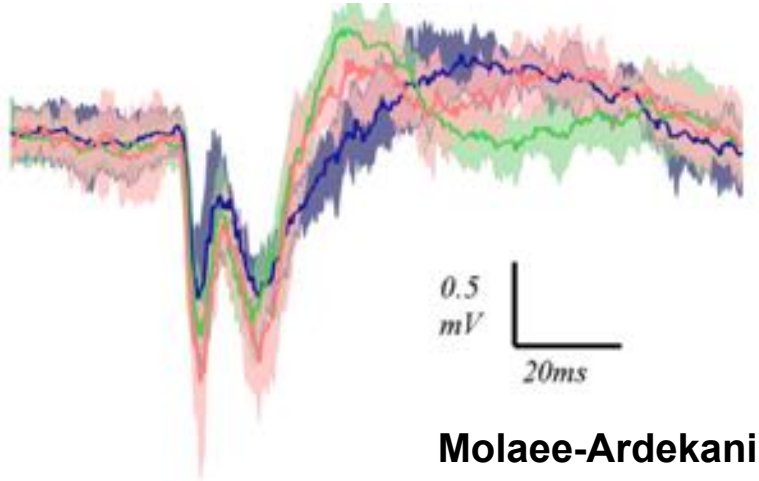
Although it is well-admitted that transcranial Direct Current Stimulation (tDCS) allows for interacting with brain endogenous rhythms, the exact mechanisms by which externally-applied fields modulate the activity of neurons remain elusive. In this study a novel computational model (a neural mass model including subpopulations of pyramidal cells and inhibitory interneurons mediating synaptic currents with either slow or fast kinetics) of the cerebral cortex was elaborated to investigate the local effects of tDCS on neuronal populations based on an in-vivo experimental study. Model parameters were adjusted to reproduce evoked potentials (EPs) recorded from the somatosensory cortex of the rabbit in response to air-puffs applied on the whiskers. EPs were simulated under control condition (no tDCS) as well as under anodal and cathodal tDCS fields. Results first revealed that a feed-forward inhibition mechanism must be included in the model for accurate simulation of actual EPs (peaks and latencies). Interestingly, results revealed that externally-applied fields are also likely to affect interneurons. Indeed, when interneurons get polarized then the characteristics of simulated EPs become closer to those of real EPs. In particular, under anodal tDCS condition, more realistic EPs could be obtained when pyramidal cells were depolarized and, simultaneously, slow (resp. fast) interneurons became de- (resp. hyper-) polarized. Geometrical characteristics of interneurons might provide some explanations for this effect.

Modeling concurrent effects in ERP (rabbit)









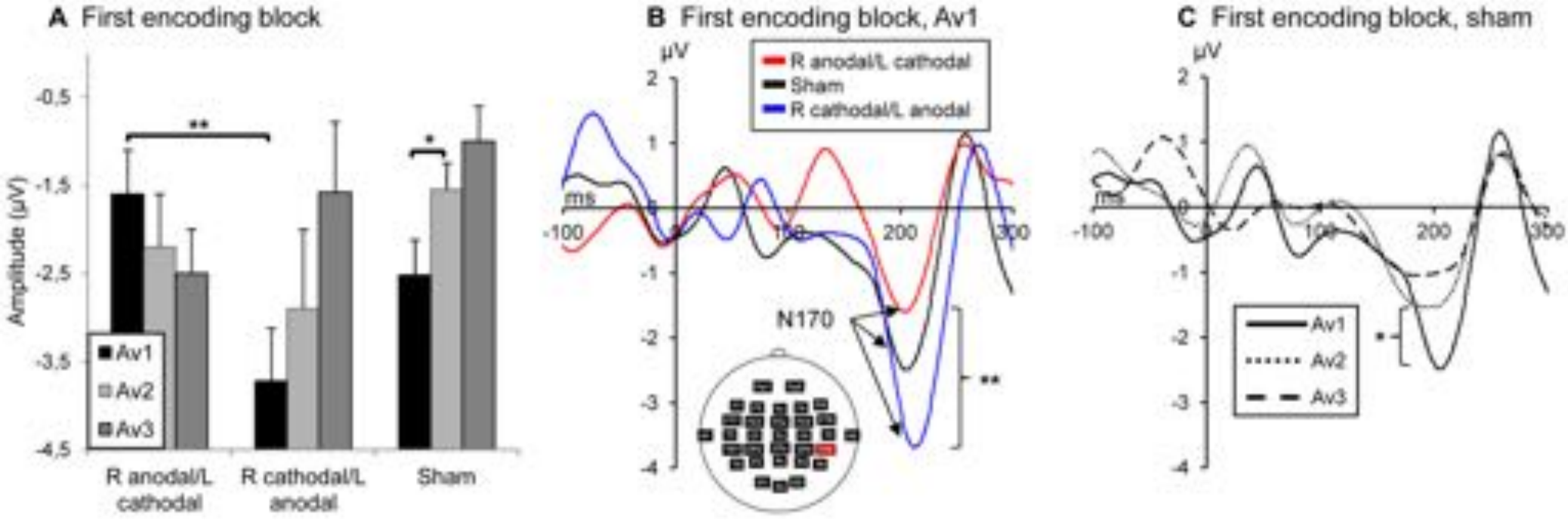
Molaee-Ardekani 2013

tDCS and ERP's

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



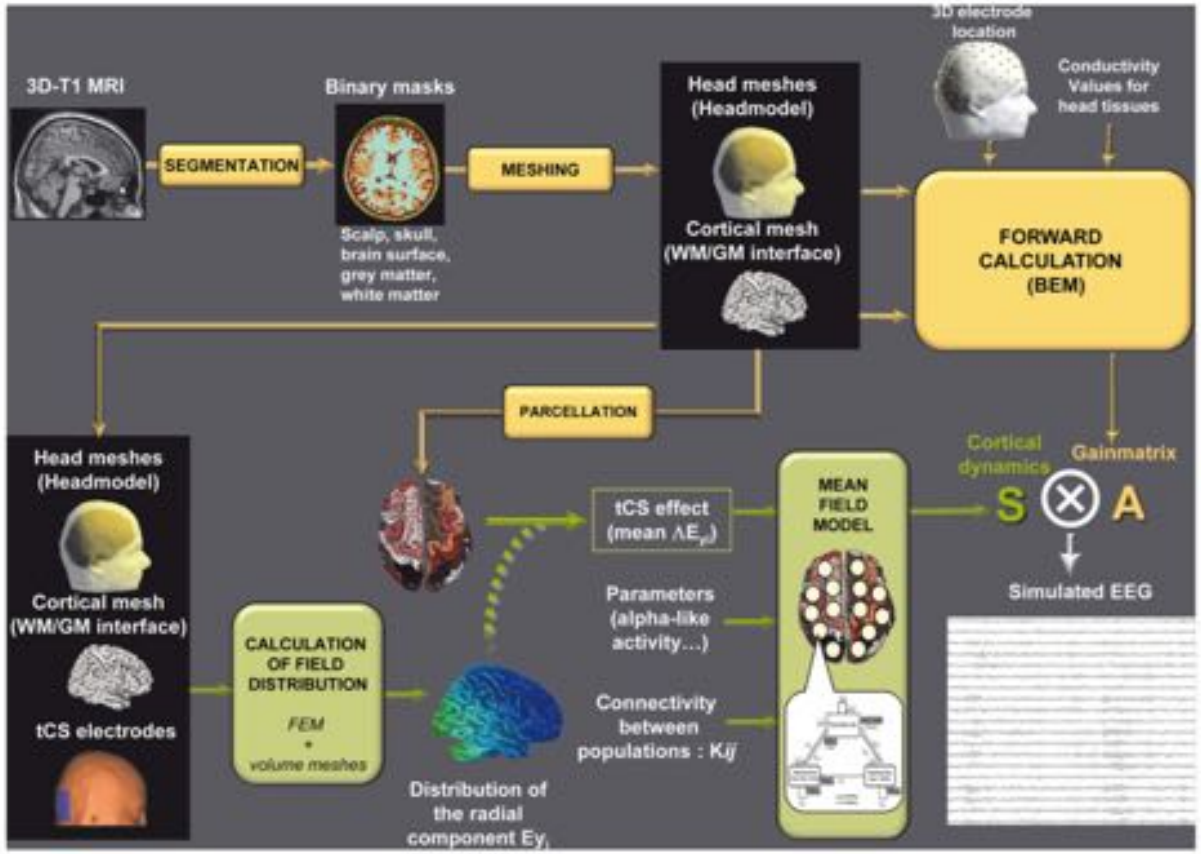
tCS+EEG modeling of concurrent effects

OPEN ACCESS Freely available online

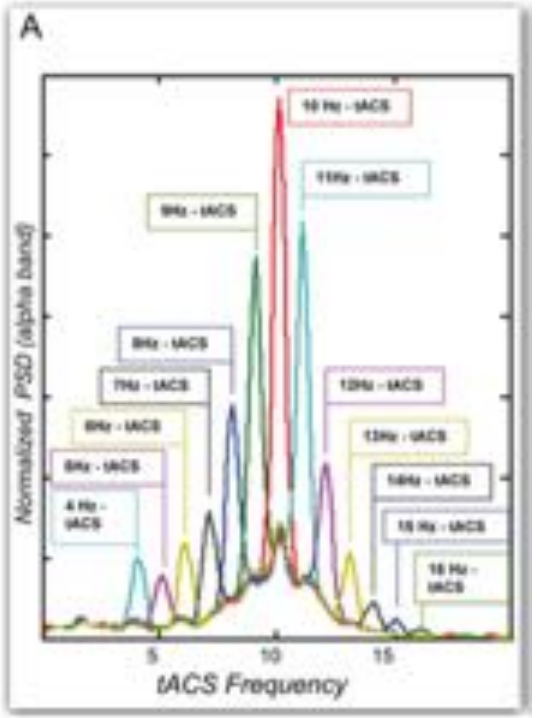
PLOS ONE

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 (plasticity)

After-effects: tDCS effects outlast application

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

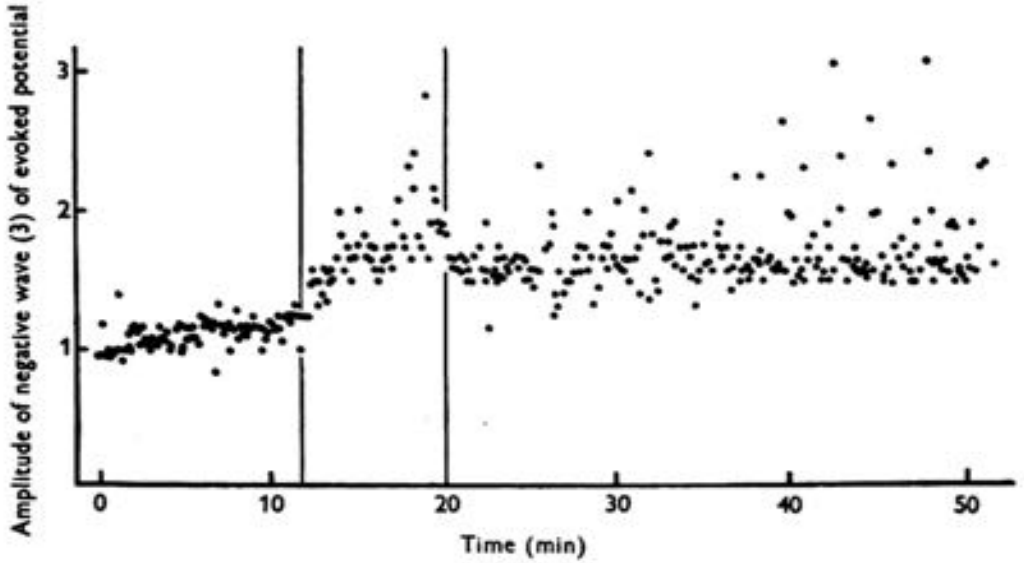


Fig. 4. The after-effect of surface-positive polarization on the peak amplitude (mV) of the evoked potential. (Negative wave (3), recorded from the depth of minimum latency.) Between the 12th and 20th min a current of 25 μA was passed radially through the somatosensory cortex. Area of exposed pia 12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

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

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.

Keeser 2012

- **Long-term effects** 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

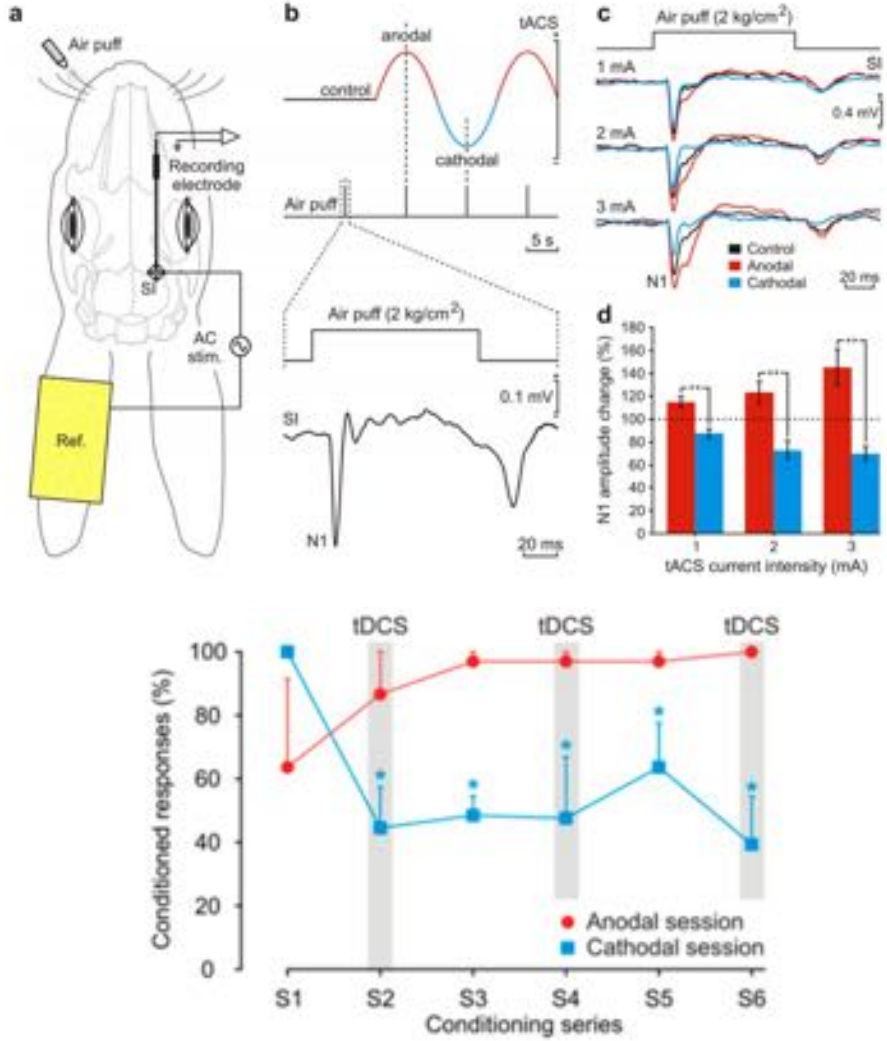
Transcranial direct current stimulation (tDCS) of the human motor cortex results in polarity-specific shifts of cortical excitability during and after stimulation. Anodal tDCS enhances and cathodal stimulation reduces excitability. Animal experiments have demonstrated that the effect of anodal tDCS is 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)

Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits

Javier Márquez-Ruiz[a], Rocio Leal-Campanario[a], Raudel Sánchez-Campusano[a], Behnam Molaee-Ardekani[b,c], Fabrice Wendling[b,c], Pedro C. Miranda[d], Giulio Ruffini[e], Agnès Gruart[a], and José María Delgado-García[a,1]

Transcranial direct-current stimulation (tDCS) is a noninvasive brain stimulation technique that has been successfully applied for modulation of cortical excitability. tDCS is capable of inducing changes in neuronal membrane potentials in a polarity-dependent manner. When tDCS is of sufficient length, synaptically driven after-effects are induced. The mechanisms underlying these after-effects are largely unknown, and there is a compelling need for animal models to test the immediate effects and after-effects induced by tDCS in different cortical areas and evaluate the implications in complex cerebral processes. Here we show in behaving rabbits that tDCS applied over the somatosensory cortex modulates cortical processes consequent to localized stimulation of the whisker pad or of the corresponding area of the ventroposterior medial (VPM) thalamic nucleus. With longer stimulation periods, poststimulation effects were observed in the somatosensory cortex only after cathodal tDCS. Consistent with the polarity-specific effects, the acquisition of classical eyeblink conditioning was potentiated or depressed by the simultaneous application of anodal or cathodal tDCS, respectively, when stimulation of the whisker pad was used as conditioned stimulus, suggesting that tDCS modulates the sensory perception process necessary for associative learning. We also studied the putative mechanisms underlying immediate effects and after-effects of tDCS observed in the somatosensory cortex. Results when pairs of pulses applied to the thalamic VPM nucleus (mediating sensory input) during anodal and cathodal tDCS suggest that tDCS modifies thalamocortical synapses at presynaptic sites. Finally, we show that blocking the activation of adenosine A1 receptors prevents the long-term depression (LTD) evoked in the somatosensory cortex after cathodal tDCS.



20 min stim leads to 1 week increase in hippocampal LTD

SCIENTIFIC REPORTS

OPEN

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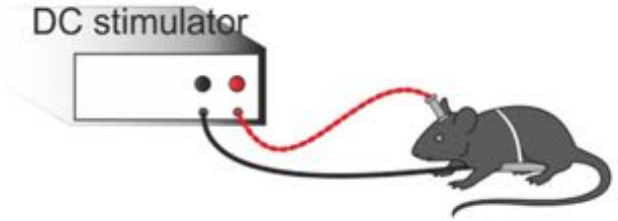
Anodal transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of Bdn expression

Maria Vittoria Podda[1,*], Sara Cocco[1,*], Alessia Mastrodonato[1], Salvatore Fusco[1], Lucia Leone[1], Saviana Antonella Barbati[1], Claudia Colussi[1,2], Cristian Ripoli[1] & Claudio Grassi[1,3]

The effects of transcranial direct current stimulation (tDCS) on brain functions and the underlying molecular mechanisms are yet largely unknown. Here we report that mice subjected to 20-min anodal tDCS exhibited one-week lasting increases in hippocampal LTP, learning and memory. These effects were associated with enhanced: i) acetylation of brain-derived neurotrophic factor (Bdnf) promoter I; ii) expression of *Bdnf* exons I and IX; iii) Bdnf protein levels. The hippocampi of stimulated mice also exhibited enhanced CREB phosphorylation, pCREB binding to *Bdnf* promoter I and recruitment of CBP on the same regulatory sequence. Inhibition of acetylation and blockade of TrkB receptors hindered tDCS effects at molecular, electrophysiological and behavioral levels. Collectively, our findings suggest that anodal tDCS increases hippocampal LTP and memory via chromatin remodeling of *Bdnf* regulatory sequences leading to increased expression of this gene, and support the therapeutic potential of tDCS for brain diseases associated with impaired neuroplasticity.



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.*

Key words: cortical excitability; EEG; graph; synchronization; tDCS

Neurovascular effects of tCS also seen … more work to follow

Systems/Circuits

The Journal of Neuroscience, July 10, 2013 • 33(28):11425–11431 • 11425

Widespread Modulation of Cerebral Perfusion Induced during and after Transcranial Direct Current Stimulation Applied to the Left Dorsolateral Prefrontal Cortex

Charlotte J. Stagg,[1]* Richard L. Lin,[1,2]* Melvin Mezue,[1,2] Andrew Segerdahl,[1,2] Yazhuo Kong,[1] Jingyi Xie,[1] and Irene Tracey[1,2]

[1]Oxford Centre for Functional Magnetic Resonance Imaging of the Brain and [2]Nuffield Division of Anaesthetics, Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom

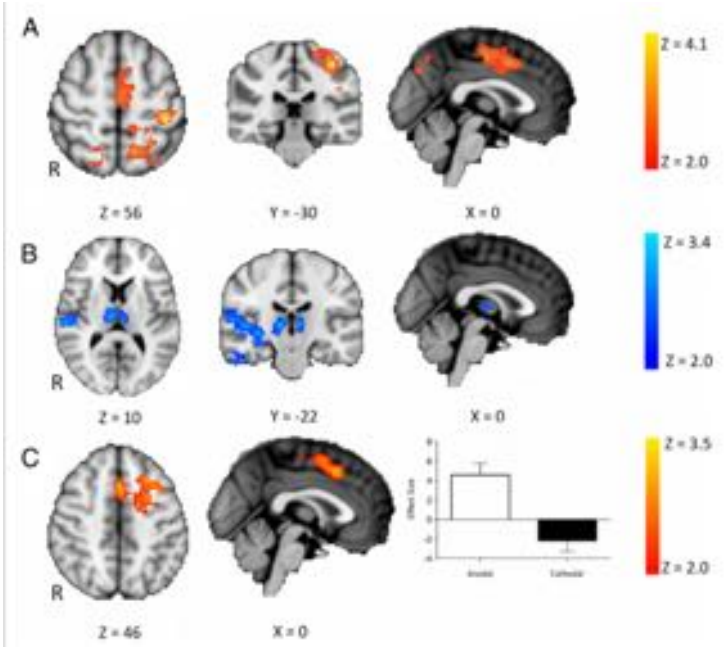


Figure 1. Brain perfusion changes during stimulation compared with baseline ($n = 12$; mixed effects, corrected cluster threshold, $Z > 2.0$, $p < 0.01$). *A*, Regions of increased perfusion during anodal stimulation [i.e., (anodal$_{stimulation}$ − anodal$_{baseline}$)]. Increases in perfusion were seen in the left primary sensory cortex, midcingulate cortex, paracingulate cortex, and left parietal cortex. There were no regions of decreased perfusion during anodal tDCS. *B*, Regions of decreased perfusion during cathodal stimulation [i.e., (cathodal$_{stimulation}$ − cathodal$_{baseline}$)]. Decreases were seen in the thalami bilaterally and the right middle and inferior temporal gyri. No regions of increased perfusion were seen during cathodal tDCS. *C*, Regions of increased perfusion during anodal tDCS compared with during cathodal tDCS [i.e., (anodal$_{stimulation}$ − anodal$_{baseline}$) − (cathodal$_{stimulation}$ − cathodal$_{baseline}$)]. Increased perfusion was seen in the L-DLPFC and the paracingulate cortex. The perfusion changes within these regions are shown on the right. No regions of increased perfusion during cathodal tDCS compared with during anodal tDCS were seen. Error bars indicate SEM. R, Right.

