Neuroelectrics –iOM workshop

Ana Maiques

March 1st, 2015

Developing Non-Invasive Neuromodulation Devices for Therapeutic Uses

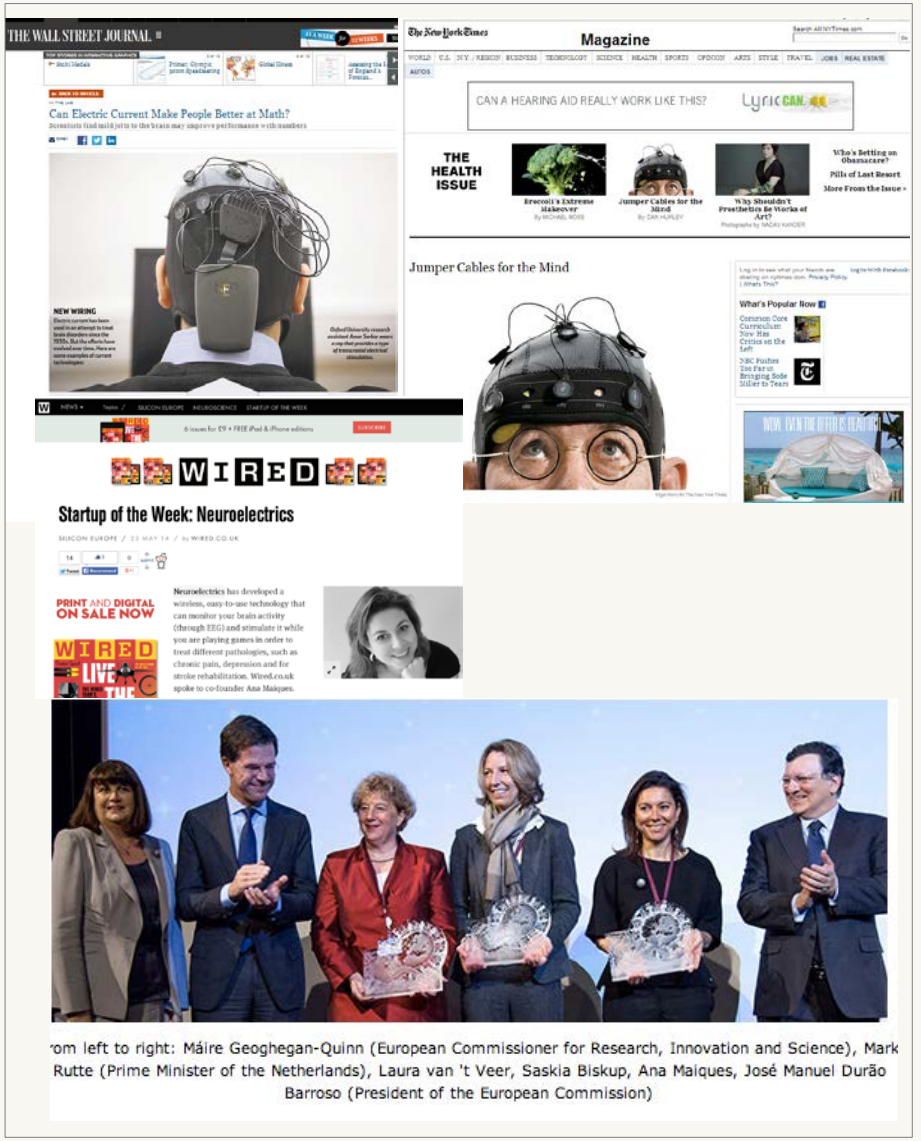
NE: the company

Entrepreneurs with strong background in Neuroscience Research and support from the European Commission

Barcelona born and rapidly growing **Boston 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

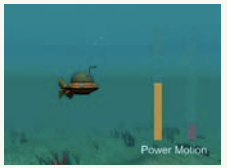
Committed to deliver high quality scientific based technologies and transform them into novel therapies and diagnostic tools

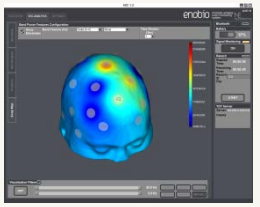


om left to right: Máire Geoghegan-Quinn (European Commissioner for Research, Innovation and Science), Mark Rutte (Prime Minister of the Netherlands), Laura van 't Veer, Saskia Biskup, Ana Maiques, José Manuel Durão Barroso (President of the European Commission)

Our current product, **software** and **cloud solutions**

NUBE EEG





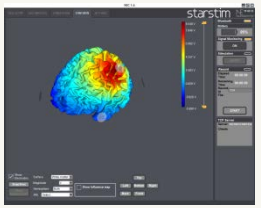
EEG Monitoring

enobio NE®

ROBUST
PRECISE
WIRELESS
EEG

8, 20 & 32 ch. versions

NIC Home



tCS Stimulation

starstim NE®

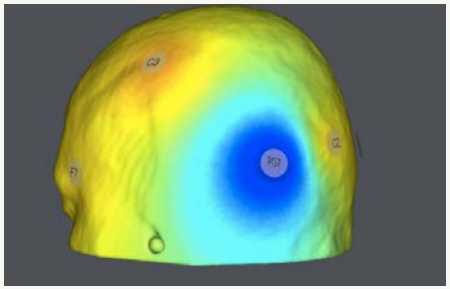
NONINVASIVE
WIRELESS tCS
NEUROSTIMULATOR

tCS research, clinic and home research versions (EEG&tCS in one)

Neuroelectrics platform: the e-brain

Diagnostic (EEG monitoring)