Concurrent diffuse optical measurement of cerebral hemodynamics and EEG during transcranial direct current stimulation (tDCS) in humans (2016)

Martina Giovannella [a], Guillem Mitjà[b], Clara Gregori-Pla[a], David Ibañez[c], Giulio Ruffini[b,c] and Turgut Durduran[a,d]

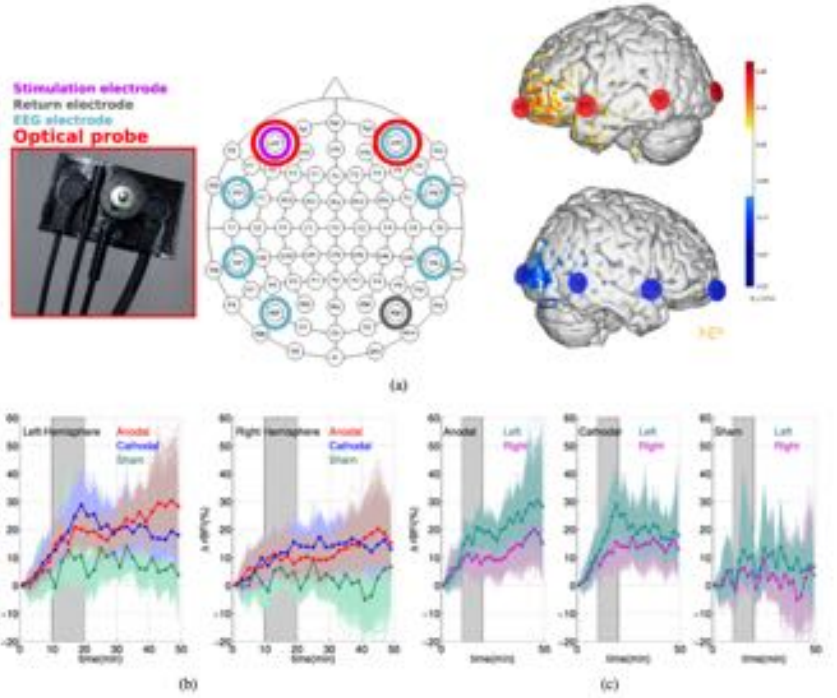


Fig. 1: a) Integrated optical probe with electrode and positioning of the optical probe, stimulation and return electrode and EEG electrodes. On the right a display of montage electrodes and electric field (normal component) generated in the anodal case (signs are reversed for cathodal) (b) CBF changes in the 3 types of stimulation on the left and right hemisphere. (c) Direct comparison for CBF changes between hemispheres for the three type of stimulation. The single line represents the mean over all the subjects, the colored area the bootstrap (fda package of R).

Some things to remember

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

When you keep control over the current density, you control also the electric field.

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

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.

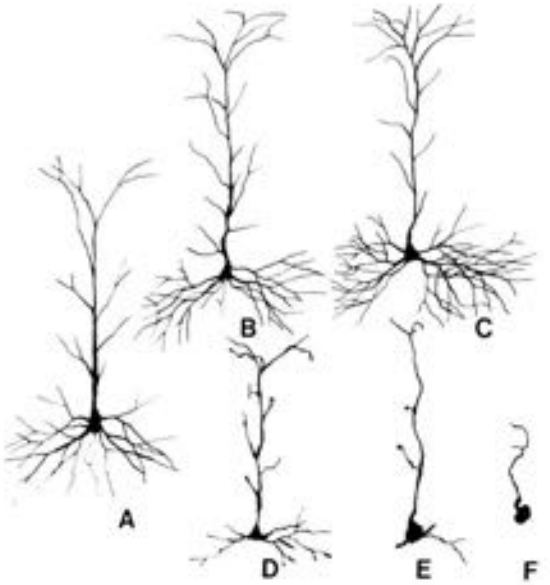
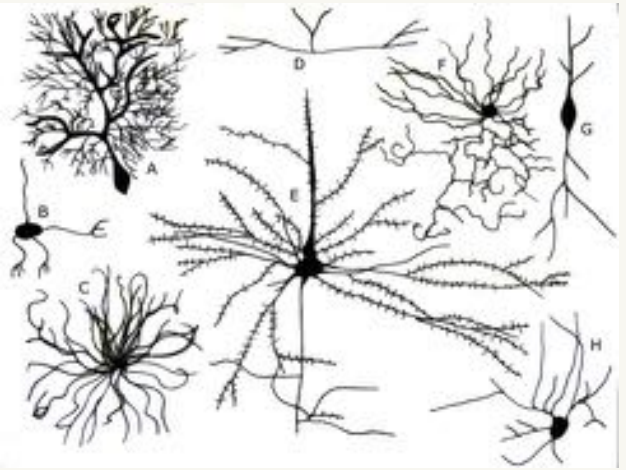
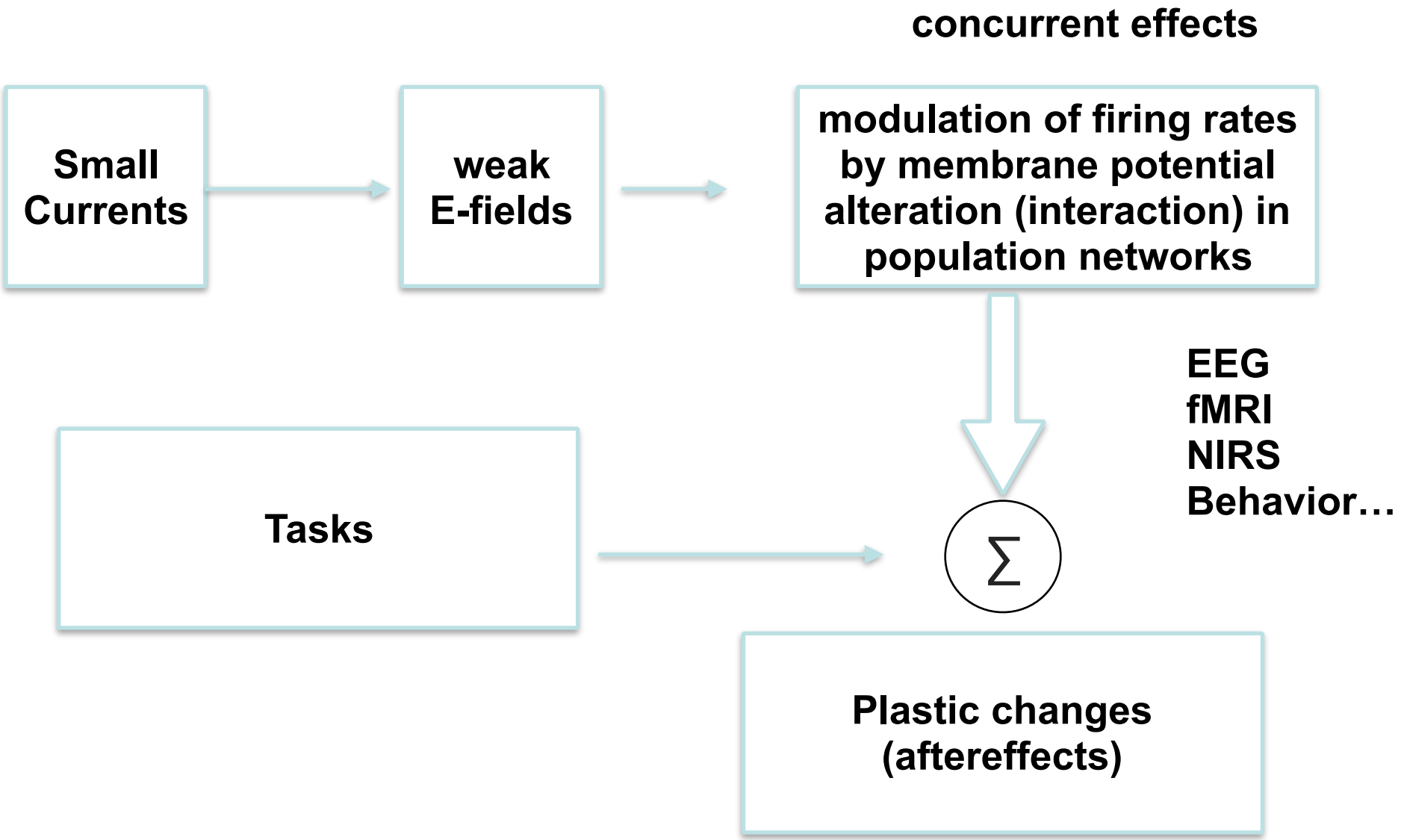


Figure 1. Two possible patterns of age-related alterations in cortical pyramidal cells. The normal mature neuron (A) may show regressive dendritic changes characterized by loss of basilar dendritic branches and eventual loss of the entire dendritic tree (D, E, F). Other neurons (B, C) may show progressive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



Summary of logic. Applies to tDCS and tACS (weak, low f fields)



tACS and beyond

Studying the interaction of oscillatory systems

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

Are we in the realm of the ephaptic? Yes, we are.

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

BY J. G. R. JEFFERYS

*From the Department of Physiology, University College London, Gower Street, London WC1E 6BT and the Sobell Department of Neurophysiology, Institute of Neurology, Queen Square, London WC1N 3BG**

(*Received 19 January 1981*)

SUMMARY

1. Monosynaptic evoked potentials were recorded from the granule cell layer of slices of guinea-pig hippocampus maintained *in vitro*. Current pulses of 25–250 msec duration were passed across the slices, between gross electrodes in the bathing liquid.

2. Polarizing current modified the excitability of the granule cells as judged by changes in their population discharge during postsynaptic responses. All durations of polarization had at least qualitatively similar effects. Conventional current from dendrites to cell bodies increased excitability (and vice versa). This is consistent with altered membrane potential of a spike trigger zone, at or close to the granule cell bodies, imposed by the fraction of polarizing current which flows intracellularly.

3. In some experiments polarization also affected the presynaptic volley and (hence?) the synaptic potential. When this occurred it was in the wrong sense to explain the concomitant changes in population spike.

4. Focal polarization, where currents were applied across the cell body layer between a small electrode on the mid or outer dendritic regions and a remote gross electrode, altered granule cell excitability in the same direction as in (2). Thus conventional current injected at the dendritic electrode increased excitability.

5. The smallest effective polarizing currents caused extracellular voltage gradients of 5–10 mV/mm, which is less than occurs in this tissue during synchronous activation of the neurones or during seizure activity. Therefore such field potentials could increase the synchrony of discharge of the granule cells.

Weak E-field Entrainment

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There are several recent 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).

Are we in the realm of the ephaptic? Yes, we are.

PHYSIOLOGICAL REVIEWS
Vol. 75, No. 4, October 1995
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Nonsynaptic Modulation of Neuronal Activity in the Brain: Electric Currents and Extracellular Ions

J. G. R. JEFFERYS

Neuronal Networks Group, Department of Physiology and Biophysics, St. Mary's Hospital Medical School, Imperial College of Science, Technology, and Medicine, London, United Kingdom

Jefferys, J. G. R. Nonsynaptic Modulation of Neuronal Activity in the Brain: Electric Currents and Extracellular Ions. *Physiol. Rev.* 75: 689–723, 1995.—Nonsynaptic interactions between neurons have been eclipsed by our increasingly detailed understanding of chemical synapses, but they do play significant roles in the nervous system. This review considers four classes of nonsynaptic interaction, mainly in mammalian brain. *1*) Electrotonic (and chemical) coupling through gap junctions has effects during development and under some, often pathological, conditions in the mature brain. *2*) Ephaptic transmission is mediated by electrical coupling between specific neuronal elements in the absence of specialized contacts, notably in the cerebellum, and in axon tracts affected by demyelination. *3*) Field effect interactions are mediated by large extracellular currents and potential fields generated by the hippocampus and other cortical structures. Both endogenous and applied electric fields alter neuronal excitability at field strengths over a few millivolts per millimeter. Weaker fields have more subtle effects, for instance, on axonal growth during development and repair and, more controversially, in behavioral responses to environmental fields. *4*) There are fluctuations in extracellular ions such as K^+, which are released during neuronal activity and which alter neuronal excitability. Field effects and ion fluctuations probably have modest effects during physiological activity but have a significant impact on epileptic seizures, and can sustain them in the absence of synaptic transmission.

I. INTRODUCTION

The issue of how neurons communicate fueled an intense debate during the decades around the turn of the

Behavioral/Systems/Cognitive

Sensitivity of Neurons to Weak Electric Fields

Joseph T. Francis,[1,4] Bruce J. Gluckman,[1,2] and Steven J. Schiff[1,3,4]

[1]Krasnow Institute for Advanced Studies and Departments of [2]Physics and Astronomy and [3]Psychology, George Mason University, Fairfax, Virginia 22030, and [4]Neuroscience Program, The George Washington University, Washington, DC 20037

Weak electric fields modulate neuronal activity, and knowledge of the interaction threshold is important in the understanding of neuronal synchronization, in neural prosthetic design, and in the public health assessment of environmental extremely low frequency fields. Previous experimental measurements have placed the threshold between 1 and 5 mV/mm, although theory predicts that elongated neurons should have submillivolt per millimeter sensitivity near 100 μV/mm. We here provide the first experimental confirmation that neuronal networks are detectably sensitive to submillivolt per millimeter electrical fields [Gaussian pulses 26 msec full width at half-maximal, 140 μV/mm root mean square (rms), 295 μV/mm peak amplitude], an order of magnitude below previous findings, and further demonstrate that these networks are more sensitive than the average single neuron threshold (185 μV/mm rms, 394 μV/mm peak amplitude) to field modulation.

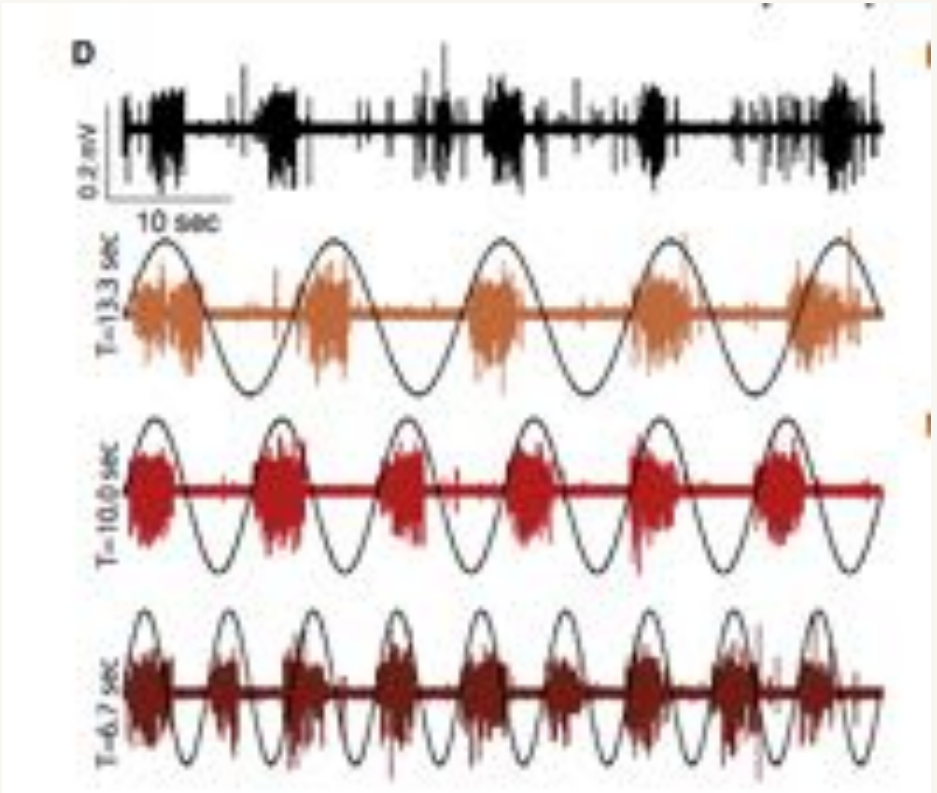
Frohlich and McCormick 2010 (in vitro)

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



Endogenously generated fields affect neural function in vitro

nature neuroscience

Ephaptic coupling of cortical neurons

Costas A Anastassiou[1,2,5], Rodrigo Perin[3,5], Henry Markram[3] & Christof Koch[1,4]

The electrochemical processes that underlie neural function manifest themselves in ceaseless spatiotemporal field fluctuations. However, extracellular fields feed back onto the electric potential across the neuronal membrane via ephaptic coupling, independent of synapses. The extent to which such ephaptic coupling alters the functioning of neurons under physiological conditions remains unclear. To address this question, we stimulated and recorded from rat cortical pyramidal neurons in slices with a 12-electrode setup. We found that extracellular fields induced ephaptically mediated changes in the somatic membrane potential that were less than 0.5 mV under subthreshold conditions. Despite their small size, these fields could strongly entrain action potentials, particularly for slow (<8 Hz) fluctuations of the extracellular field. Finally, we simultaneously measured from up to four patched neurons located proximally to each other. Our findings indicate that endogenous brain activity can causally affect neural function through field effects under physiological conditions.

Weak endogenous fields can guide spike waves in vitro

Systems/Circuits

Can Neural Activity Propagate by Endogenous Electrical Field?

Chen Qiu, Rajat S. Shivacharan, Mingming Zhang, and Dominique M. Durand
Department of Biomedical Engineering, Neural Engineering Center, Case Western Reserve University, Cleveland, Ohio 44106

It is widely accepted that synaptic transmissions and gap junctions are the major governing mechanisms for signal traveling in the neural system. Yet, a group of neural waves, either physiological or pathological, share the same speed of ~0.1 m/s without synaptic transmission or gap junctions, and this speed is not consistent with axonal conduction or ionic diffusion. The only explanation left is an electrical field effect. We tested the hypothesis that endogenous electric fields are sufficient to explain the propagation with *in silico* and *in vitro* experiments. Simulation results show that field effects alone can indeed mediate propagation across layers of neurons with speeds of 0.12 ± 0.09 m/s with pathological kinetics, and 0.11 ± 0.03 m/s with physiologic kinetics, both generating weak field amplitudes of ~2–6 mV/mm. Further, the model predicted that propagation speed values are inversely proportional to the cell-to-cell distances, but do not significantly change with extracellular resistivity, membrane capacitance, or membrane resistance. *In vitro* recordings in mice hippocampi produced similar speeds (0.10 ± 0.03 m/s) and field amplitudes (2.5–5 mV/mm), and by applying a blocking field, the propagation speed was greatly reduced. Finally, osmolarity experiments confirmed the model's prediction that cell-to-cell distance inversely affects propagation speed. Together, these results show that despite their weak amplitude, electric fields can be solely responsible for spike propagation at ~0.1 m/s. This phenomenon could be important to explain the slow propagation of epileptic activity and other normal propagations at similar speeds.

Schmidt 2014 (in vitro)

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Research

Endogenous Cortical Oscillations Constrain Neuromodulation by Weak Electric Fields

Stephen L. Schmidt [a,e], Apoorva K. Iyengar [b], A. Alban Foulser [g], Michael R. Boyle [a,e], Flavio Fröhlich [a,c,d,e,f,*]

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[b] Department of Biology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
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Resonance

ABSTRACT

Background: Transcranial alternating current stimulation (tACS) is a non-invasive brain stimulation modality that may modulate cognition by enhancing endogenous neocortical oscillations by application of sine-wave electric fields. Yet, the role of endogenous network activity in enabling and shaping the effects of tACS has remained unclear.

Objective: We combined optogenetic stimulation and multichannel slice electrophysiology to elucidate how the effect of a weak sine-wave electric field depends on the ongoing cortical oscillatory activity. We hypothesized that endogenous cortical oscillations constrain neuromodulation by tACS.

Methods: We studied the effect of weak sine-wave electric fields on oscillatory activity in mouse neocortical slices. Optogenetic control of the network activity enabled the generation of *in vivo*-like cortical oscillations for studying the temporal relationship between network activity and sine-wave electric field stimulation.

Results: Weak electric fields enhanced endogenous oscillations but failed to induce a frequency shift of the ongoing oscillation for stimulation frequencies that were not matched to the endogenous oscillation. This constraint on the effect of electric field stimulation imposed by endogenous network dynamics was limited to the case of weak electric fields targeting *in vivo*-like network dynamics. Together, these results suggest that the key mechanism of tACS may be enhancing, but not overriding, intrinsic network dynamics.

Conclusion: Our results contribute to understanding the inconsistent tACS results from human studies and propose that stimulation precisely adjusted in frequency to the endogenous oscillations is key to rational design of non-invasive brain stimulation paradigms.

Behavioral/Systems/Cognitive

Transcranial Electric Stimulation Entrains Cortical Neuronal Populations in Rats

Simal Ozen,[1] Anton Sirota,[1,2] Mariano A. Belluscio,[1] Costas A. Anastassiou,[3,4] Eran Stark,[1] Christof Koch,[3,5] and György Buzsáki[1]

[1]Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, New Jersey 07102, [2]Centre for Integrative Neuroscience, University of Tübingen, Tübingen 72076, Germany, [3]Division of Biology, California Institute of Technology, Pasadena, California 91125, [4]Department of Bioengineering, Imperial College, London, London SW7 2AZ, United Kingdom, and [5]Department of Brain and Cognitive Engineering, Korea University, Seoul 136-701, Korea

Low intensity electric fields have been suggested to affect the ongoing neuronal activity *in vitro* and in human studies. However, the physiological mechanism of how weak electrical fields affect and interact with intact brain activity is not well understood. We performed *in vivo* extracellular and intracellular recordings from the neocortex and hippocampus of anesthetized rats and extracellular recordings in behaving rats. Electric fields were generated by sinusoid patterns at slow frequency (0.8, 1.25 or 1.7 Hz) via electrodes placed on the surface of the skull or the dura. Transcranial electric stimulation (TES) reliably entrained neurons in widespread cortical areas, including the hippocampus. The percentage of TES phase-locked neurons increased with stimulus intensity and depended on the behavioral state of the animal. TES-induced voltage gradient, as low as 1 mV/mm at the recording sites, was sufficient to phase-bias neuronal spiking. Intracellular recordings showed that both spiking and subthreshold activity were under the combined influence of TES forced fields and network activity. We suggest that TES in chronic preparations may be used for experimental and therapeutic control of brain activity.

Ali 2013
(in vivo)

Systems/Circuits

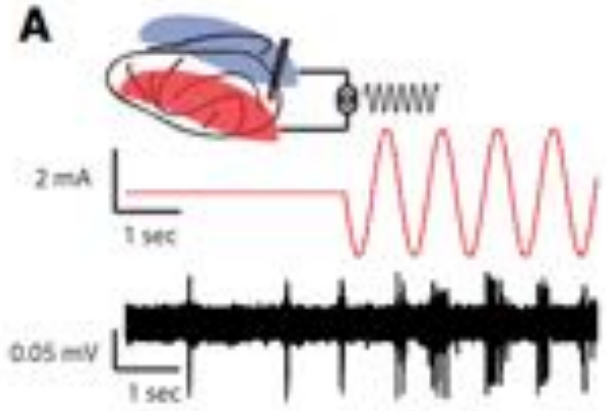
Transcranial Alternating Current Stimulation Modulates Large-Scale Cortical Network Activity by Network Resonance

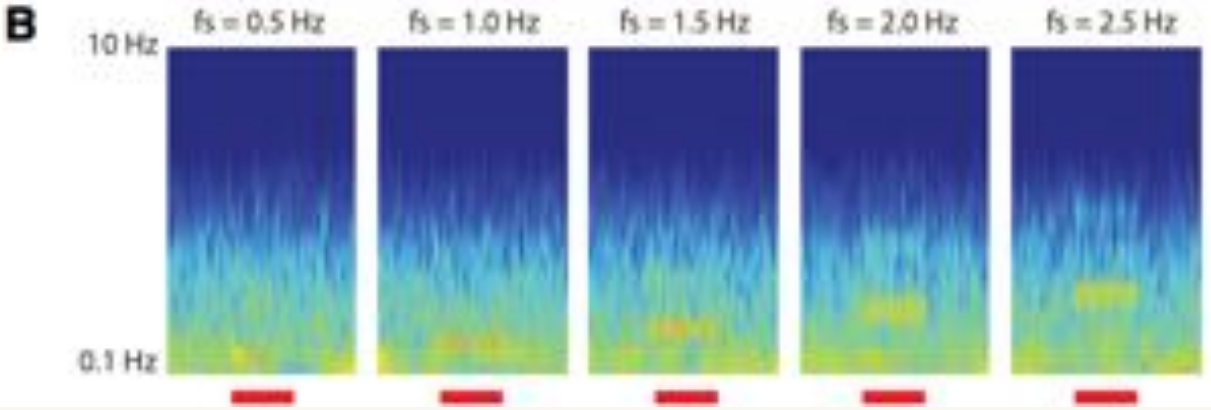
Mohsin M. Ali,[1,6,7] Kristin K. Sellers,[1,6] and Flavio Fröhlich[1,2,3,5]

Departments of [1]Psychiatry, [2]Cell Biology and Physiology, and [3]Biomedical Engineering, [4]Neurobiology Curriculum, and [5]Neuroscience Center, and Departments of [6]Computer Science and [7]Biology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599

Transcranial direct current stimulation (tDCS) has emerged as a potentially safe and effective brain stimulation modality that alters cortical excitability by passing a small, constant electric current through the scalp. tDCS creates an electric field that weakly modulates the membrane voltage of a large number of cortical neurons. Recent human studies have suggested that sine-wave stimulation waveforms [transcranial alternating current stimulation (tACS)] represent a more targeted stimulation paradigm for the enhancement of cortical oscillations. Yet, the underlying mechanisms of how periodic, weak global perturbations alter the spatiotemporal dynamics of large-scale cortical network dynamics remain a matter of debate. Here, we simulated large-scale networks of spiking neuron models to address this question in endogenously rhythmic networks. We identified distinct roles of the depolarizing and hyperpolarizing phases of tACS in entrainment, which entailed moving network activity toward and away from a strong nonlinearity provided by the local excitatory coupling of pyramidal cells. Together, these mechanisms gave rise to resonance dynamics characterized by an Arnold tongue centered on the resonance frequency of the network. We then performed multichannel extracellular recordings of multiunit firing activity during tACS in anesthetized ferrets (*Mustela putorius furo*), a model species with a gyrencephalic brain, to verify that weak global perturbations can selectively enhance oscillations at the applied stimulation frequency. Together, these results provide a detailed mechanistic understanding of tACS at the level of large-scale network dynamics and support the future design of activity-dependent feedback tACS paradigms that dynamically tailor stimulation frequency to the spectral peak of ongoing brain activity.

J. Neurosci., July 3, 2013 • 33(27):11262–11275 • 11273





Zaehle 2010 (humans + EEG)

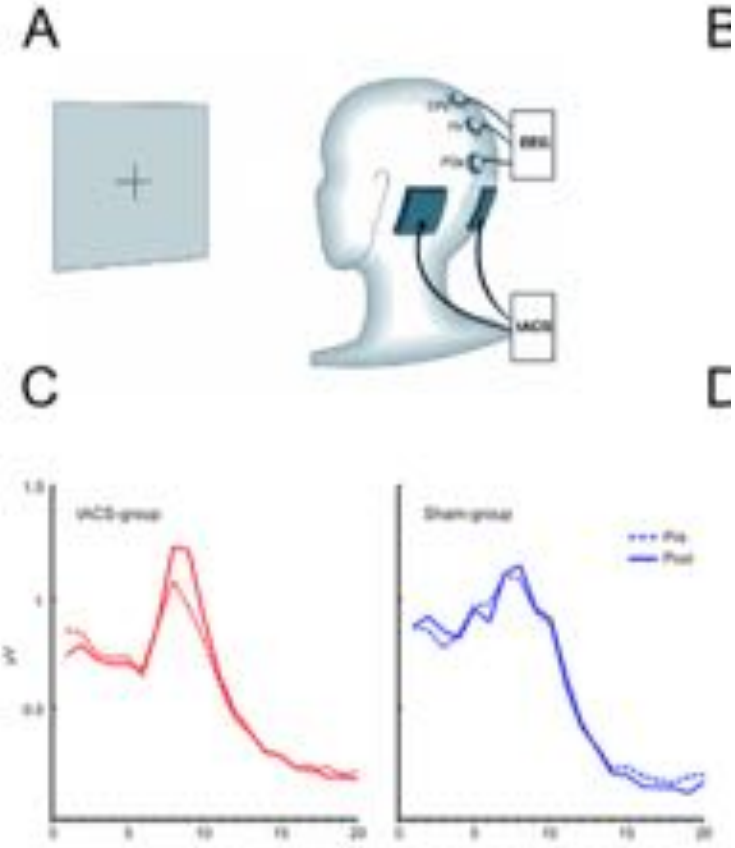
Transcranial Alternating Current Stimulation Enhances Individual Alpha Activity in Human EEG

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

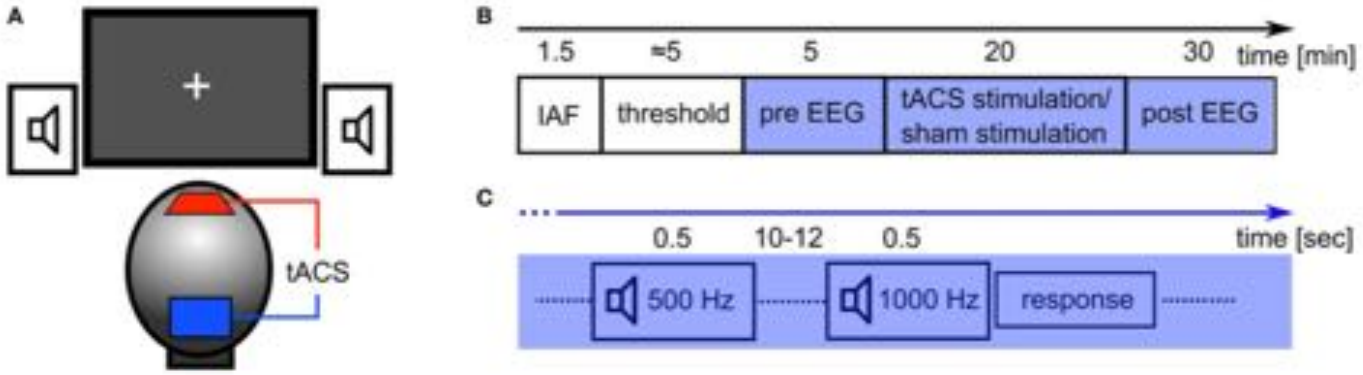
Non-invasive electrical stimulation of the human cortex by means of transcranial direct current stimulation (tDCS) has been instrumental in a number of important discoveries in the field of human cortical function and has become a well-established method for evaluating brain function in healthy human 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

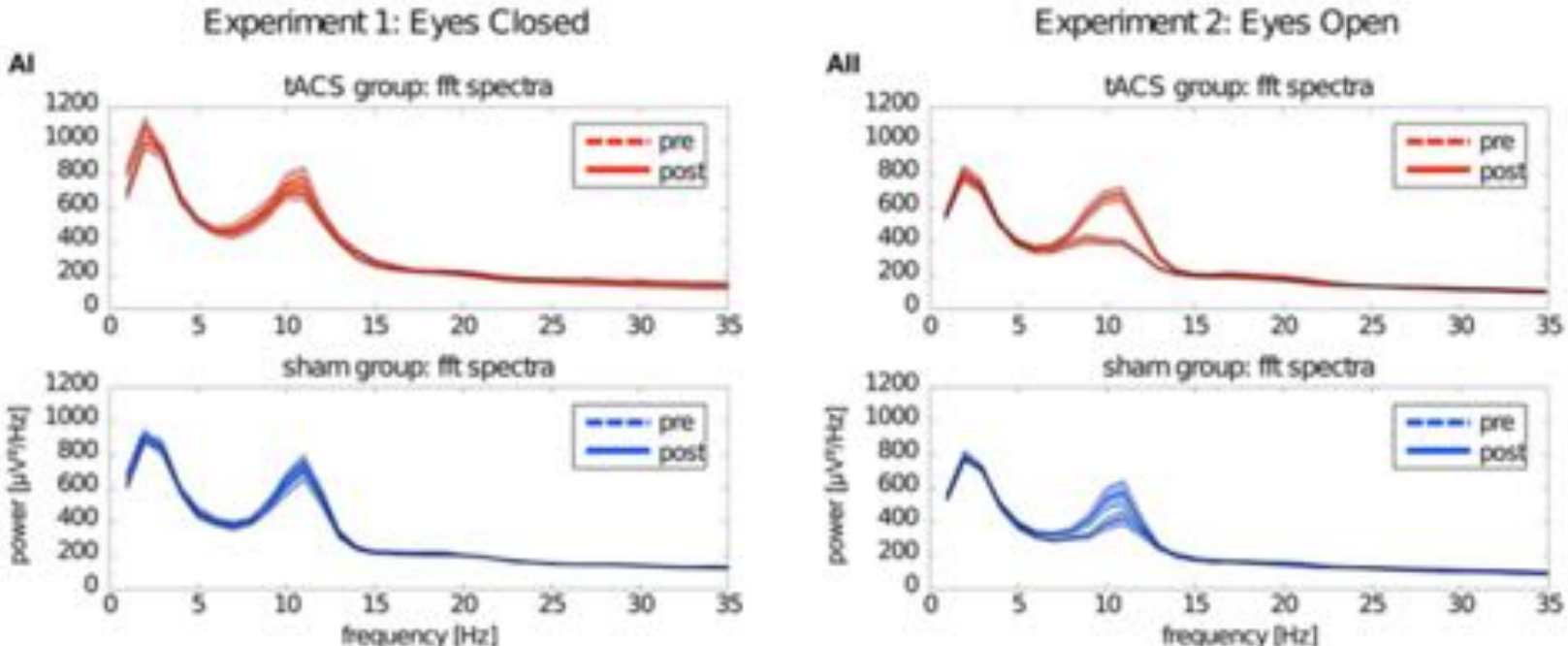
Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states

*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



ORIGINAL RESEARCH ARTICLE

Front. Hum. Neurosci., 25 May 2016 | http://dx.doi.org/10.3389/fnhum.2016.00245

Sustained Aftereffect of α-tACS Lasts Up to 70 min after Stimulation

 Florian H. Kasten[1],  James Dowsett[1,2] and  Christoph S. Herrmann[1,3]*

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[2]German Center for Vertigo and Balance Disorders, Klinikum Grosshadern, Ludwig Maximilian University of Munich, Munich, Germany

[3]Research Center Neurosensory Science, Carl von Ossietzky University, Oldenburg, Germany

Transcranial alternating current stimulation (tACS) has been repeatedly demonstrated to increase power of endogenous brain oscillations in the range of the stimulated frequency after stimulation. In the alpha band this aftereffect has been shown to persist for at least 30 min. However, in most experiments the aftereffect exceeded the duration of the measurement. Thus, it remains unclear how the effect develops beyond these 30 min and when it decays. The current study aimed to extend existing findings by monitoring the physiological aftereffect of tACS in the alpha range for an extended period of 90 min post-stimulation. To this end participants received either 20 min of tACS or sham stimulation with intensities below their individual sensation threshold at the individual alpha frequency (IAF). Electroencephalogram (EEG) was acquired during 3 min before and 90 min after stimulation. Subjects performed a visual vigilance task during the whole measurement. While the enhanced power in the individual alpha band did not return back to pre-stimulation baseline in the stimulation group, the difference between stimulation and sham diminishes after 70 min due to a natural alpha increase of the sham group.

Helfrich 2014 (humans+EEG)

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Entrainment of Brain Oscillations by Transcranial Alternating Current Stimulation

Randolph F. Helfrich,[1,*] Till R. Schneider,[1] Stefan Rach,[2,3] Sina A. Trautmann-Lengsfeld,[1] Andreas K. Engel,[1,4] and Christoph S. Herrmann[2,3,4]
[1]Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany
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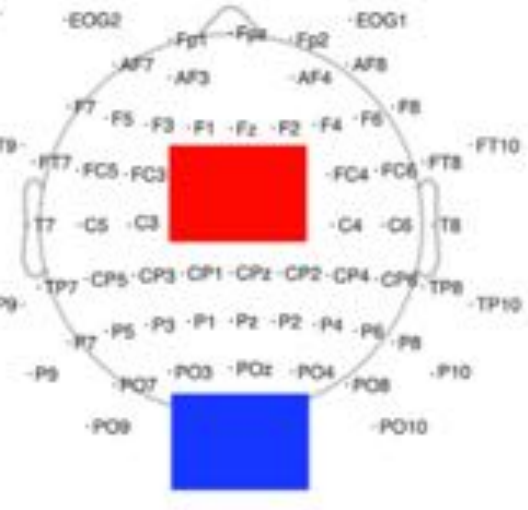
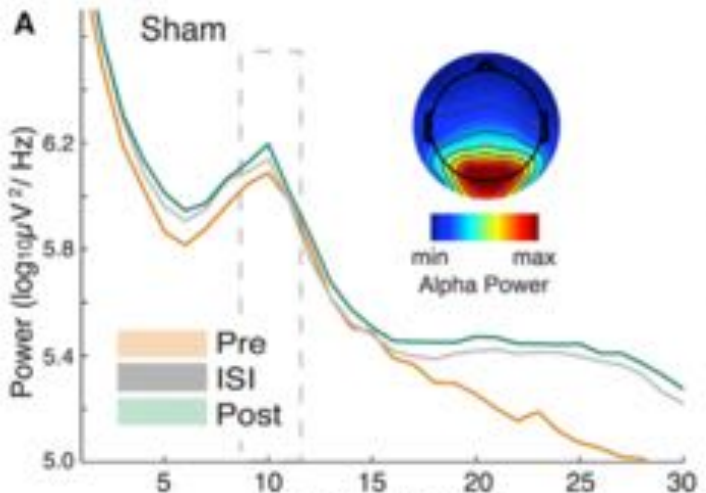
Summary

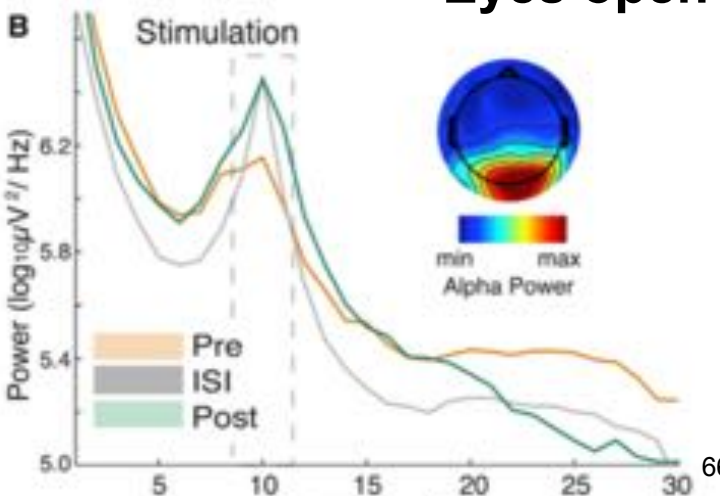
Novel methods for neuronal entrainment [1–4] provide the unique opportunity to modulate perceptually relevant brain oscillations [5, 6] in a frequency-specific manner and to study their functional impact on distinct cognitive functions. Recently, evidence has emerged that tACS (transcranial alternating current stimulation) can modulate cortical oscillations [7–9]. However, the study of electrophysiological effects has been hampered so far by the absence of concurrent electroencephalogram (EEG) recordings. Here, we applied 10 Hz tACS to the parieto-occipital cortex and utilized simultaneous EEG recordings to study neuronal entrainment during stimulation. We pioneer a novel approach for simultaneous tACS-EEG recordings and successfully separate stimulation artifacts from ongoing and event-related cortical activity. Our results reveal that 10 Hz tACS increases parieto-occipital alpha activity and synchronizes cortical oscillators with similar intrinsic frequencies to the entrainment frequency. Additionally, we demonstrate that tACS modulates target detection performance in a

PAF Power up with 10 Hz tACS in EO

Eyes open

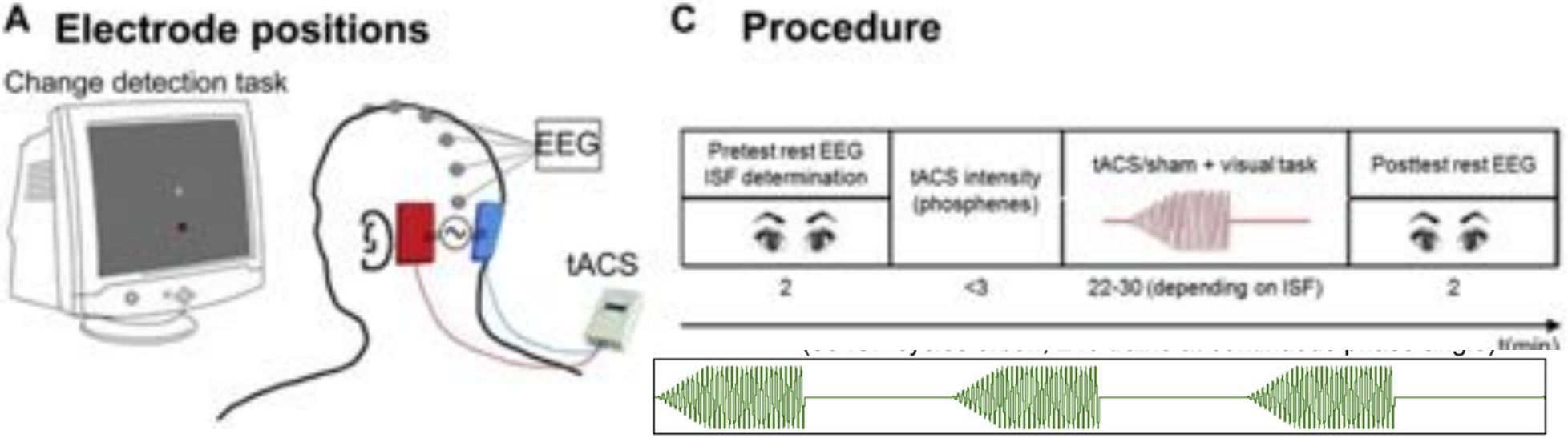


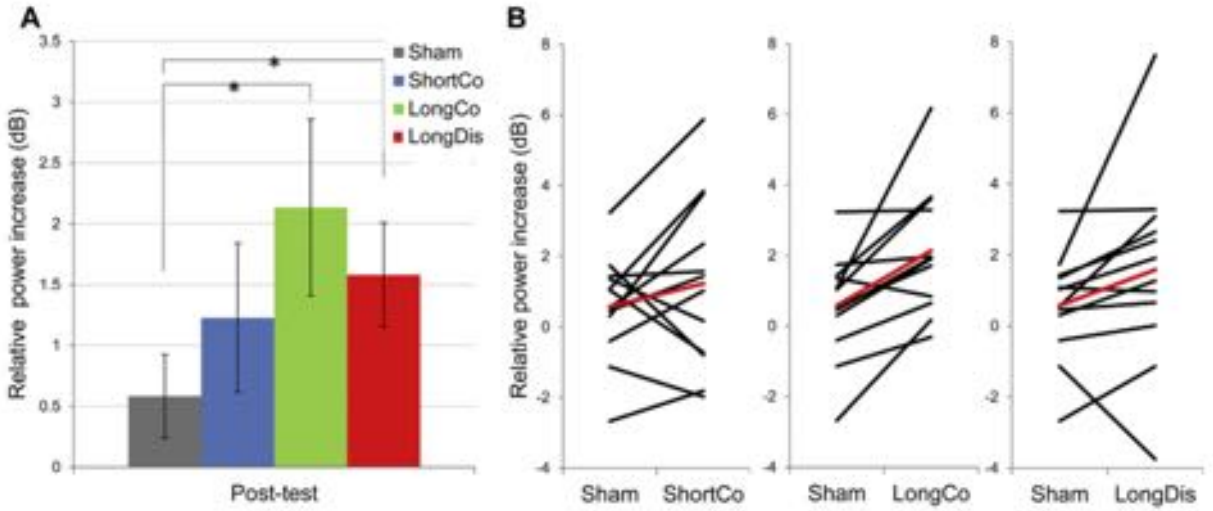




Alpha Power Increase After Transcranial Alternating Current Stimulation at Alpha Frequency (α-tACS) Reflects Plastic Changes Rather Than Entrainment 2015

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-

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Mapping entrained brain oscillations during transcranial alternating current stimulation (tACS)

Matthias Witkowski [a,1], Eliana Garcia Cossio [a,b,c,1], Bankim S. Chander [a], Christoph Braun [d,e], Niels Birbaumer [b], Stephen E. Robinson [f], Surjo R. Soekadar [a,b,*]