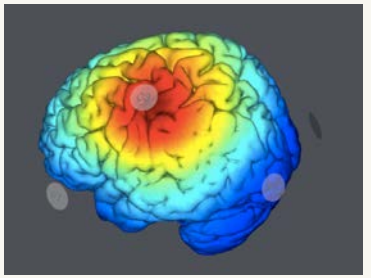
- Propietary Wireless Easy to use EEG of 8/20/32 electrodes medical graded (EU) device
- Dry electrodes
- Capable of home out of the hospital recording
- Real time 3D visualisation of brainwaves features
- Propietary EEG data analysis
- Linked to Neurosurfer (neurofeedback games) and Oculus VR platform



NUBE cloud

Only cloud controlled wireless EEG and stimulation technology in the market targeting home use

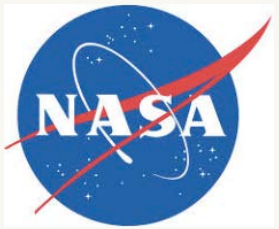
- **Therapy (Electrical Stimulation)**
  - ✓ Propietary Wireless Easy to use tCS medical graded (EU) device
  - ✓ DC, AC, RN electrical stimulation + EEG in 8 channels
  - ✓ Monitoring and Stimulating and the same time
  - ✓ Cloud controlled home stimulation platform
  - ✓ Proprietary electric field simulation models for personalized protocols



Sales Coverage

Quality **clients**

Boston Children Hospital



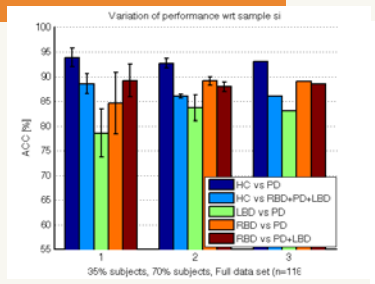
Opportunities: EEG as a diagnostic tool

- Dynamic and direct measure on brain activity
- Allows for long term studies out of lab/clinic
- EEG is intensely used to research brain function, and clinically for sleep and epilepsy, for example
- Cost-efficient technology
- Research domain criteria

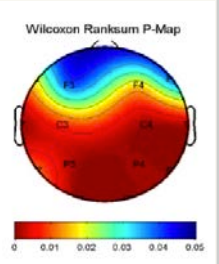
Parkinson Disease

- Michael J. Fox Foundation funding to our sister company
- Preliminary EEG data showing early prediction of PD eight years prior to disease symptoms (118 patients study with 99% accuracy).
- Multi-site Follow up large study approved by Michael J.Fox Foundation

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH



N = 118



Multielectrode tCS multifocal

Targeted multi electrode montages offer the opportunity for more precise, meaningful stimulatio

Brain function is mediated by networks: let's go after them!!

Contents lists available at ScienceDirect

NeuroImage

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

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

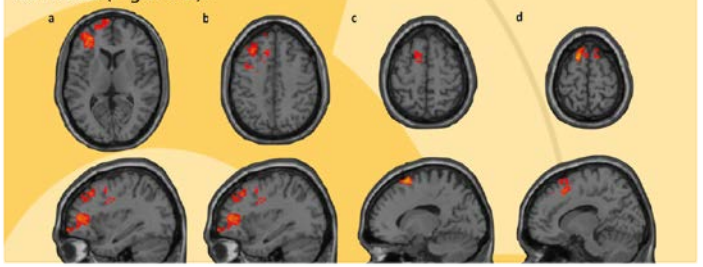
Giulio Ruffini [a,b,*], Michael D. Fox [c,d], Oscar Ripolles [b], Pedro Cavaleiro Miranda [b,e], Alvaro Pascual-Leone [d,f]

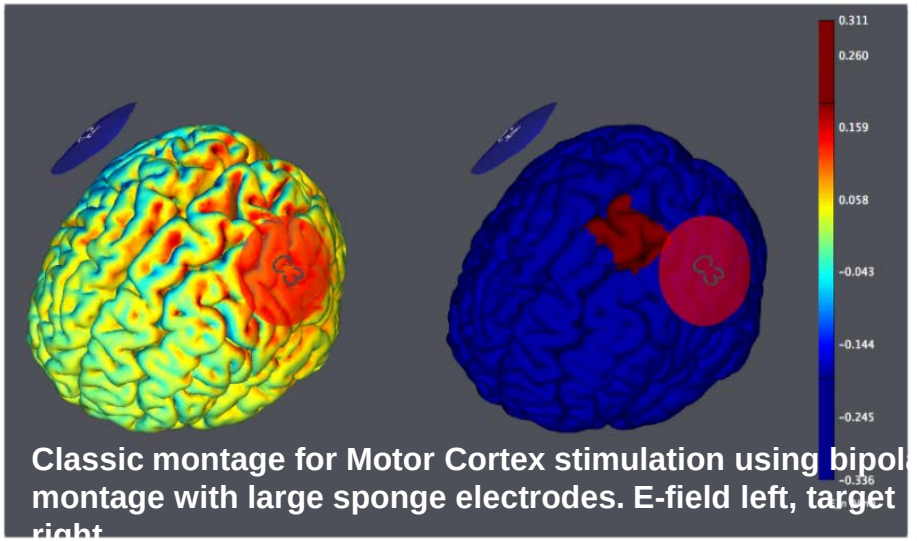
Optimized multielectrode tDCS modulates corticolimbic networks

G. Ruffini*[a,b], C. Martinez-Ruiz de Lara[c], I. Martinez-Zalacain[c], O. Ripolles[a], M. Subira[c], E. Via[c], G. Mitja[a], J. Munuera[e], J. M. Menchón[c,d], C. Soriano-Mas[c,d], Narcis Cardoner[c,d]