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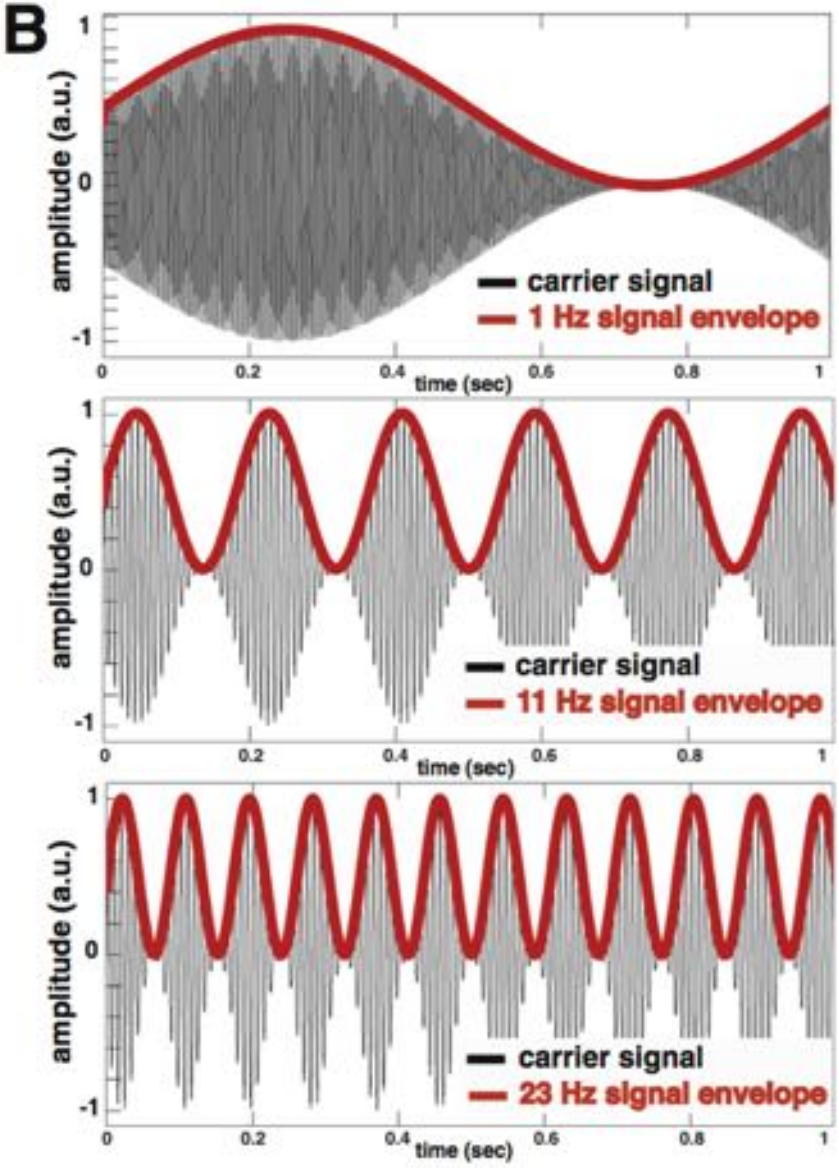
Entrainment
Transcranial alternating current stimulation
Whole-head magnetoencephalography

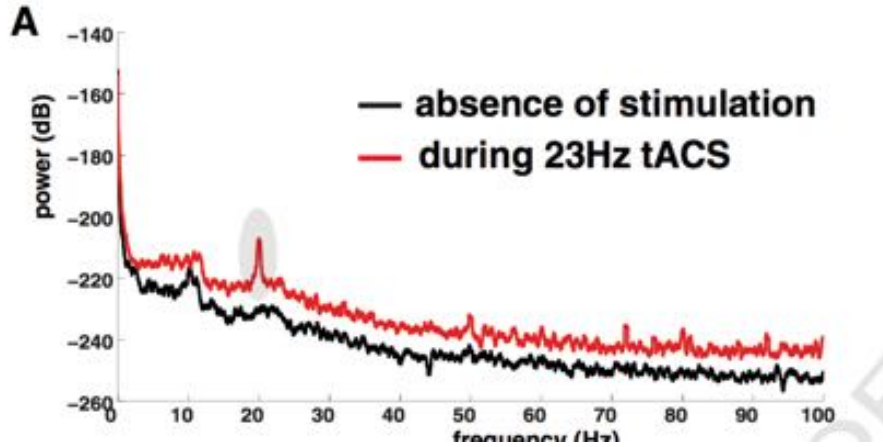
ABSTRACT

Transcranial alternating current stimulation (tACS), a non-invasive and well-tolerated form of electric brain stimulation, can influence perception, memory, as well as motor and cognitive function. While the exact underlying neurophysiological mechanisms are unknown, the effects of tACS are mainly attributed to frequency-specific entrainment of endogenous brain oscillations in brain areas close to the stimulation electrodes, and modulation of spike timing dependent plasticity reflected in gamma band oscillatory responses. tACS-related electromagnetic stimulator artifacts, however, impede investigation of these neurophysiological mechanisms. Here we introduce a novel approach combining amplitude-modulated tACS during whole-head magnetoencephalography (MEG) allowing for artifact-free source reconstruction and precise mapping of entrained brain oscillations underneath the stimulator electrodes. Using this approach, we show that reliable reconstruction of neuromagnetic low- and high-frequency oscillations including high gamma band activity in stimulated cortical areas is feasible opening a new window to unveil the mechanisms underlying the effects of stimulation protocols that entrain brain oscillatory activity.

Mapping entrained brain oscillations during transcranial alternating current stimulation (tACS)

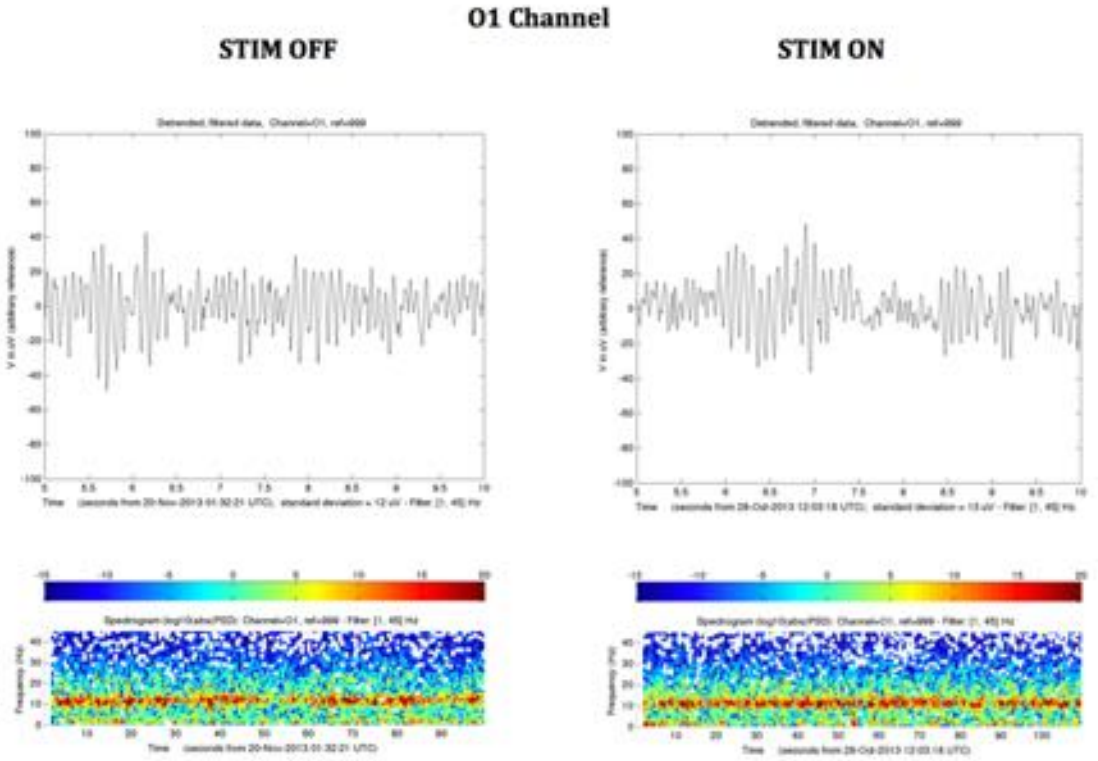
Matthias Witkowski [a,1], Eliana Garcia Cossio [a,b,c,1], Bankim S. Chander [a], Christoph Braun [d,e], Stephen E. Robinson [f], Surjo R. Soekadar [a,b,*]





Closed loop stimulation is here (MatNIC)

- It is now possible to stimulate and record EEG concurrently with tDCS, and w. limitations, tACS
- Explore sequential stim/record protocols using the MatNIC Matlab API to control Starstim remotely and programatically
- Adjust stimulation parameters based on collected EEG data: now possible



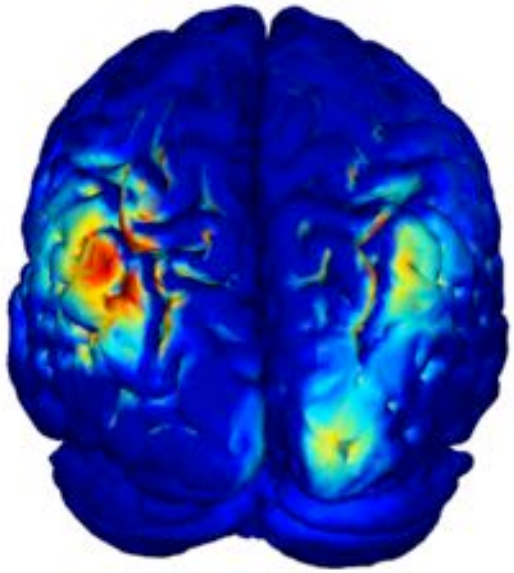
Challenges

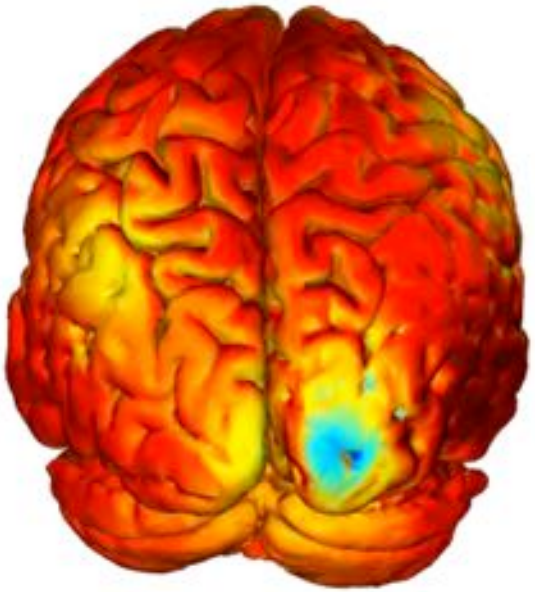
Alpha frequency and distribution is quite subject-dependent.

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)





SCIENTIFIC REPORTS

OPEN

Synthetic tactile perception induced by transcranial alternating-current stimulation can substitute for natural sensory stimulus in behaving rabbits

Received: 15 September 2015
Accepted: 16 December 2015
Published: 21 January 2016

Javier Márquez-Ruiz[1,*], Claudia Ammann[1,*], Rocío Leal-Campanario[1], Giulio Ruffini[2], Agnès Gruart[1] & José M. Delgado-García[1]

The use of brain-derived signals for controlling external devices has long attracted the attention from neuroscientists and engineers during last decades. Although much effort has been dedicated to establishing effective brain-to-computer communication, computer-to-brain communication feedback for "closing the loop" is now becoming a major research theme. While intracortical microstimulation of the sensory cortex has already been successfully used for this purpose, its future application in humans partly relies on the use of non-invasive brain stimulation technologies. In the present study, we explore the potential use of transcranial alternating-current stimulation (tACS) fo perception in alert behaving animals. More specifically, we determined the effects of local field potentials (LFPs) and motor output and tested its capability for inducing t using classical eyeblink conditioning in the behaving animal. We demonstrated that somatosensory cortex vibrissa area could indeed substitute natural stimuli during tr associative learning paradigm.

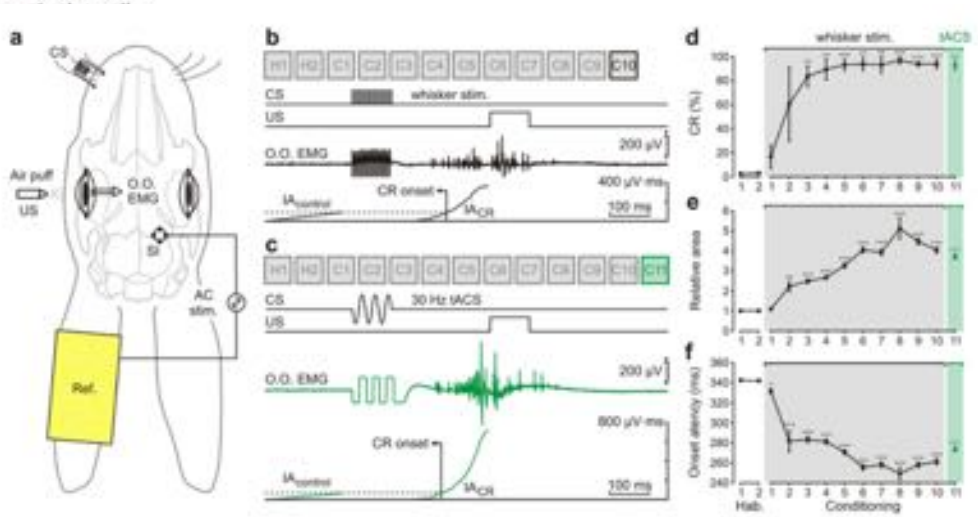


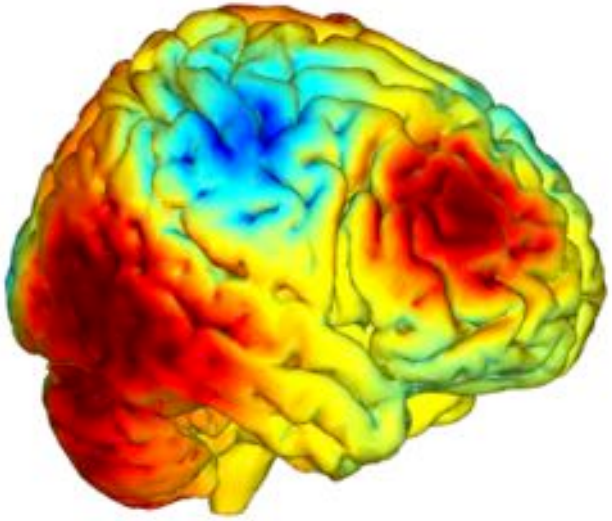
Figure 3. tACS of the somatosensory cortex substitute whisker stimulation during classical eyeblink conditioning. (a) Experimental design for tACS of primary somatosensory cortex (SI) and eyeblink

tACS … how?

Using EEG Cortical mapping to define targets for tCS (very consistent approach in terms of assumptions)

E.g., for tACS: alpha band Eyes Closed EEG data: use EEG cortical activity to guide tACS locations +frequencies+ relative phases. Relative phases important!

FEM based cortical map of eyes closed spontaneous EEG data (alpha).



Red: inward, blue: outward oriented dipoles

Cohen Kadosh Lab

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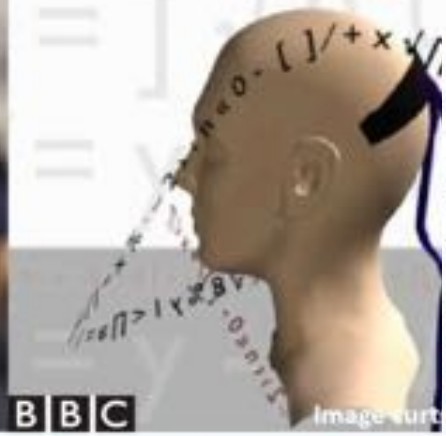
tRNS

We conduct research on the psychological and biological factors that shape learning and cognitive achievement, numerical cognition, synaesthesia, and time perception. Our research has basic and translational implications and has won us numerous awards and recognition

Electric current to the brain 'boosts maths ability'



Our pioneering research has revealed that we can enhance cognition using mild non-invasive brain sti

Long-term enhancement of brain function and cognition using cognitive training and brain stimulation.

Snowball A., Tachtsidis I., Popescu T., Thompson J., Delazer M., Zamarian L., Zhu T., Cohen Kadosh R.

DOI
10.1016/j.cub.2013.04.045

Noninvasive brain stimulation has shown considerable promise for enhancing cognitive functions by the long-term manipulation of neuroplasticity. However, the observation of such improvements has been focused at the behavioral level, and enhancements largely restricted to the performance of basic tasks. Here, we investigate whether transcranial random noise stimulation (TRNS) can improve learning and subsequent performance on complex arithmetic tasks. TRNS of the bilateral dorsolateral prefrontal cortex (DLPFC), a key area in arithmetic, was

TYPE
Journal article

JOURNAL
Curr Biol

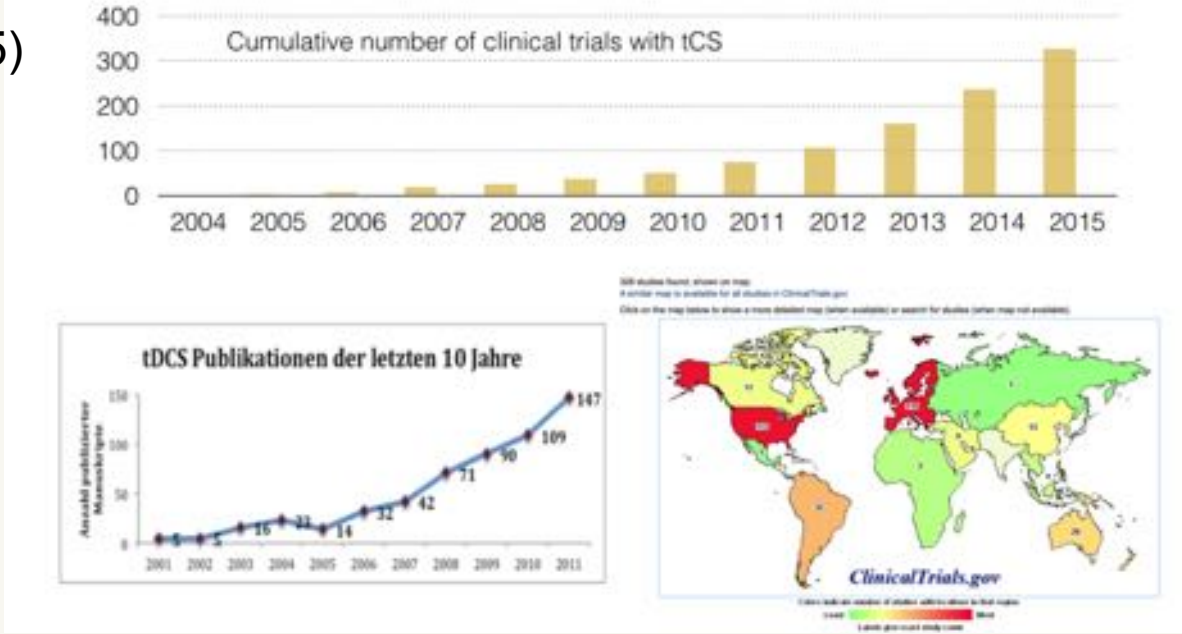
Permalink | Original publicatio

Clinical translation

Opportunities: tCS Clinical Research

tCS Clinical Publications so far
(as gathered by PubMed Jan 2015)

- **Pain: 127**
- **Depression: 137**
- **Stroke rehabilitation: 194**
- **Cognitive Enhancement: 200**
- **Addictive disorders: 18**
- **Epilepsy: 20**
- Parkinson's: 28
- Alzheimer's: 16



Main issues – in addition to small N in proper randomized crossover studies – are probably protocol un-specificity and heterogeneity and patient selection, which weaken results and make meta-analysis very challenging.

Nevertheless, there are "signals" in several of these cases worth studying in depth

Contents lists available at SciVerse ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Research

Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy

Narong Auvichayapat [a,1], Alexander Rotenberg [b,2], Roman Gersner [b,2], Sudarat Ngodklang [c,1], Somsak Tiamkao [d,1], Wichittra Tassaneeyakul [e,2], Paradee Auvichayapat [c,*,1]

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[b] Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA
[c] Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand
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Focal seizures
Partial seizures
Clinical neurophysiology
Transcranial direct current stimulation

ABSTRACT

Background: Cathodal transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation method for suppressing regional cortical excitability. We examine the safety and antiepileptic efficacy of cathodal tDCS in children with refractory focal epilepsy. Although a prior cathodal tDCS trial in adults with epilepsy revealed EEG improvement, neither the antiepileptic potential nor the safety and tolerability of tDCS has been tested in children.

Method: The study consisted of three phases: 1) a 4-week pre-treatment monitoring period with vital sign measures, EEG, seizure diary, and baseline quality of life (QOL) questionnaire; 2) a single treatment with 1 mA cathodal tDCS for 20 min with cathode positioned over the seizure focus and anode on the contralateral shoulder; 3) follow-ups immediately after stimulation, and at 24, 48 h, and 4 weeks after tDCS with continued seizure diary and epileptic discharge counts on EEG; the QOL questionnaire was also repeated 4 weeks after stimulation. Patients were randomized to receive either single session active or sham tDCS 1 mA, 20 min.

Results: Thirty six children (6–15 years) with focal epilepsy were enrolled, 27 in active and 9 in sham group. All patients tolerated tDCS well. No serious adverse events occurred. Active tDCS treatment was associated with significant reductions in epileptic discharge frequency immediately and 24 and 48 h after tDCS. Four weeks after treatment, a small (clinically negligible but statistically significant) decrease in seizure frequency was also detected.

Conclusion: A single session of cathodal tDCS improves epileptic EEG abnormalities for 48 h and is well-tolerated in children.

International Journal of Neuropsychopharmacology (2014), **17**, 1443–1452. © CINP 2014
doi:10.1017/S1461145714000418

ARTICLE

Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis

Pedro Shiozawa[1,2], Felipe Fregni[3], Isabela M. Benseñor[1], Paulo A. Lotufo[1], Marcelo T. Berlim[4], Jeff Z. Daskalakis[5], Quirino Cordeiro[2] and André. R. Brunoni[1,6]

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[3] *Neuromodulation Laboratory, Spaulding Rehabilitation Center – Harvard Medical School, Boston, MA, USA*
[4] *Department of Psychiatry, McGill University, Montreal, Canada*
[5] *Centre for Addiction and Mental Health (CAMH) Collaborative Program in Neuroscience, University of Toronto, Canada*
[6] *Service of Interdisciplinary Neurosciences (Lim-27), Department and Institute of Psychiatry, University of São Paulo, São Paulo, Brazil*

Abstract

Transcranial direct cranial stimulation (tDCS) is a promising non-pharmacological intervention for treating major depressive disorder (MDD). However, results from randomized controlled trials (RCTs) and meta-analyses are mixed. Our aim was to assess the efficacy of tDCS as a treatment for MDD. We performed a systematic review in Medline and other databases from the first RCT available until January 2014. The main outcome was the Hedges' *g* for continuous scores; secondary outcomes were the odds ratio (ORs) to achieve response and remission. We used a random-effects model. Seven RCTs ($n=259$) were included, most with small sample sizes that assessed tDCS as either a monotherapy or as an add-on therapy. Active *vs.* sham tDCS was significantly superior for all outcomes ($g=0.37$; 95% CI 0.04–0.7; ORs for response and remission were, respectively, 1.63; 95% CI=1.26–2.12 and 2.50; 95% CI=1.26–2.49). Risk of publication bias was low. No predictors of response were identified, possibly owing to low statistical power. In summary, active tDCS was statistically superior to sham tDCS for the acute depression treatment, although its role as a clinical intervention is still unclear owing to the mixed findings and heterogeneity of the reviewed studies. Further RCTs with larger sample sizes and assessing tDCS efficacy beyond the acute depressive episode are warranted.

Received 24 December 2013; Reviewed 17 February 2014; Revised 21 February 2014; Accepted 6 March 2014; First published online 8 April 2014

Key words: Major depressive disorder, meta-analysis, non-pharmacological therapies, systematic review, transcranial direct current stimulation.

Closed-Loop Control of Epilepsy by Transcranial Electrical Stimulation

Antal Berényi,[1,2,3] Mariano Belluscio,[1] Dun Mao,[1] György Buzsáki[1,2]*

Many neurological and psychiatric diseases are associated with clinically detectable, altered brain dynamics. The aberrant brain activity, in principle, can be restored through electrical stimulation. In epilepsies, abnormal patterns emerge intermittently, and therefore, a closed-loop feedback brain control that leaves other aspects of brain functions unaffected is desirable. Here, we demonstrate that seizure-triggered, feedback transcranial electrical stimulation (TES) can dramatically reduce spike-and-wave episodes in a rodent model of generalized epilepsy. Closed-loop TES can be an effective clinical tool to reduce pathological brain patterns in drug-resistant patients.

A successful, although not well-understood, therapy in drug-resistant cases of Parkinson's disease and depression is deep brain stimulation (*1*–*3*), in which high-frequency stimulation is applied continuously. In many diseases, such as epilepsies, events recur unpredictably and often are separated by long interictal intervals (*4*–*6*). In such instances, a closed-loop, transient feedback control could abort seizure episodes without inducing detrimental side effects of continuous stimulation (*7*–*13*). We attempted to achieve seizure control by means of closed-loop transcranial electrical stimulation (TES) in a rodent model of generalized ("petit mal") epilepsy (*14*, *15*) because previous experiments have shown that even very weak TES can reliably entrain neurons in widespread cortical areas (*16*–*20*).

We first demonstrated the effect of TES on cortical excitability. Local field potentials (LFPs) and multiple-unit activity (MUA) were recorded by chronically implanted tripolar electrodes (Fig. 1A) and placed in the deep and superficial layers of the frontal and parietal cortical areas (*21*). TES was applied either between the left and right

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*To whom correspondence should be addressed. E-mail: gyorgy.buzsaki@nyumc.org

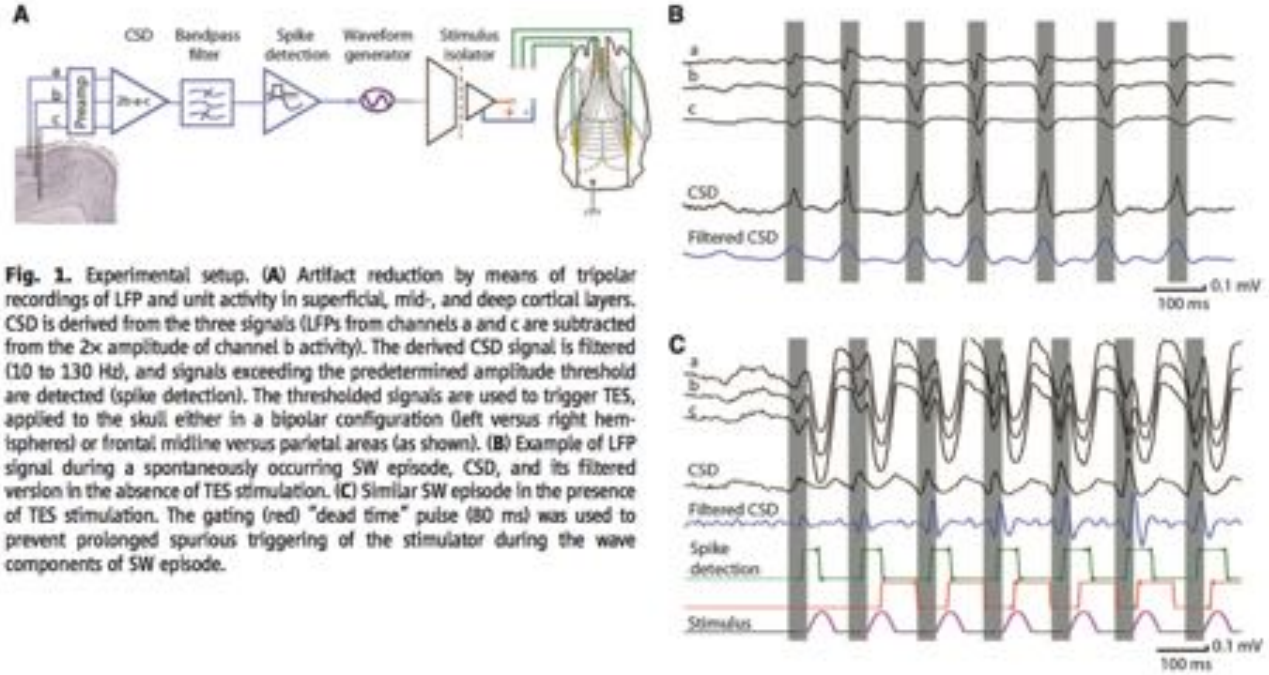


Fig. 1. Experimental setup. **(A)** Artifact reduction by means of tripolar recordings of LFP and unit activity in superficial, mid-, and deep cortical layers. CSD is derived from the three signals (LFPs from channels a and c are subtracted from the 2× amplitude of channel b activity). The derived CSD signal is filtered (10 to 130 Hz), and signals exceeding the predetermined amplitude threshold are detected (spike detection). The thresholded signals are used to trigger TES, applied to the skull either in a bipolar configuration (left versus right hemispheres) or frontal midline versus parietal areas (as shown). **(B)** Example of LFP signal during a spontaneously occurring SW episode, CSD, and its filtered version in the absence of TES stimulation. **(C)** Similar SW episode in the presence of TES stimulation. The gating (red) "dead time" pulse (80 ms) was used to prevent prolonged spurious triggering of the stimulator during the wave components of SW episode.

Current Evidence in stroke rehab

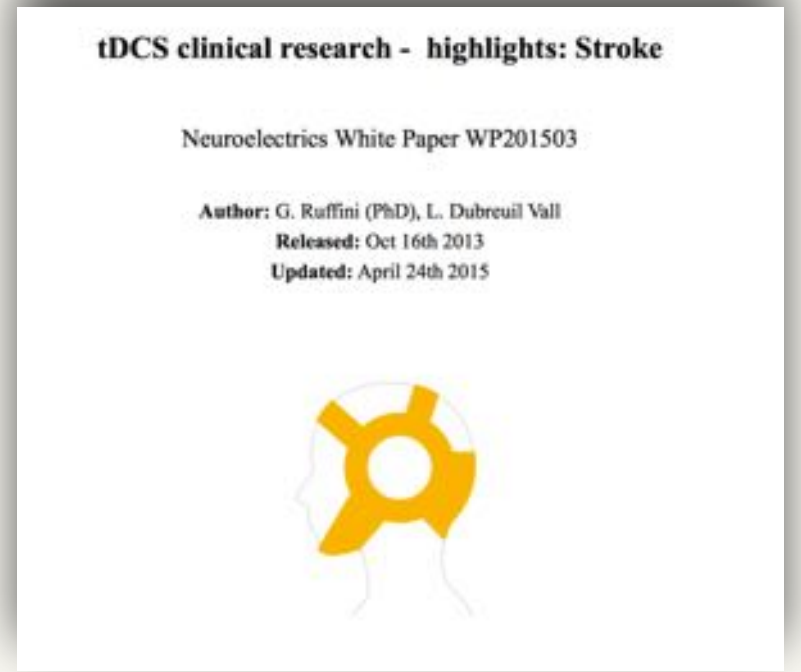
A number of studies by now strongly suggest the efficacy of tDCS in stroke.

The studies in our search show in general positive results. We have analyzed 47 papers meeting our criteria, from 2005 to 2015.

The total number of subjects in these studies was **873**, with 65% of subjects in studies with positive outcomes.

If we restrict the analysis to papers dealing with chronic stroke the percent of subjects in studies with a positive outcome increases to 82% (231 out of 281 subjects).

If we further restrict the analysis to those studies with chronic patients in which tDCS was administered concurrently with therapy, the positive rate increases further to 84% (156 out of 186 subjects were in studies with positive results). The analogous rate for non-chronic stroke patients is low, of 44%.



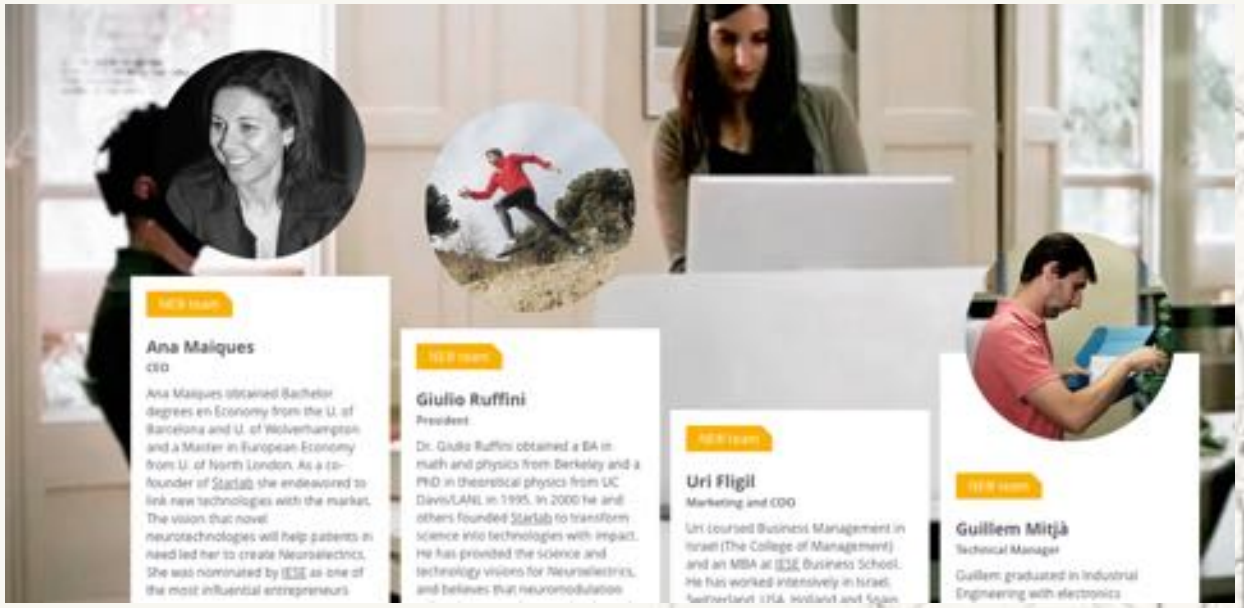
wiki.neuroelectrics.com

Conclusions

- tCS is physiologically meaninful: it has an impact: concurrent and after application
- Multielectrode systems are here, tCS means tDCS, tACS, tRNS are beyond (but weak currents with bandwidth <1000 Hz)
- Safe in current research environment? Yes. NOT for consumer market though.
- We have some basic understanding of mechanisms — need to continue research!
- Biophysically models are powerful and will get better. Initial validation is here, need more.
- Clinical translation needs work, which is underway.

Thank you!

And thanks to all the NE team and Advisors



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

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

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,

Guillem Mitjà
Technical Manager

Guillem graduated in Industrial Engineering with electronics

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. 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

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. Roi Cohen Kadosh
Kadosh Lab, U. of Oxford

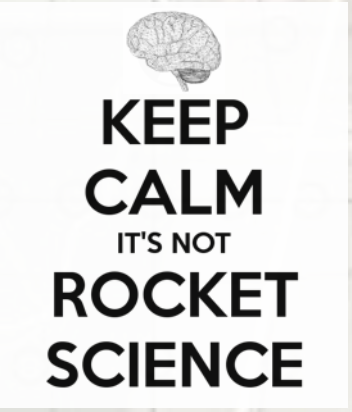
Wellcome RCD Fellow and University Research Lecturer at the University of Oxford, Prof. Kadosh is a leader in the study of the neuropsychological mechanisms of numerical and magnitude processing using advanced techniques such as tCS/tES. His main research focuses on the psychological and biological factors 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.

Asilomar, June 2nd 2016

Modeling and optimizing tCS

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

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 … ?

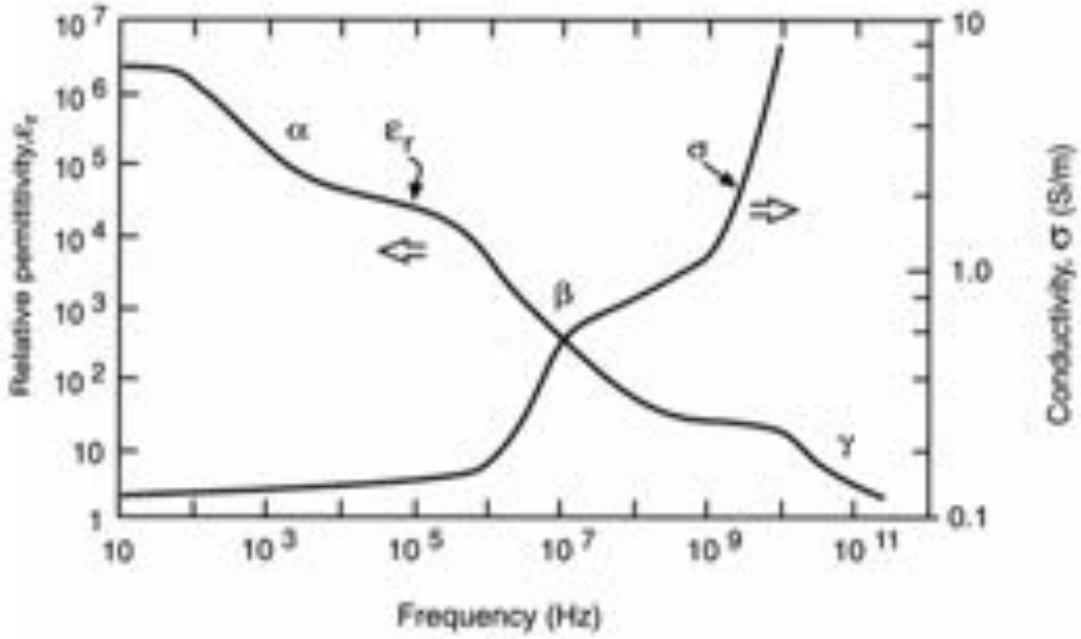


Figure 2.1 – Frequency variation of dielectric properties of typical soft tissue (from [Reilly:1998aa])

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

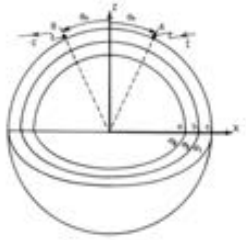


Fig. 3. Geometry for the three-concentric-sphere proof.

Annals of Biomedical Engineering, Vol. 19, pp. 317–328, 1991
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0090-6964/91 $3.00 + .00
1991 Pergamon Press plc

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

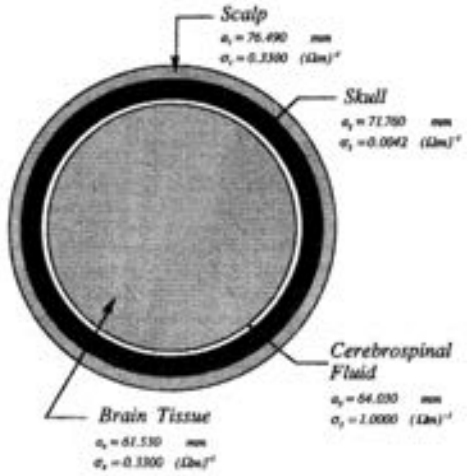
A Theoretical Comparison of Electric and Magnetic Stimulation of the Brain

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

IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, VOL. 43, NO. 9, SEPTEMBER 1996 939

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*

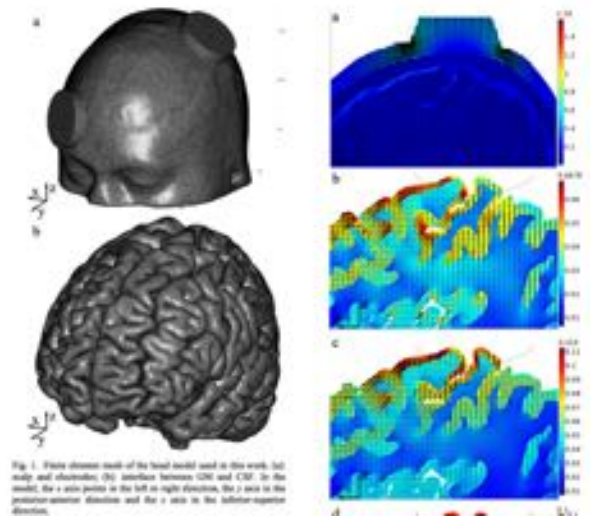


Modeling comes of age: realistic FEM models

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



Brain Stimulation (2011) 4, 169–74

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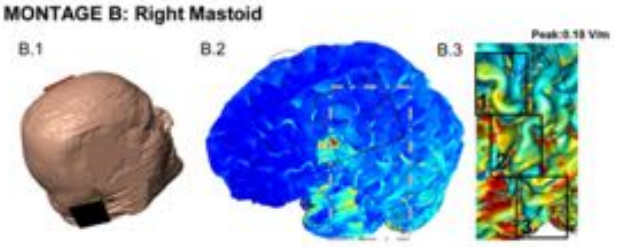
BRAIN
STIMULATION

www.brainstimjrnl.com

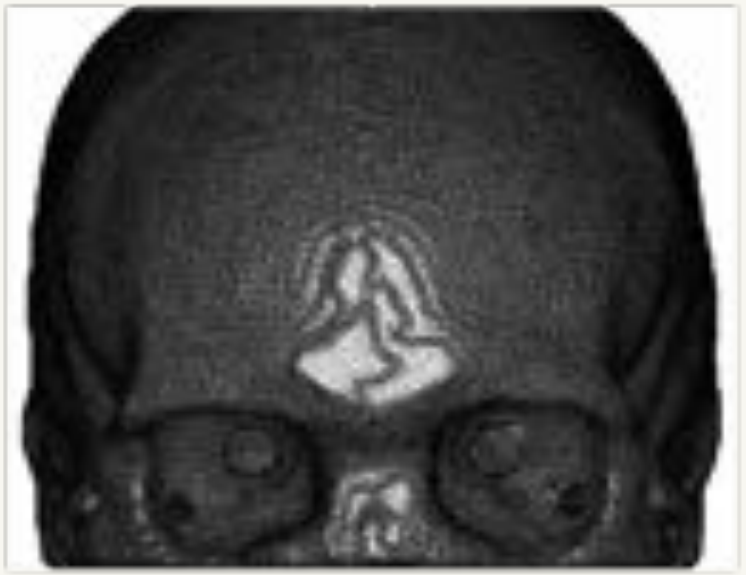
Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient

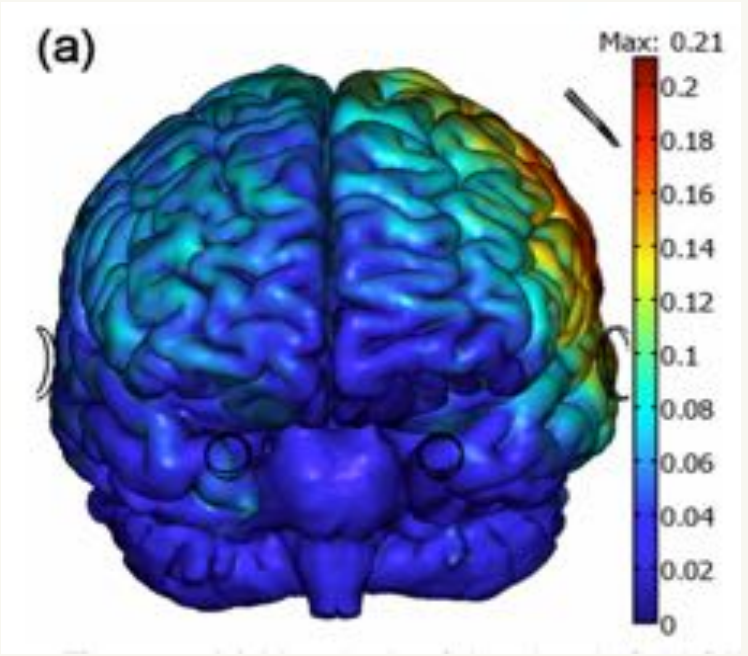
Abhishek Datta,[a] Julie M. Baker,[b] Marom Bikson,[a] Julius Fridriksson[b]



FEM and Poisson's equation: electric fields

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





The electric field in the cortex during transcranial current stimulation

Pedro Cavaleiro Miranda [a,b,*], Abeye Mekonnen [a], Ricardo Salvador [a], Giulio Ruffini [c]

NeuroImage 70 (2013) 48–58

Contents lists available at SciVerse ScienceDirect

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

The electric field in the cortex during transcranial current stimulation

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Transcranial direct current stimulation
Electric field
Cortex
Modelling
Electrode size
Focality