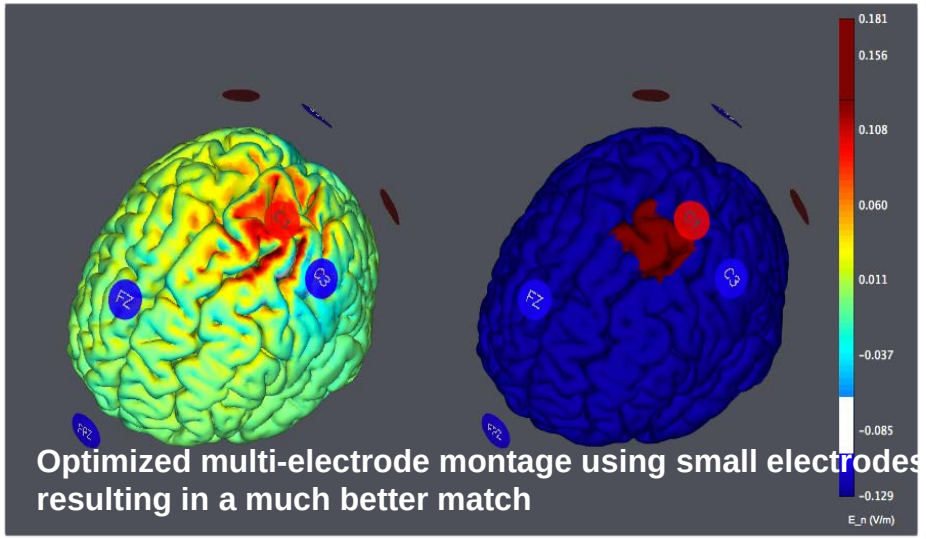
Results

The multielectrode montage resulted in significantly higher fALFF values in frontopolar, middle and superior prefrontal cortices (Figure 2).





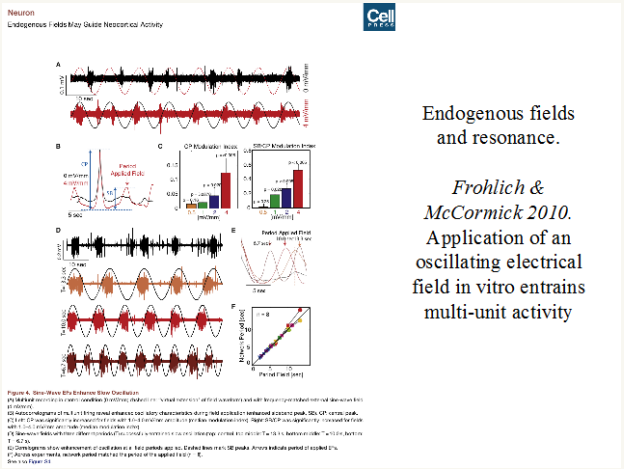
Classic montage for Motor Cortex stimulation using bipolar montage with large sponge electrodes. E-field left, target right



Optimized multi-electrode montage using small electrodes, resulting in a much better match

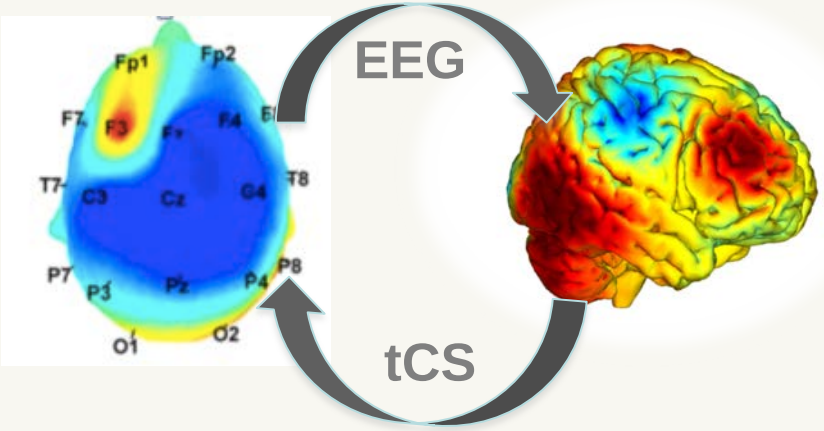
EEG & tCS: closing the loop

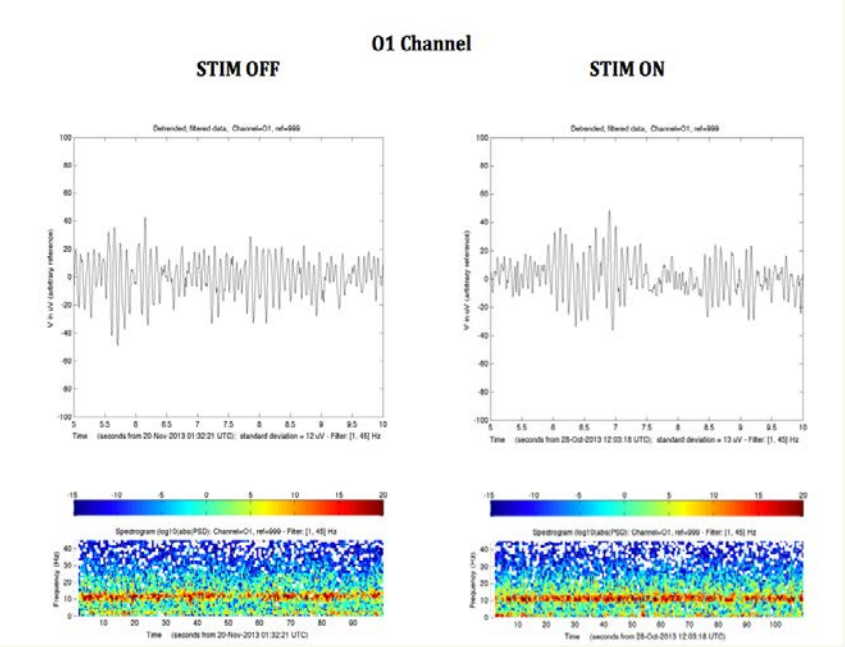
- Concept: Use EEG to adapt tCS parameters to better target some cortical circuits.
- Uses as feedback inputs EEG activity, accelerometry, EMG or others
- Parameters to optimize can include intensity at different electrodes, frequencies, phases, etc.
- Can be applied with tDCS, tACS, tRNS or endogenous waves
- Resonance phenomena with tACS already seen in vitro and in humans and predicted by models