ABSTRACT

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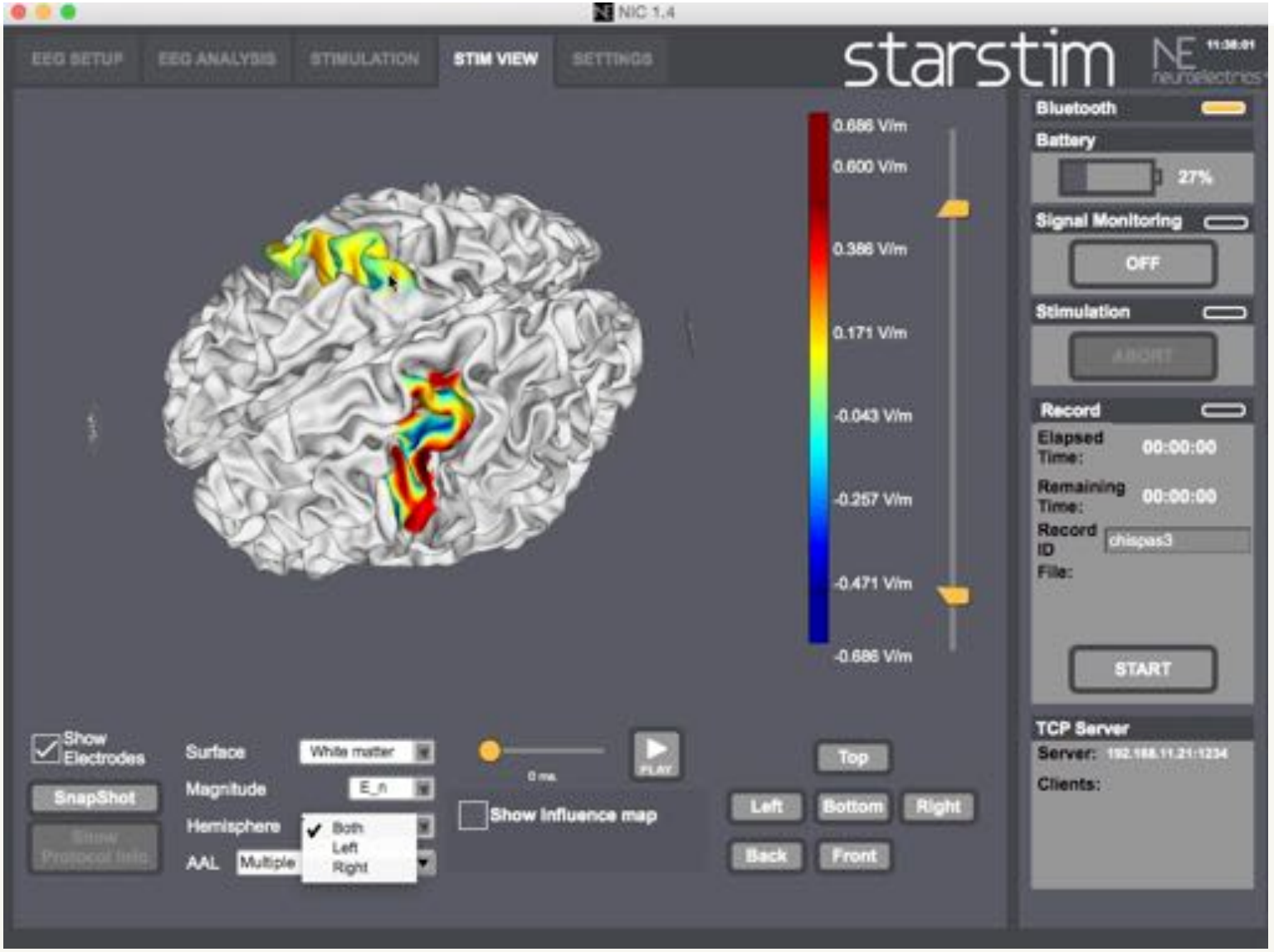
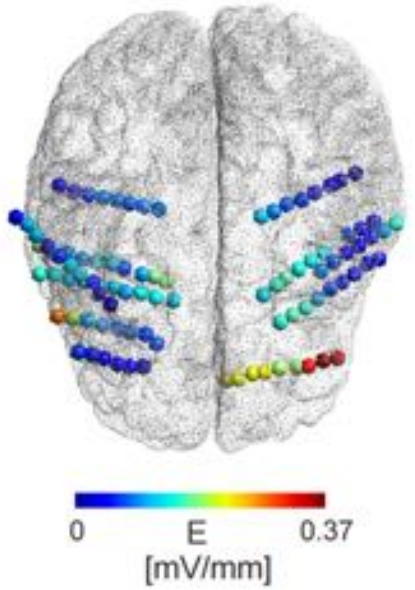
Visualizing the E field



Intracranial electric fields from measurements in humans and primates

Spatiotemporal structure of intracranial electric fields induced by transcranial electric stimulation in human and nonhuman primates

Alexander Opitz[1,2], Arnaud Falchier[1], Chao-Gan Yan[1,3], Erin Yeagle[4], Gary Linn[1,5], Pierre Megevand[4], Axel Thielscher [6,7,8], Michael P. Milham[1,2], Ashesh Mehta[4], Charles Schroeder[1,9]



Transcranial electric stimulation (TES) is an emerging technique, developed to non-invasively modulate brain function. However, the spatiotemporal distribution of the intracranial electric fields induced by TES remains poorly understood. In particular, it is unclear how much current actually reaches the brain, and how it distributes across the brain. Lack of this basic information precludes a firm mechanistic understanding of TES effects. In this study we directly measure the spatial and temporal characteristics of the electric field generated by TES using stereotactic EEG (s-EEG) electrode arrays implanted in cebus monkeys and surgical epilepsy patients. We found a small frequency dependent decrease (10%) in magnitudes of TES induced potentials and negligible phase shifts over space. Electric field strengths were strongest in superficial brain regions with maximum values of about 0.5 mV/mm. Our results provide crucial information for the interpretation of human TES studies and the optimization and design of TES stimulation protocols. In addition, our findings have broad implications concerning electric field propagation in non-invasive recording techniques such as EEG/MEG.

Physics > Biological Physics

Application of the reciprocity theorem to EEG inversion and optimization of EEG-driven transcranial current stimulation (tCS, including tDCS, tACS, tRNS)

Giulio Ruffini

(Submitted on 16 Jun 2015 (v1), last revised 17 Jun 2015 (this version, v2))

Multichannel transcranial current stimulation (tCS) systems offer the possibility of EEG-guided optimized, non-invasive brain stimulation. In this brief technical note I explain how it is possible to use tCS electric field realistic brain model to create a forward "lead-field" matrix and, from that, an EEG inverter for cortical mapping. Starting from EEG I show how to generate 2D cortical surface dipole fields that could produce the observed EEG electrode voltages. The main tool is the reciprocity theorem derived by Helmholtz. The application of reciprocity for the generation of a forward mapping matrix (lead field matrix as is sometimes known) is well known [Rush and Driscoll, 1969], but here we will use it in combination with the realistic head models of [Miranda et al 2013] to provide cortical mapping solutions compatible with realistic head model tCS optimization. I also provide a generalization of the reciprocity theorem [Helmholtz 1853] to the case of multiple electrode contact points and dipole sources, and discuss its uses in non-invasive brain stimulation based on EEG. This, as far as I know, is a novel result. Applications are discussed.

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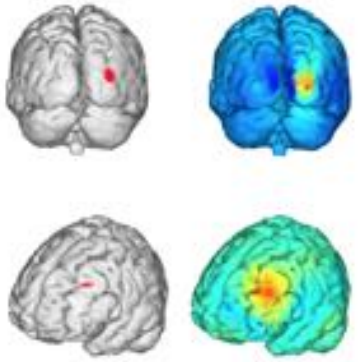
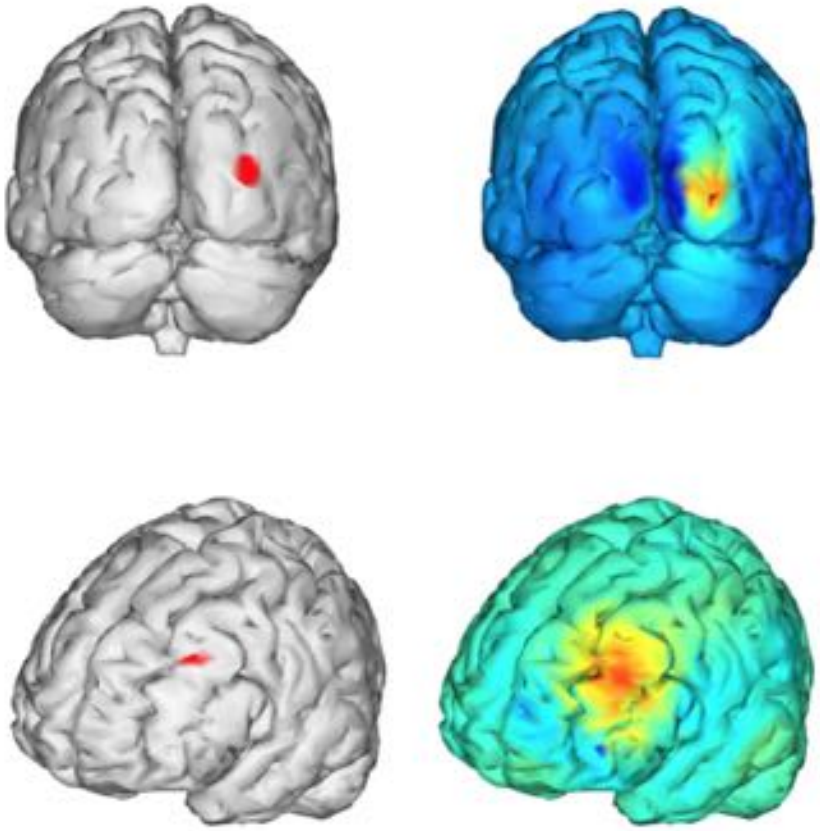
Subjects:	**Biological Physics (physics.bio-ph)**; Medical Physics (physics.med-ph)
Report number:	Neuroelectrics Barcelona SL - TN0008
Cite as:	arXiv:1506.04835 [physics.bio-ph]
	(or arXiv:1506.04835v2 [physics.bio-ph] for this version)



Submission history

From: Giulio Ruffini [view email]
[v1] Tue, 16 Jun 2015 05:15:55 GMT (1557kb,D)
[v2] Wed, 17 Jun 2015 21:38:29 GMT (1389kb,D)

Using head models for EEG forward and inverse modeling



Application of the reciprocity theorem to EEG inversion and optimization of EEG-driven tCS (tDCS, tACS and tRNS)

Author: Giulio Ruffini (giulio.ruffini@neuroelectrics.com)
Date: June 10 2015

arXiv:1506.04835v2 [physics.bio-ph] 17 Jun 2015

Summary

Multichannel transcranial current stimulation systems offer the possibility of EEG-guided optimized brain stimulation. In this brief technical note I explain how it is possible to use transcranial current stimulation tCS (which includes tDCS, tACS and tRNS among others[1]) electric field realistic brain models to create a forward "lead-field" matrix and, from that, an EEG inverter for cortical mapping. Starting from EEG we show how to generate 2D cortical surface dipole fields that could generate the observed EEG electrode voltages. The main tool is the reciprocity theorem derived by Helmholtz. The application of reciprocity for the generation of a forward mapping matrix (lead field matrix as is sometimes known) is well known [Rush1969[2]], but here we will use it in combination with the realistic head models of [Miranda2013[3]] to provide cortical mapping solutions compatible with realistic head model tCS optimization.

I also provide a generalization of the reciprocity theorem [Helmholtz1853[4]] to the case of multiple electrode contact points and EEG dipole sources, and discuss its uses in non-invasive brain stimulation based on EEG. This can be used to guide for optimization of transcranial current stimulation with multiple channels based on EEG. This, as far as I know, is a novel result.

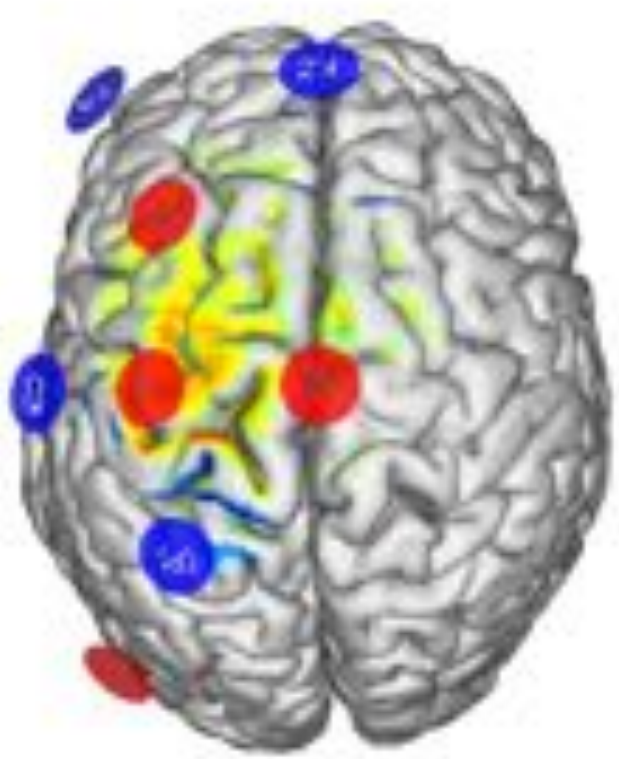
Going Multichannel (MtCS)

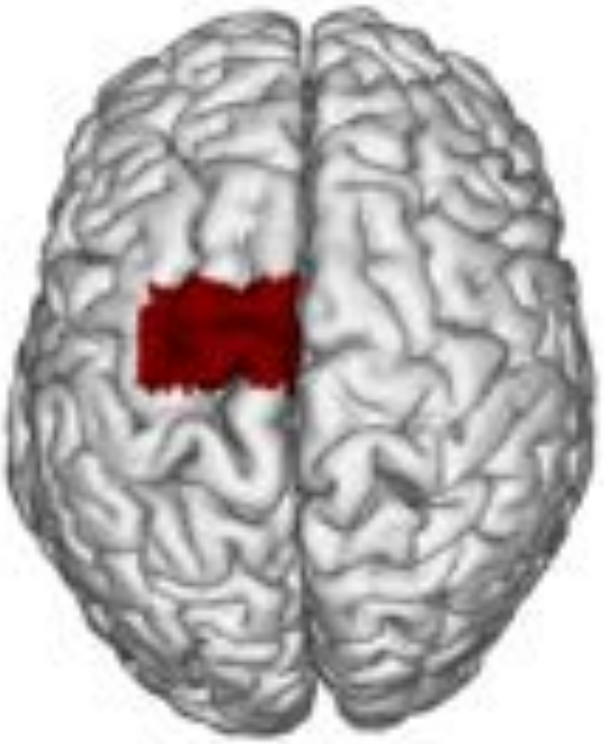
Motivation

1- Achieving more focality, precision

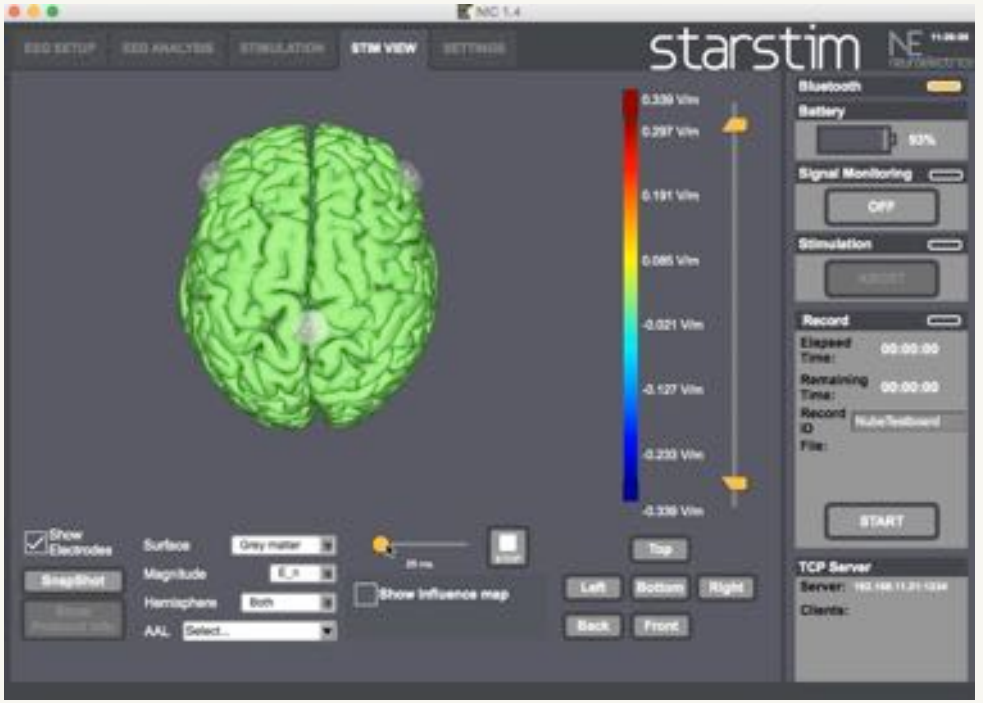
2- Targeting the brain as network

Targeting the Sup MC: 8 “Pi” electrodes





Lustenberger et al 2015: MtACS



CORTEX 67 (2015) 74–82

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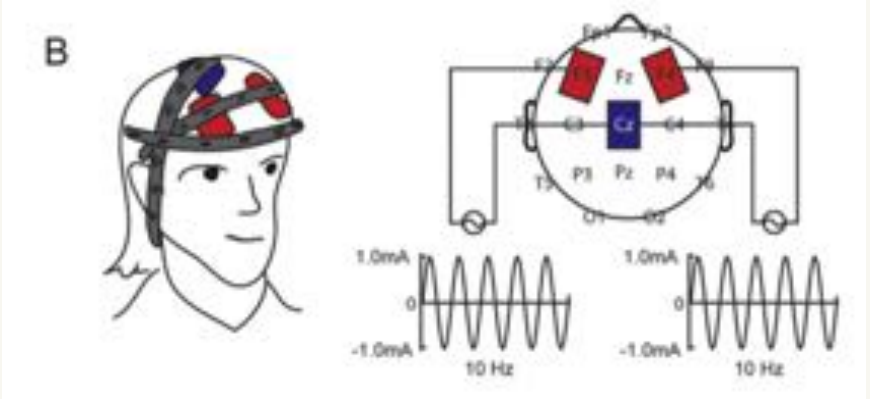
ELSEVIER

Cortex

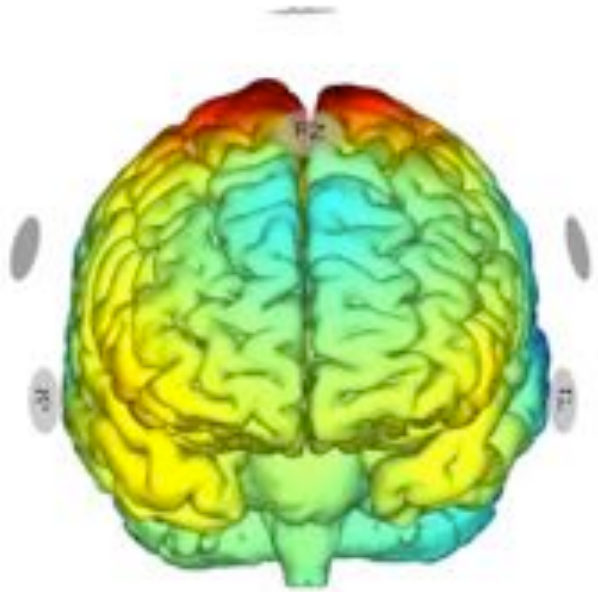
Research report

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,*]



MtCS protocol configuration: phase control



How do you configure up to, say, 32 Channels for stimulation?

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.

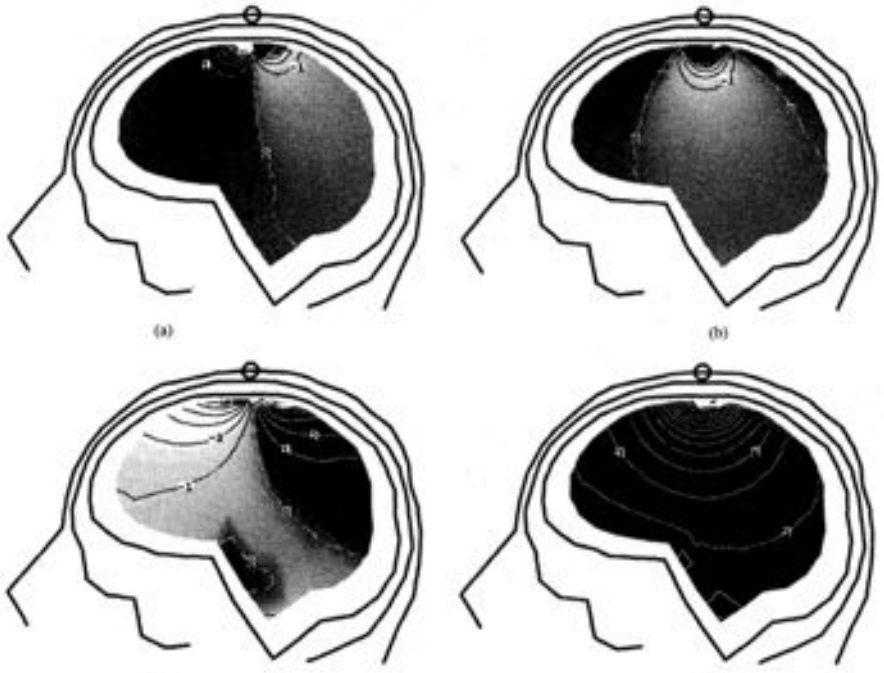


Fig. 3. Laplacian sensitivities for (a) horizontal and (b) vertical dipoles and potential sensitivities for (c) horizontal and (d) vertical dipoles in a cross section of the human head. The observation point is marked by a circle. Isofunction lines are drawn at linear intervals of 1 $V \cdot A^{-1} \cdot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

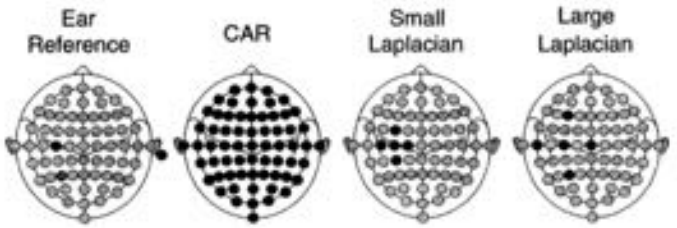


Fig. 1. Electrode locations used in the application of each spatial filter method to the activity recorded from C3 (red). During data acquisition, all elect are referred to the ear reference. For the CAR and Laplacian methods, the activity at the green electrodes is averaged and subtracted from the activity