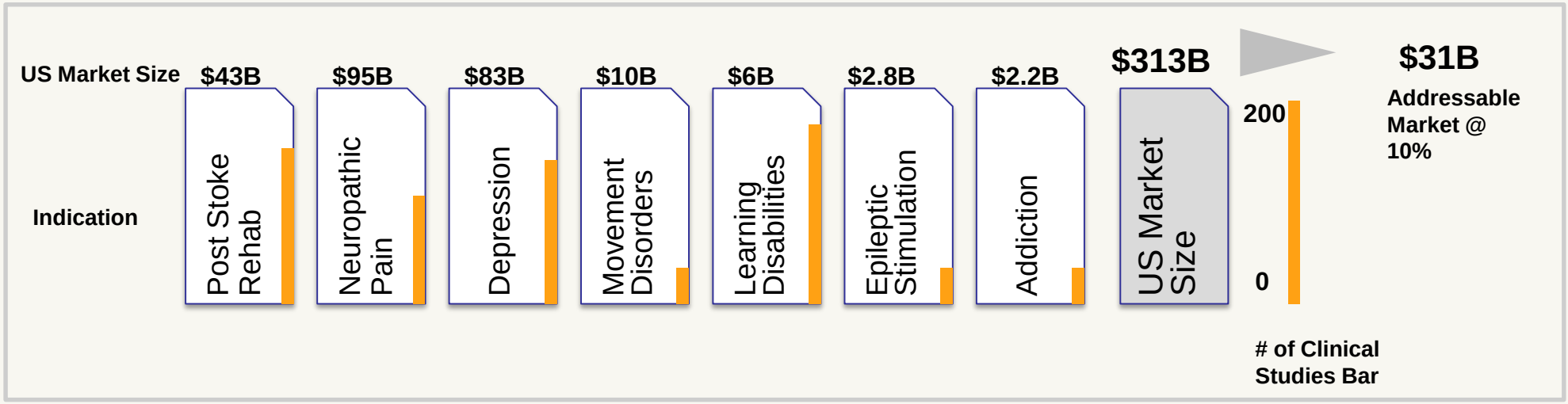
Endogenous fields and resonance.

Frohlich & McCormick 2010. Application of an oscillating electrical field in vitro entrains multi-unit activity





Opportunities for **therapeutic use**



Publications so far

(as gathered by PubMed Jan 2015)

Pain: 127

Depression: 137

Stroke rehabilitation: 194

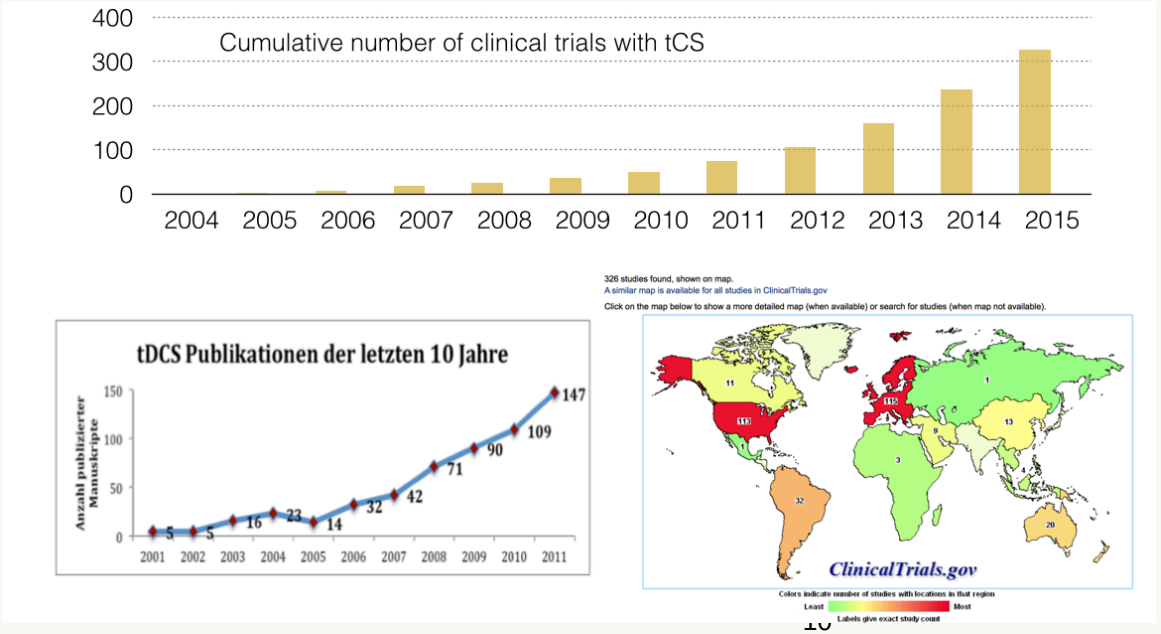
Cognitive Enhancement: 200

Addictive disorders: 18

Epilepsy: 20

Parkinson's: 28

Alzheimer's: 16



From the **Basic Science**

MILLER LAB

nature neuroscience

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

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.

Frequency-specific hippocampal-prefrontal interactions during associative learning

Scott L Brincat[1,2] & Earl K Miller[1,2]

Universität Göttingen

To **clinical translation**-BIMDC

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

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]

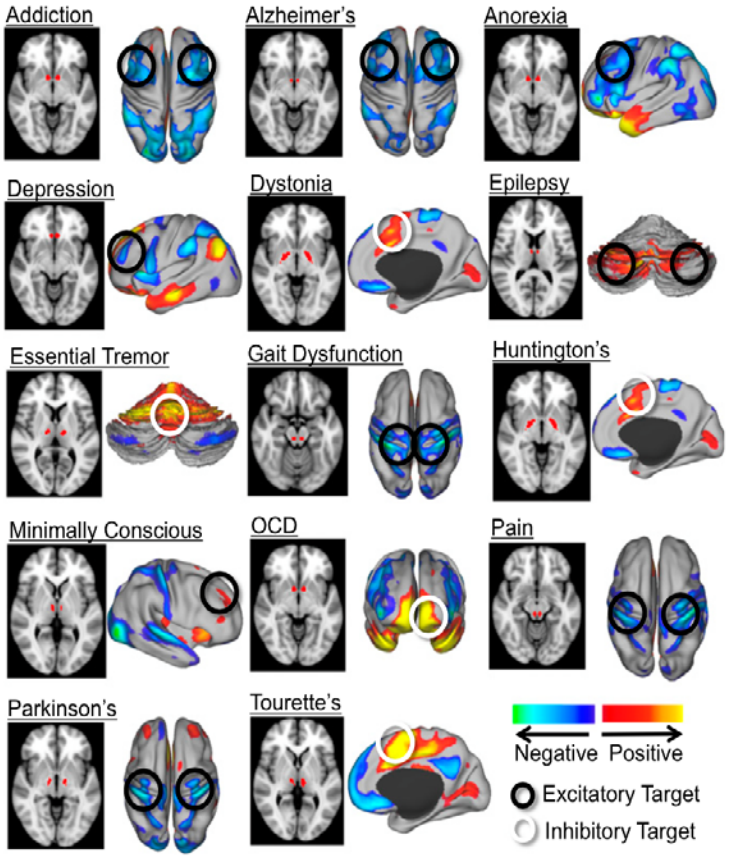
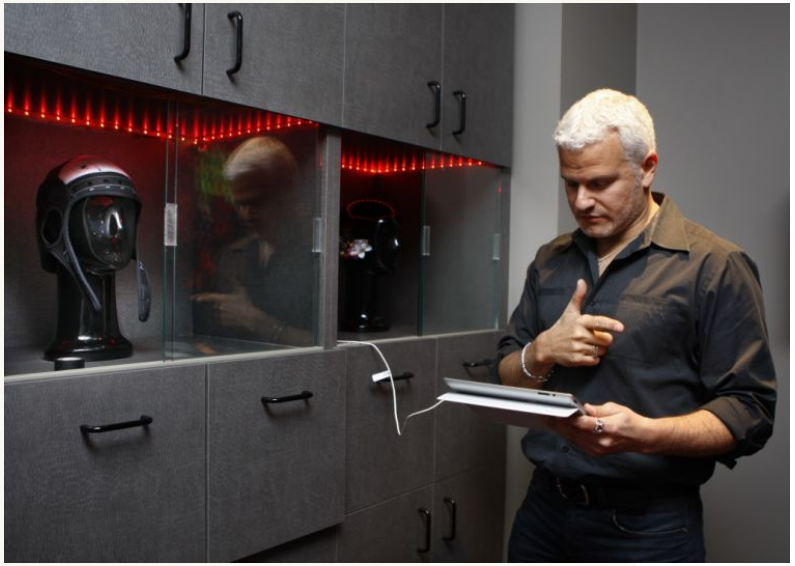


Fig. 2. Sites for invasive and noninvasive brain stimulation with the best evidence of therapeutic efficacy in each disease are functionally connected. For each disease, the site at which DBS is most effective is shown in red. Resting-state functional connectivity with this site is shown along with the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

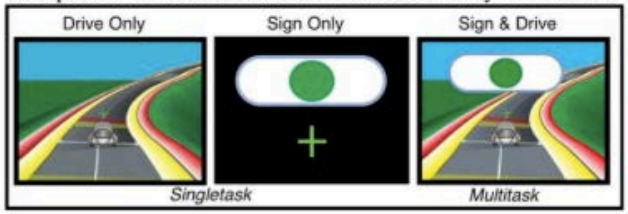
Cognitive enhacement in older adults



UCSF

Video game training enhances cognitive control in older adults

Based on our research characterizing top-down modulation deficits in older adults, we designed a therapeutic intervention for these individuals to try and address these observed deficiencies. These efforts led to the creation of a custom-designed three-dimensional video game (NeuroRacer) that requires participants to perform a perceptual discrimination task and a visuomotor adaptation task both by themselves as well as simultaneously (that is, multitasking).



tCS for Cognition Enhancement – **Numerical Competence**

Clinical Neurophysiology

Volume 124, Issue 10, October 2013, Pages e58–e59

OP 6. Stimulating the brain while playing a computer-based maths game to enhance domain-specific and domain-general cognitive abilities

C.Y. Looi[a], M. Duta[a], S. Huber[b], H.-C. Nuerk[b], R. Cohen Kadosh[a]

Published as: *Curr Biol.* 2010 November 23; 20(22): 2016–2020.

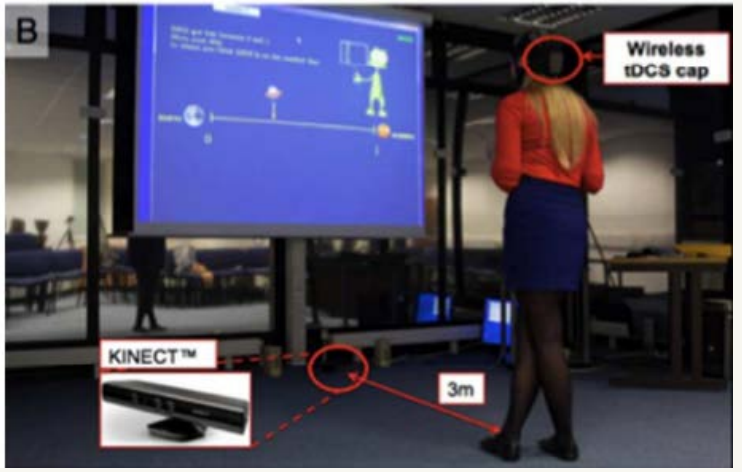
Modulating Neuronal Activity Produces Specific and Long-Lasting Changes in Numerical Competence