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

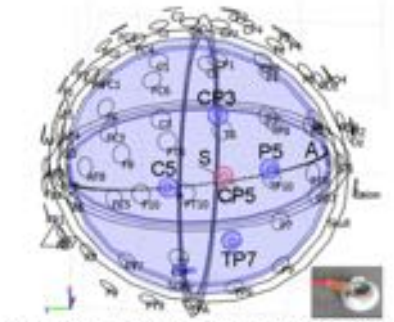
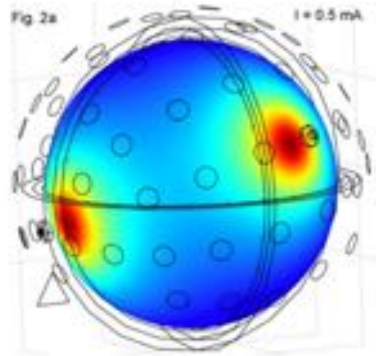


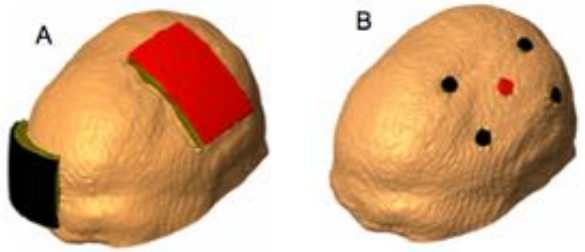
Fig. 1. Representation of the electrode montage M3, where t
cathode is placed on the left hemisphere at CP5 (red electrode) a
the four anodes are placed around the cathode at C5, TP7, P5 and C
(blue electrodes). The radial line (S) in the brain under CP5 and t
arc (A) on the surface of the brain and 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

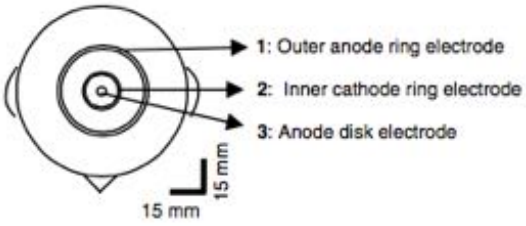


IOP Publishing
J. Neural Eng. 5 (2008) 163–174
Journal of Neural Engineering
doi:10.1088/1741-2560/5/2/007

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)

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

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[f] Institut Guttmann, Hospital de Neurorehabilitació, Institut Universitari adscrit a la Universitat Autònoma de Barcelona, Barcelona, Spain

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Targeted stimulation
Multifocal stimulation
Human head model
TES
NIBS
fMRI
PET
rs-fcMRI

ABSTRACT

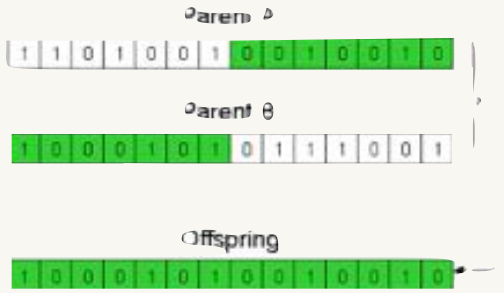
Recently, multifocal transcranial current stimulation (tCS) devices using several relatively small electrodes have been used to achieve more focal stimulation of specific cortical targets. However, it is becoming increasingly recognized that many behavioral manifestations of neurological and psychiatric 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

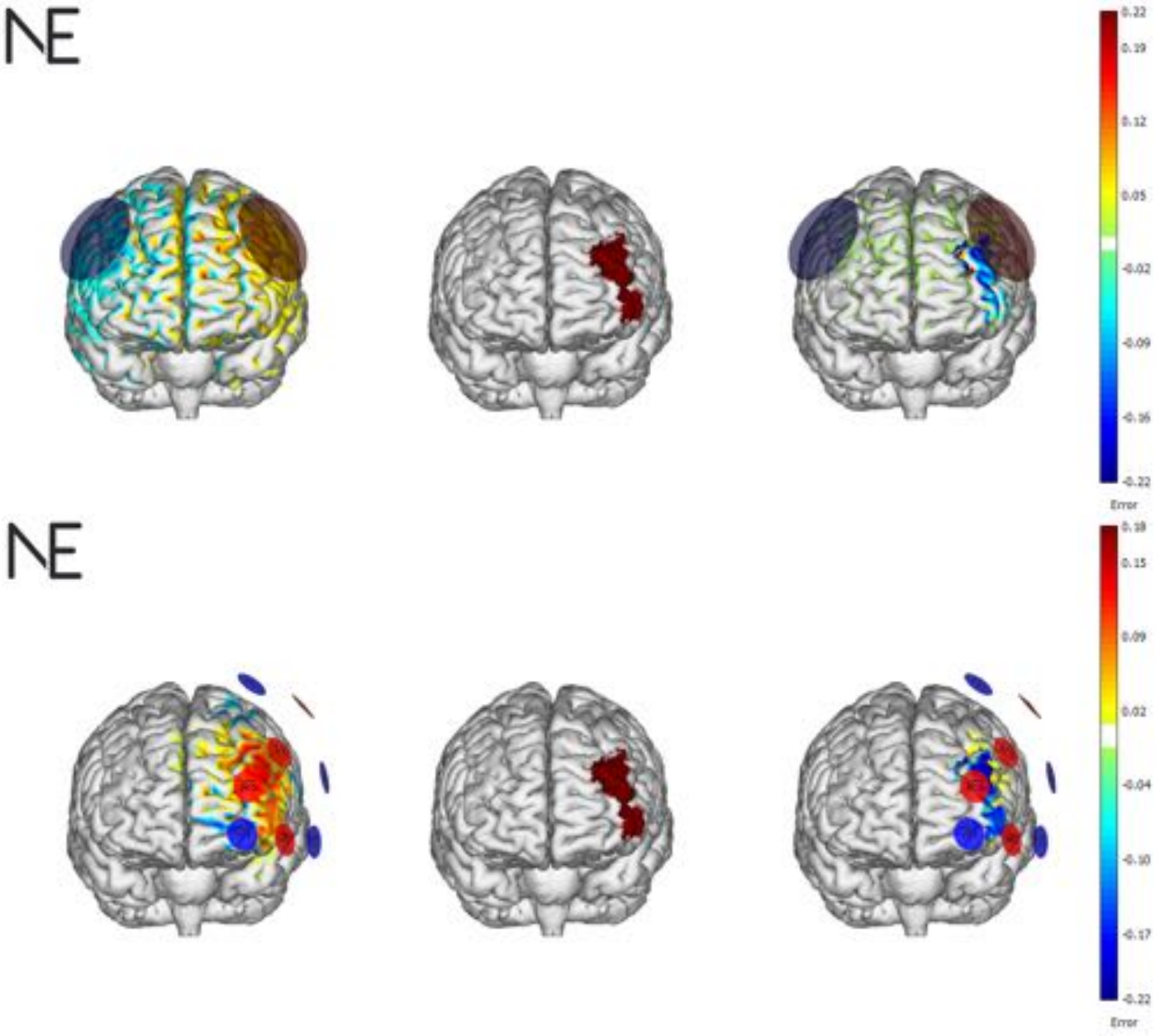
- Working with extended, weighted targets from neuroimaging, or discrete targets (e.g., BA or AAL)
- Optimizing using normal and tangential components of E fields on cortical surface
- Use of genetic algorithms to work with electrode subsets
- Developed for Starstim, with up to ~70 electrode positions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



Example: Targeting the DLPFC

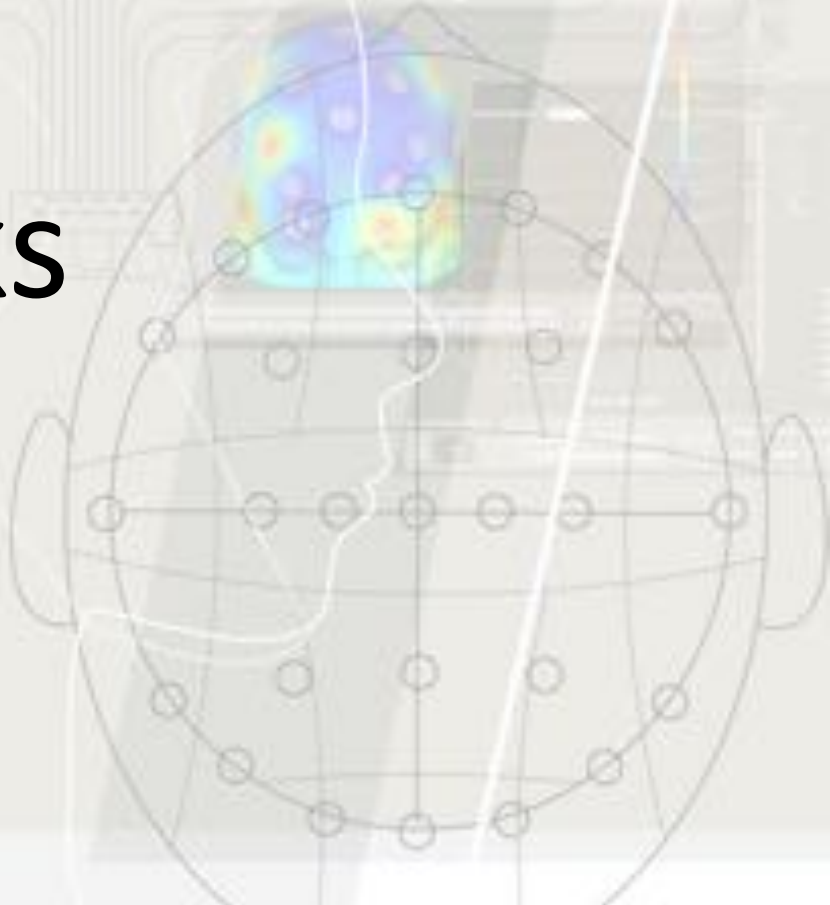
- **Stimulation type:** tDCS
- **Target:** Left dorsolateral prefrontal cortex (BA46)
- **Electric field in target area:** 0.25 V/m excitatory
- **Electrode type:** PITRODE (π cm^2Ag/AgCl/gel electrode)
- **Max current any electrode:** 1 and 2 mA
- **Max total injected current:** 4 mA
- **Max number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

Targeting the DLPFC: 2 sponges vs 8 channels



Optimizing MtCS (II):

Targeting networks



Example: targeting a network: example with DBS Depression seed using rs-fMRI data

- 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

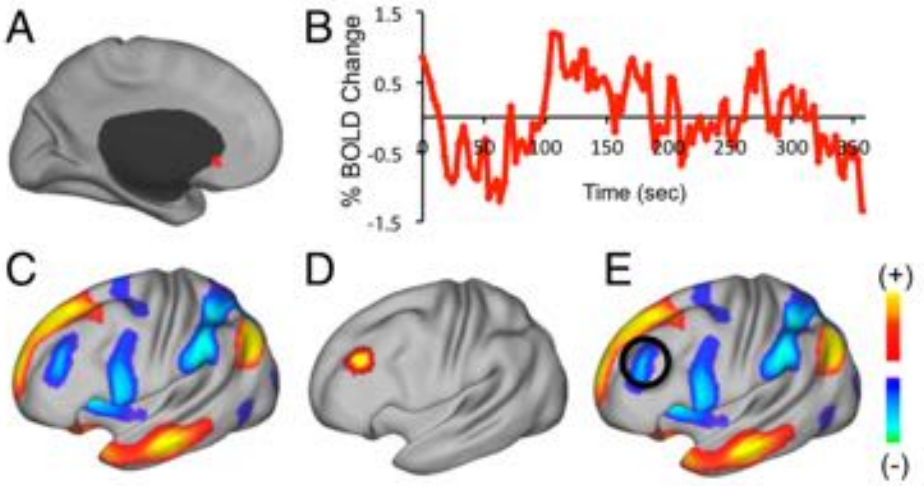


Fig. 1. Methodological approach for linking sites for invasive and non-invasive brain stimulation. (*A*) An ROI is created at a DBS site with reported efficacy for a given disease, in this case the subgenual cingulate for depression. (*B*) For each of 1,000 normal subjects, spontaneous modulations in 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

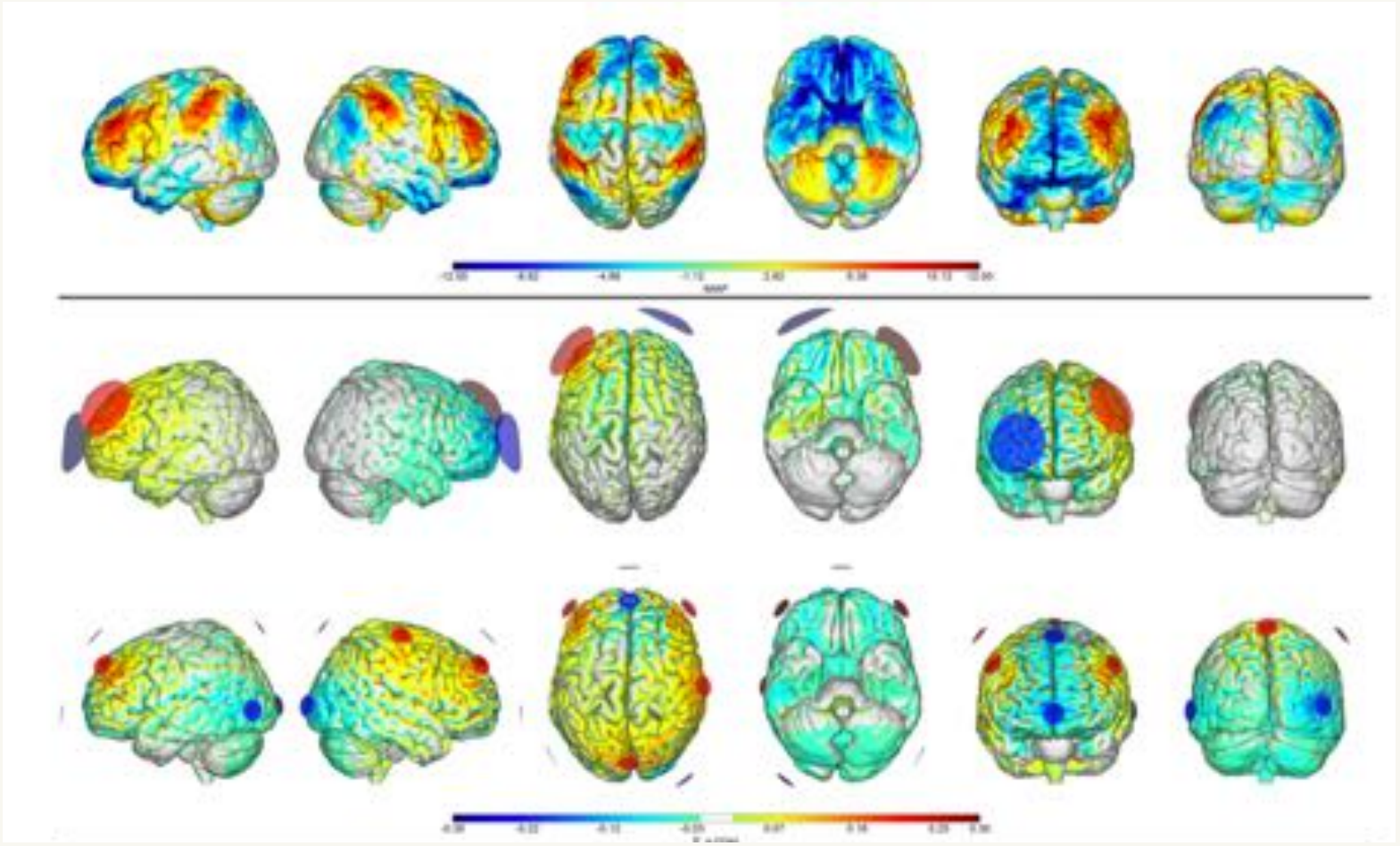
Distributed target map (depression SG seed /8Ch)

neuroelectrics®

TARGET:

Classical:

Modern:



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

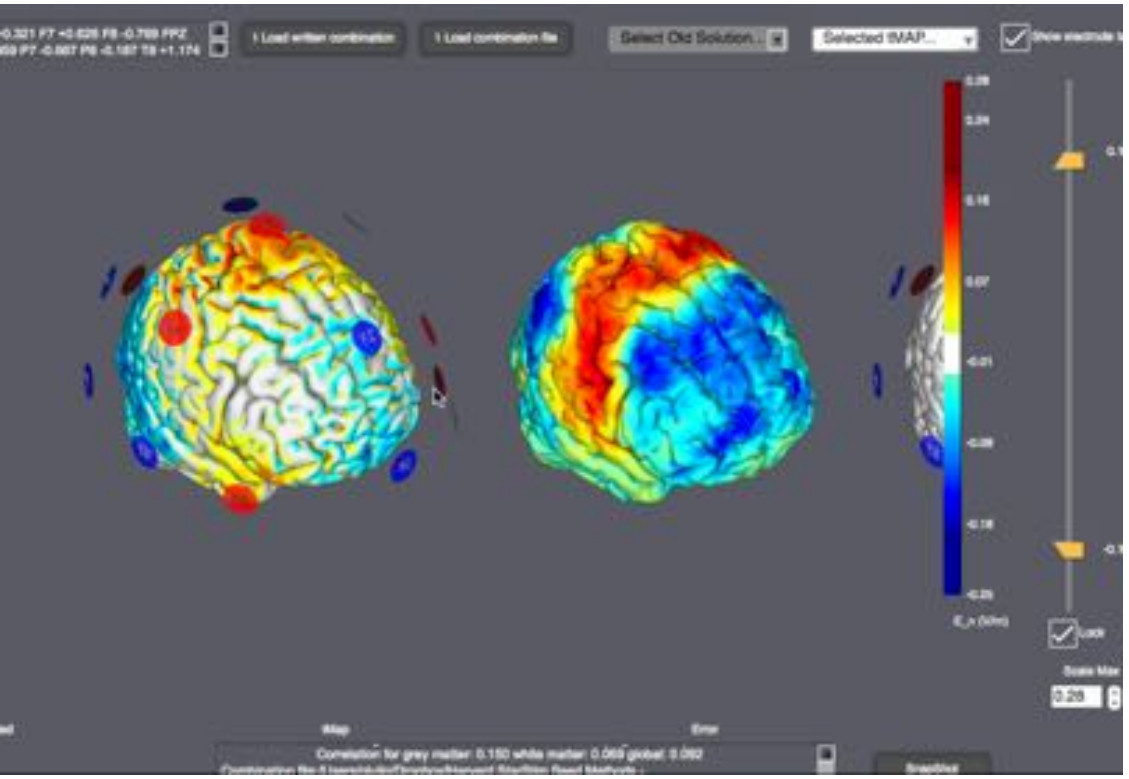
Ruffini et al 2014

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



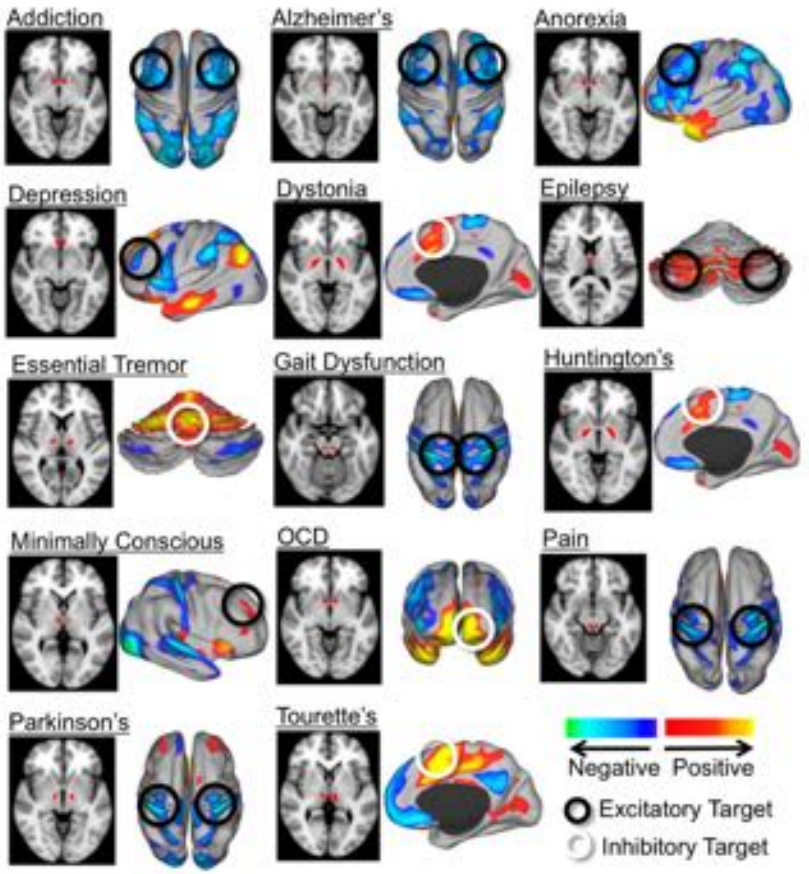
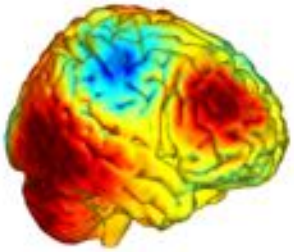
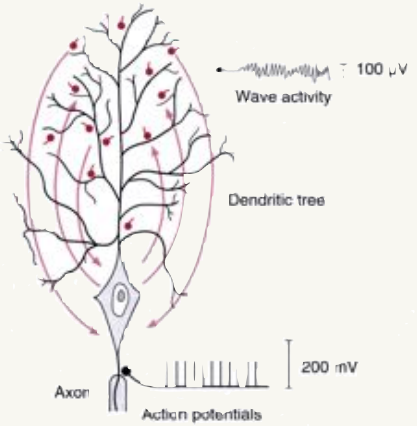


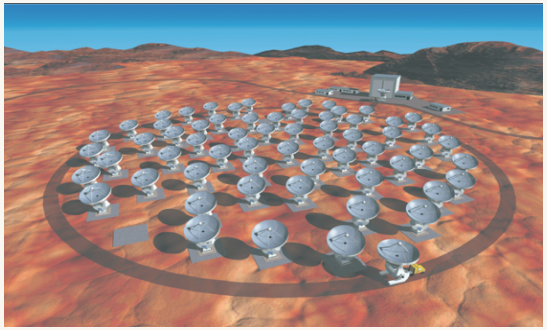
Fig. 2. Sites for invasive and noninvasive brain stimulation with the best evidence of therapeutic efficacy in each disease are functionally connected. For each disease, the site at which DBS is most effective is shown in red. Resting-state functional connectivity with this site is shown along with the 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.