Roi Cohen Kadosh[1,*], **Sonja Soskic**[2], **Teresa Iuculano**[1,3], **Ryota Kanai**[3], and **Vincent Walsh**[3]

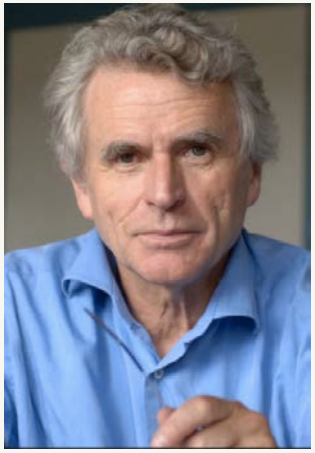
[1]Department of Experimental Psychology and Oxford Centre for Functional MRI of the Brain, University of Oxford, Oxford OX1 3UD, UK

[2]University College London Medical School, Department of Life Sciences, University College London, London WC1E 6BT, UK

[3]Institute of Cognitive Neuroscience, University College London, London WC1N 3AR, UK



To better Brain Computer Interface



Prof. Niels Birbaumer

Dr. Surjo Soekadar

EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

- Soekadar SR, Witkowski M, Vitiello N, Birbaumer N. **An EEG/EOG-based hybrid brain-neural computer interaction (BNCI) system to control an exoskeleton for the paralyzed h**and. Biomed Tech (Berl). 2014; doi: 10.1515/bmt-2014-0126 [in press].
- Witkowski M, Cortese M, Cempini M, Mellinger J, Vitiello N, Soekadar SR. **Enhancing brain-machine interface (BMI) control of a hand exoskeleton using electrooculography (EOG)**. Journal of NeuroEngineering and Rehabilitation 2014, 11:165, doi:10.1186/1743-0003-11-165.
- Soekadar SR, Birbaumer N, Slutzky MW, Cohen LG. Brain-**Machine Interfaces In Neurorehabilitation of Stroke**. Neurobiol Dis. 2014; doi: 10.1016/j.nbd.2014.11.025 [in press].

Stroke Rehab

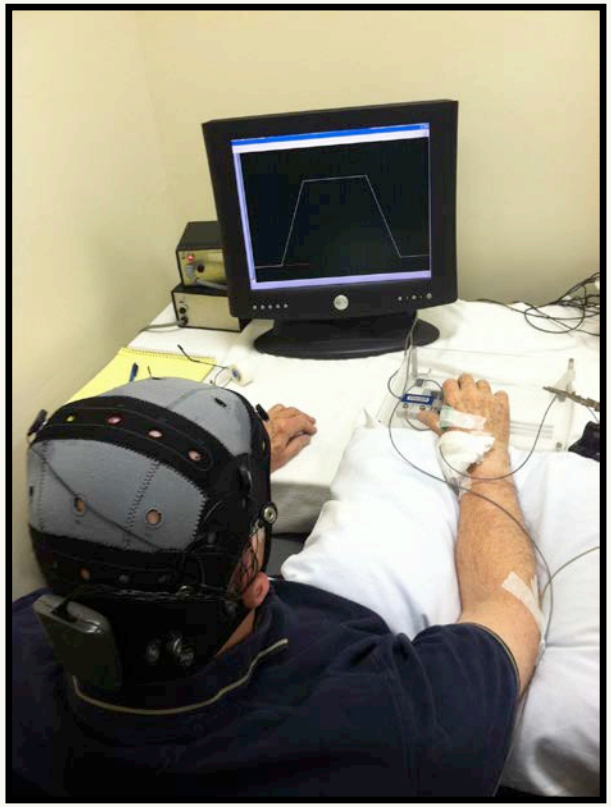
The difference in rehab is BURKE

Intensity dependent effects of tDCS on corticospinal excitability in chronic Spinal Cord Injury

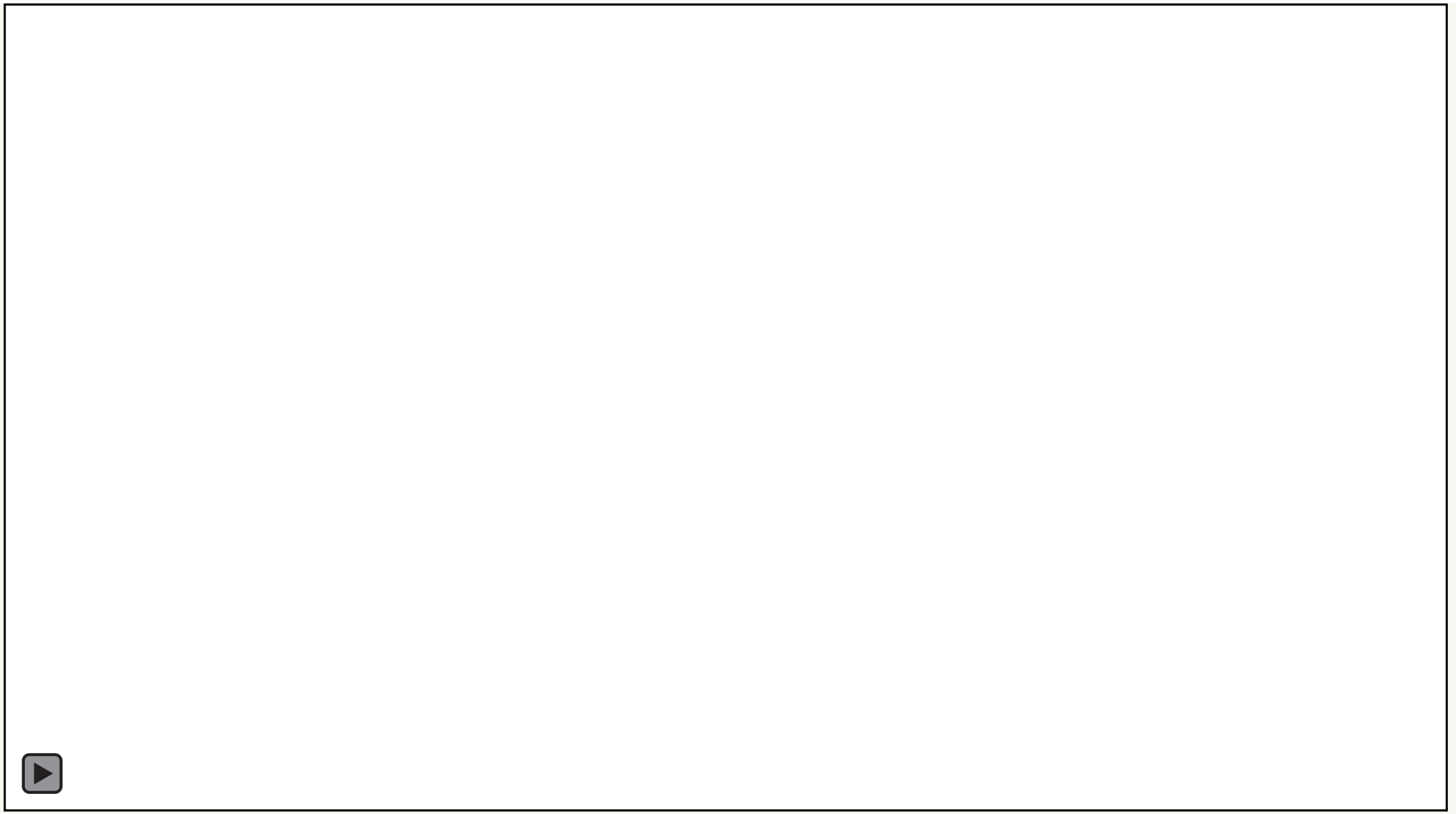
Preliminary results were presented in a poster at the ASNR (American Society of Neurorehabilitation) 2013 meeting in San Diego and the 30th International Congress of Clinical Neurophysiology Conference 2014.

Lynda M. Murray, PhD, Dylan J. Edwards, PhD, Giulio Ruffini, PhD, Douglas Labar, MD PhD, Argyrios Stampas, MD, Alvaro Pascual-Leone, MD PhD, Mar Cortes, MD

Received: May 23, 2014; Received in revised form: October 7, 2014; Accepted: November 3, 2014; Published Online: November 22, 2014

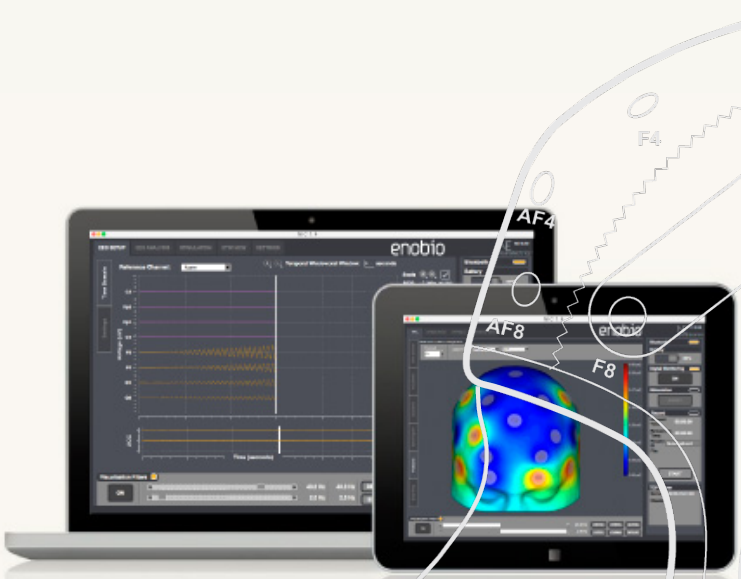


Neurophatic pain



Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury (Soler et al, 2010)

Future Home



- Long-term effects and 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
- With repeated use, modulation of brain activity with tCS alters brain connectivity

Safety aspects

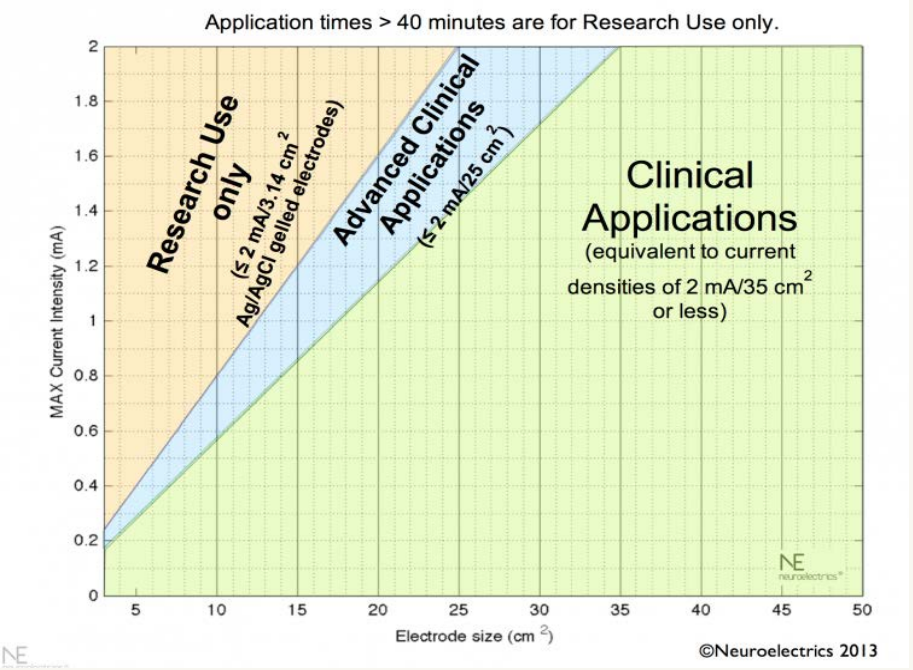
After thousands of hours of stimulation, short term ill effects associated to tCS in <u>controlled</u> settings remain scarce and minor