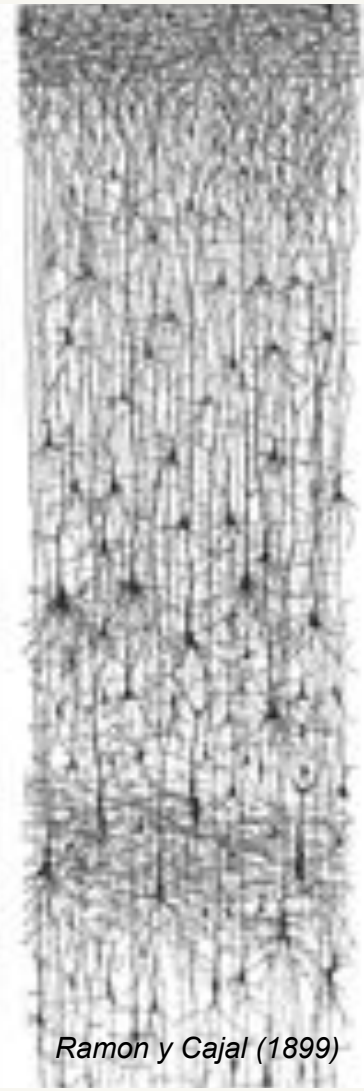
Basics on **EEG** & **tCS**

- 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.





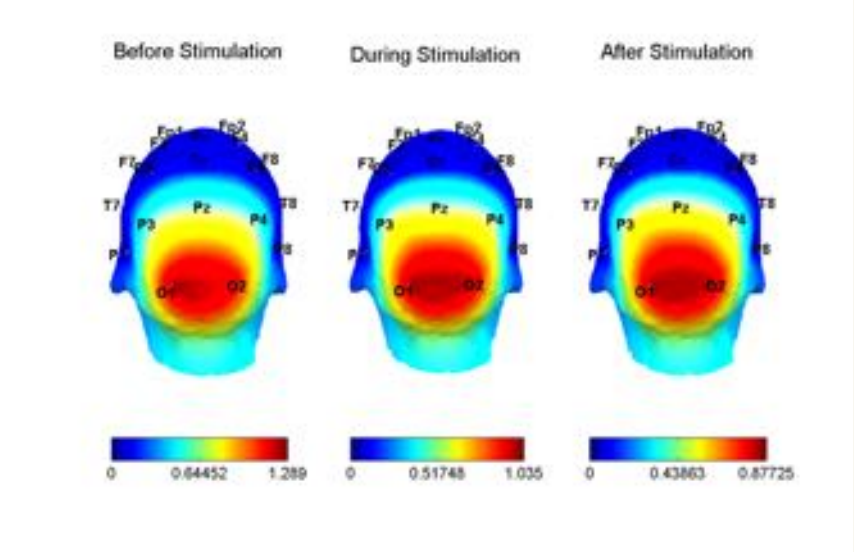




Ramon y Cajal (1899)

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]

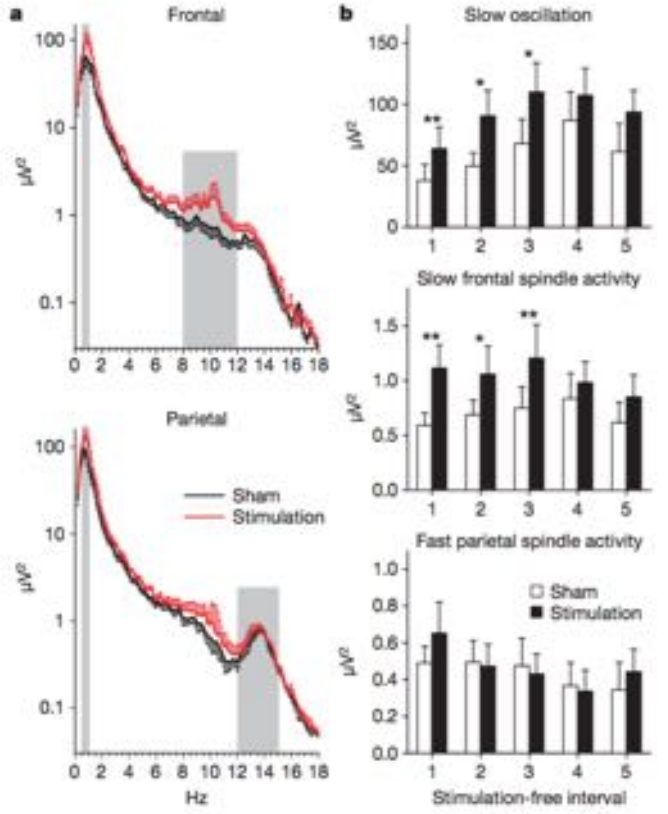


Figure 3 | EEG activity during the 1-min intervals between periods of slow oscillation stimulation and between corresponding periods of sham stimulation. **a**, Average power spectrum (across first three stimulation-free intervals) at the midline frontal and parietal sites. Shaded areas indicate frequency 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.

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

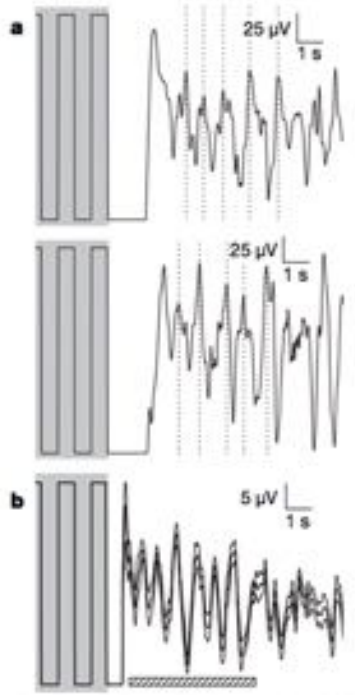
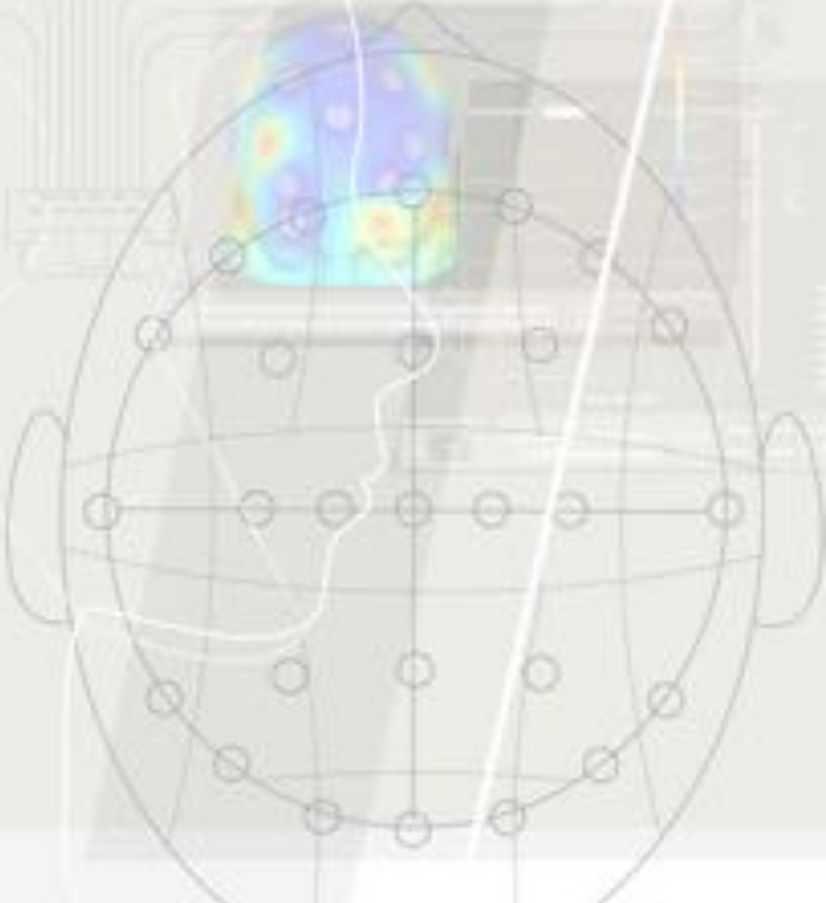
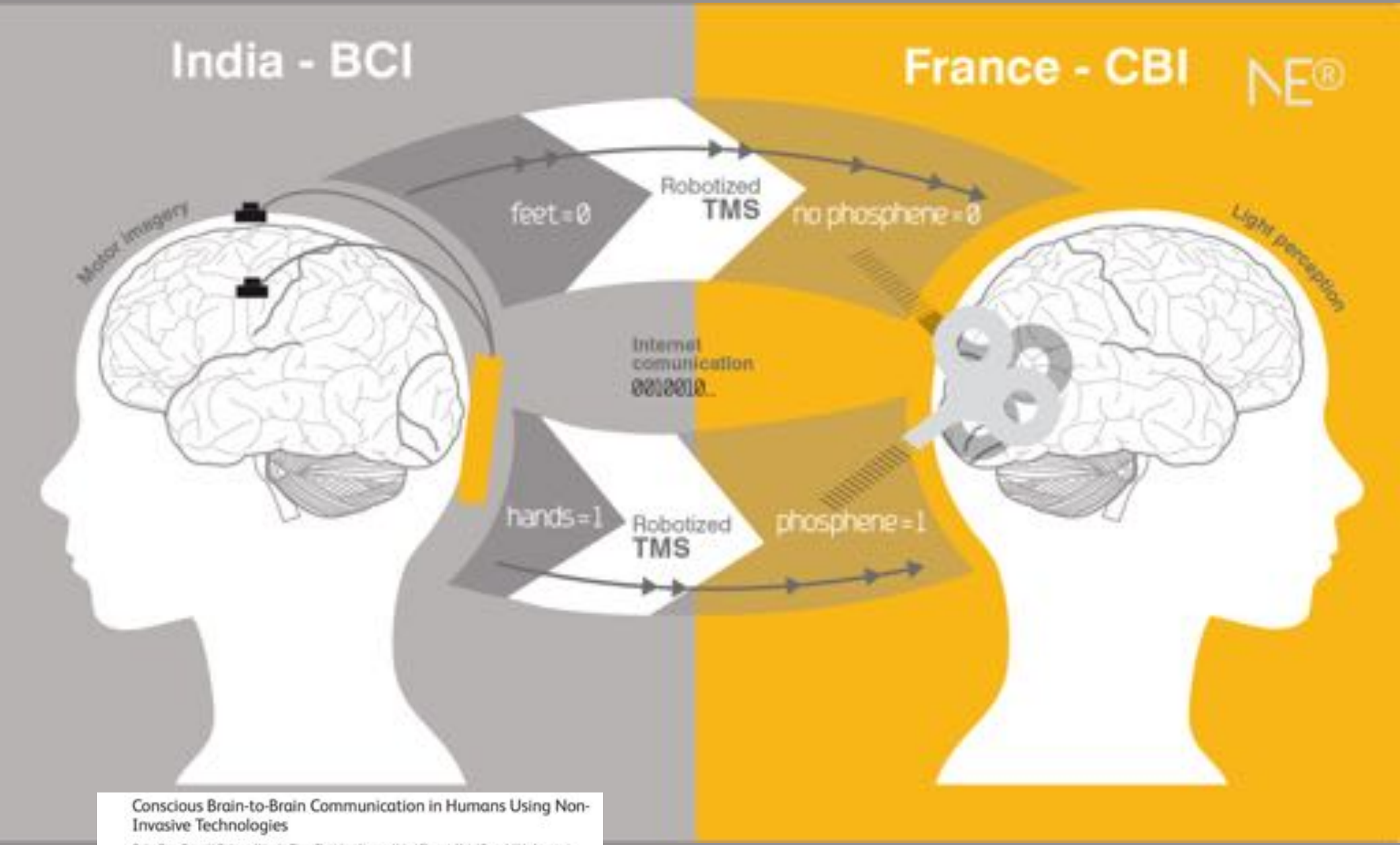


Figure 2 | Synchronization of slow oscillatory EEG activity. **a**, EEG recordings during the last seconds of a 5-min stimulation period (shaded areas) and first few seconds of a stimulation-free interval of two individua at prefrontal sites (Fz). **b**, Corresponding mean ±s.e.m. across all subject 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.

tCS and B2B





Conscious Brain-to-Brain Communication in Humans Using Non-Invasive Technologies

Carles Grau, Romuald Ginhoux, Alejandro Riera, Thanh Lan Nguyen, Hubert Chauvat, Michel Berg, Julià L. Amengual, Alvaro Pascual-Leone, Giulio Ruffini

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Synthetic tactile perception induced by transcranial alternating-current stimulation can substitute for natural sensory stimulus in behaving rabbits

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The use of brain-derived signals for controlling external devices has long attracted the attention from neuroscientists and engineers during last decades. Although much effort has been dedicated to establishing effective brain-to-computer communication, computer-to-brain communication feedback for "closing the loop" is now becoming a major research theme. While intracortical microstimulation of the sensory cortex has already been successfully used for this purpose, its future application in humans partly relies on the use of non-invasive brain stimulation technologies. In the present study, we explore the potential use of transcranial alternating-current stimulation (tACS) for synthetic tactile perception in alert behaving animals. More specifically, we determined the effects of tACS on sensory local field potentials (LFPs) and motor output and tested its capability for inducing tactile perception using classical eyeblink conditioning in the behaving animal. We demonstrated that tACS of the primary somatosensory cortex vibrissa area could indeed substitute natural stimuli during training in the associative learning paradigm.

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Transcranial direct current stimulation of the motor cortex in waking resting state induces motor imagery

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ABSTRACT

This study investigates if anodal and cathodal transcranial direct current stimulation (tDCS) of areas above the motor cortex (C3) influences spontaneous motor imagery experienced in the waking resting state. A randomized triple-blinded design was used, combining neurophysiological techniques with tools of quantitative mentation report analysis from cognitive linguistics. The results indicate that while spontaneous motor imagery rarely occurs under sham stimulation, general and athletic motor imagery (classified as athletic disciplines), is induced by anodal tDCS. This insight may have implications beyond basic consciousness research. Motor imagery and corresponding motor cortical activation have been shown to benefit later motor performance. Electrophysiological manipulations of motor imagery could in the long run be used for rehabilitative tDCS protocols benefitting temporarily immobile clinical patients who cannot perform specific motor imagery tasks – such as dementia patients, infants with developmental and motor disorders, and coma patients.

Physics > Biological Physics

Application of the reciprocity theorem to EEG inversion and optimization of EEG-driven transcranial current stimulation (tCS, including tDCS, tACS, tRNS)

Giulio Ruffini

(Submitted on 16 Jun 2015 (v1), last revised 17 Jun 2015 (this version, v2))

Multichannel transcranial current stimulation (tCS) systems offer the possibility of EEG-guided optimized, non-invasive brain stimulation. In this brief technical note I explain how it is possible to use tCS electric field realistic brain model to create a forward "lead-field" matrix and, from that, an EEG inverter for cortical mapping. Starting from EEG I show how to generate 2D cortical surface dipole fields that could produce the observed EEG electrode voltages. The main tool is the reciprocity theorem derived by Helmholtz. The application of reciprocity for the generation of a forward mapping matrix (lead field matrix as is sometimes known) is well known [Rush and Driscoll, 1969], but here we will use it in combination with the realistic head models of [Miranda et al 2013] to provide cortical mapping solutions compatible with realistic head model tCS optimization. I also provide a generalization of the reciprocity theorem [Helmholtz 1853] to the case of multiple electrode contact points and dipole sources, and discuss its uses in non-invasive brain stimulation based on EEG. This, as far as I know, is a novel result. Applications are discussed.

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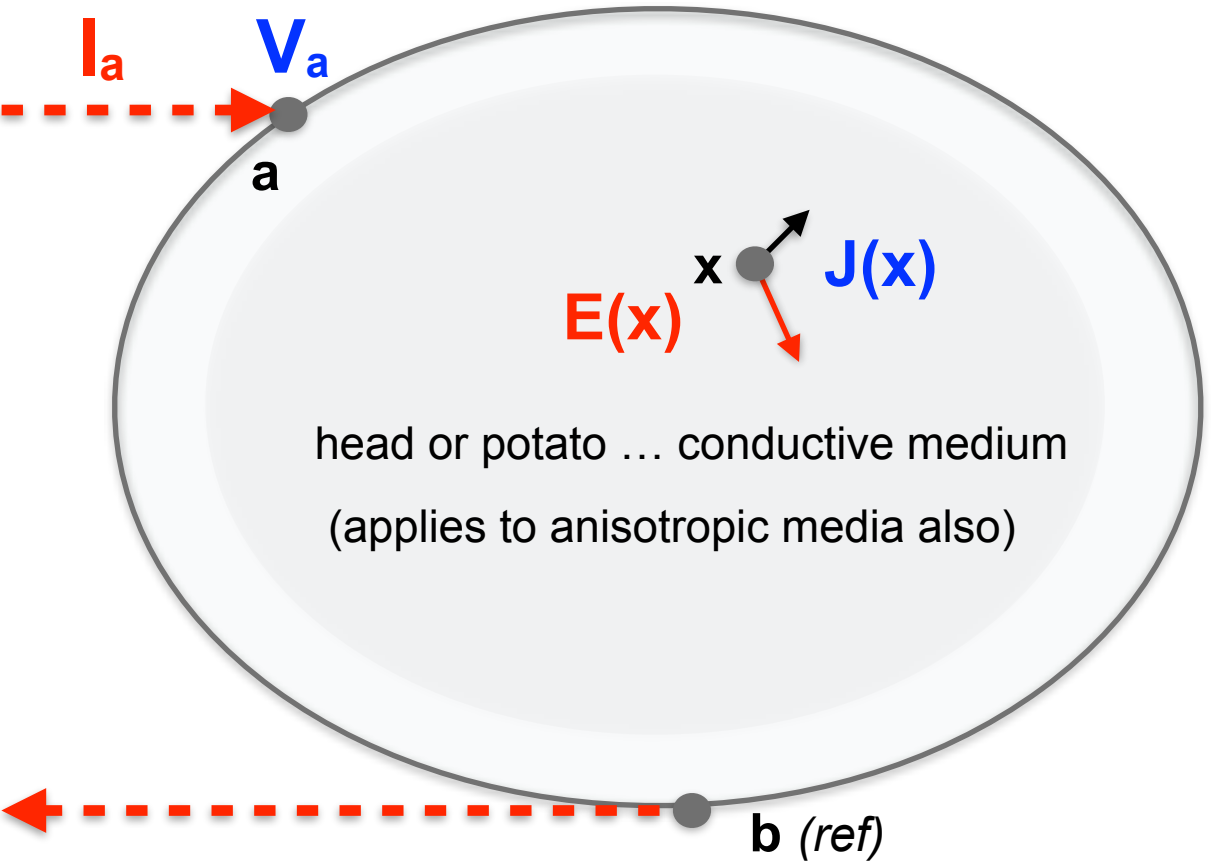
Reciprocity theorem (Hemholtz 1853)

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),

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

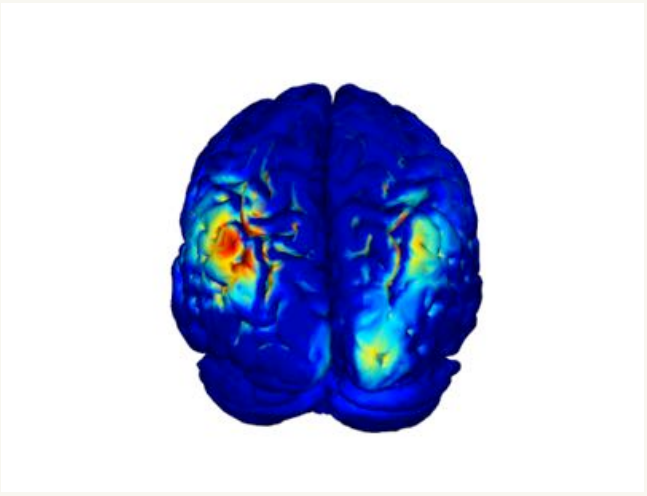
Here E(x) are the electric fields generated by I_a currents, and V_a the scalp potentials generated by the EEG sources J(x).

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).

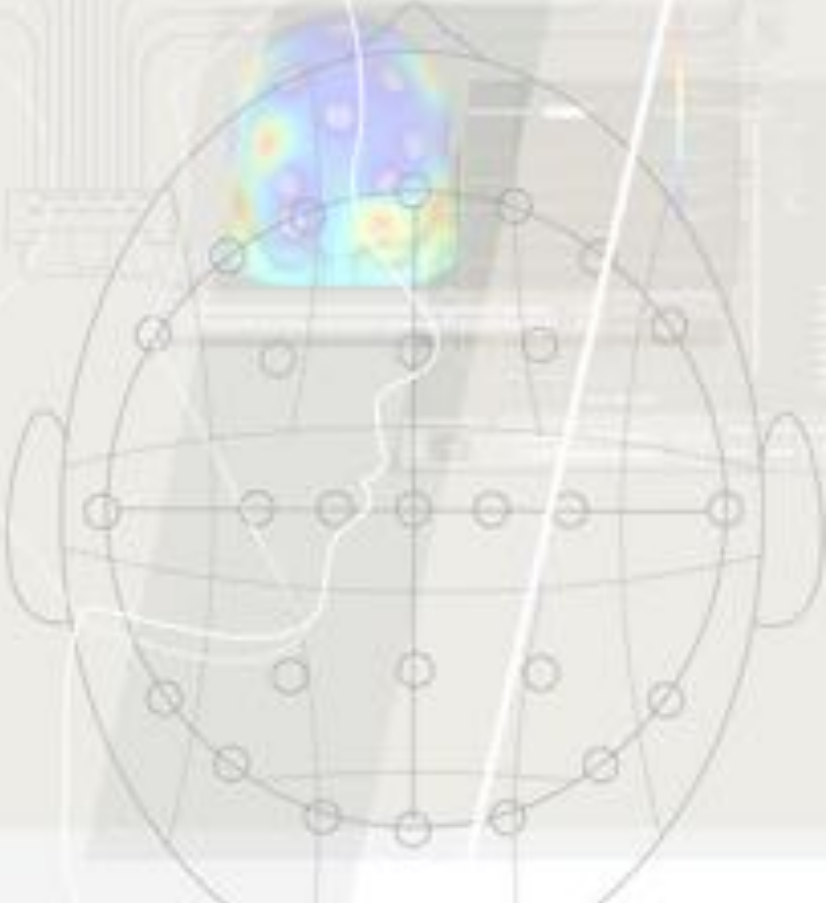
A limitation is that you will not really know what size electric fields you are generating, cannot add a weight map to work with weighted correlation, etc. But still, give some constraints on currents it provides a recipe to optimize currents to EEG sources. This can be especially useful in close-loop 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! Now possible with Starstim 2 (2016)
4. Theoretical analysis (e.g., number of electrodes?)



The future



The Future

- Models represent the state of the art in our understanding what tCS produces physically. They will be improved over time using the scientific method. Validation ongoing!
- 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.

Thank you!

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