Devices need to implement safety measures

Starstim designed for safety:

- Current at electrode < 2 mA
- Max injected current < 4 mA
- Programmend duration < 1 h
- Impedance check before stimulation
- Impedance check during stimulation
- For use with our electrodes and cap only

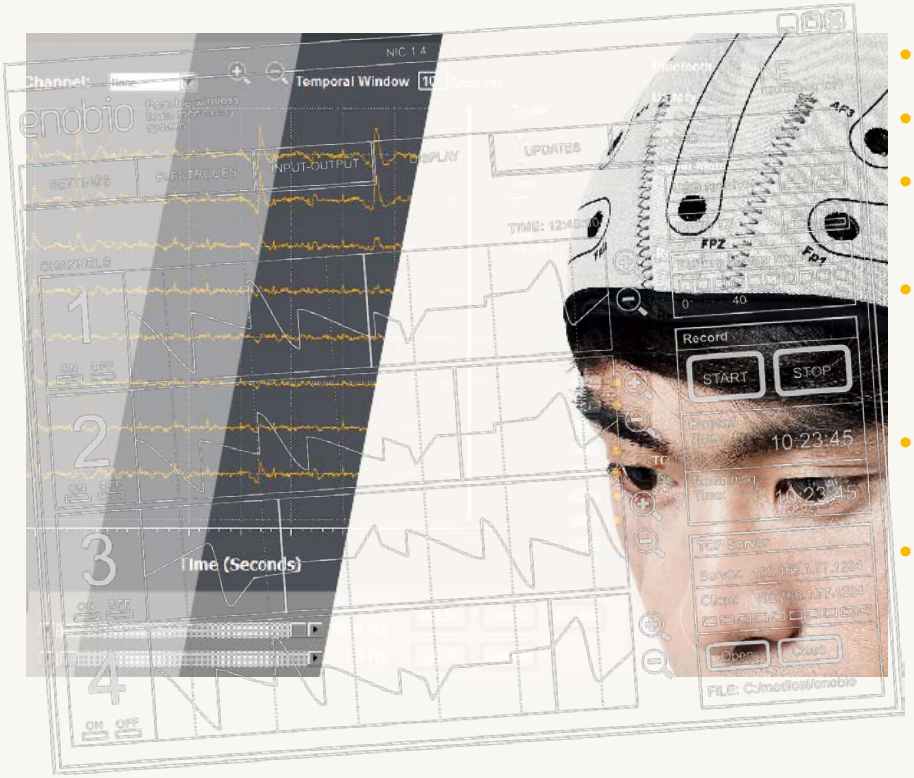
– Our safety record is excellent



Safety-**short term**

- Short term tDCS safety is well established using good practices both with sponges or Ag/AgCl electrodes +gel.
- Ill effects limited to skin irritation or small burns in rare cases (probably due to wrong placement of sponges)
- Safety verified in adults with intact skulls, no implants, etc. Other grups much less studied.
- Research studies carefully specify and limit duration, intensity, repetition of sessions.
- Other forms of tCS (such as tACS, tRNS) less studied

Long term Safety



- Long term safety not so clear
- tCS has demonstrated physiological effects
- **Stimulation affects brain connectivity and brain function.**
- Effects depend on many factors: montange, intensity, duration, repetition framework, brain state. Age probably important.
- Response function of brain not 100% understood. E.g., intensity: more is less? Enhacement at a price (Ioculano & Kadosh 2013)?
- Classical paradigms employing large stimulation areas probably affect large areas of the brain
- Need to understand these phenomena well in a controlled fashion (i.e., medical, research settings) bofore unleashing tCS to the public.

What “**controlled fashion**” means

Today: lab, clinical settings

Transition to **tele-monitored home use** to better understand impact of repeated use in natural settings (NE has already begun doing this with partners)

Use of repeatable montages; protocols aiming for specificity of stimulation effects (e.g., targeted rather than “shotgun”).

[Protocol = specification of electrode type, positions, current type and intesity, duration, session sequencing.]

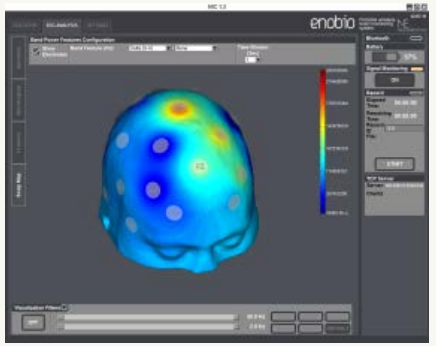
Modeling of electric fields

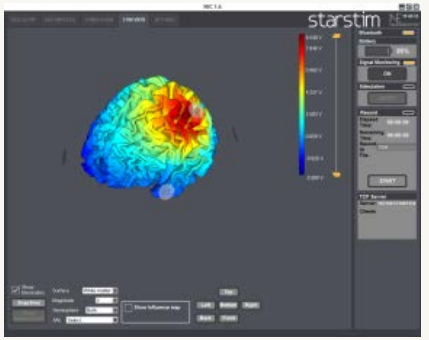
Coregistration to study physiological effects such as EEG, fMRI, etc.

Safety documentation to continue checking for short term effects

Ethical issues

- Participation in NERRI EU project
- Participation in Public Events
- At European level we collaborate with experts such Prof. Julian Savulesco
- Control over sales



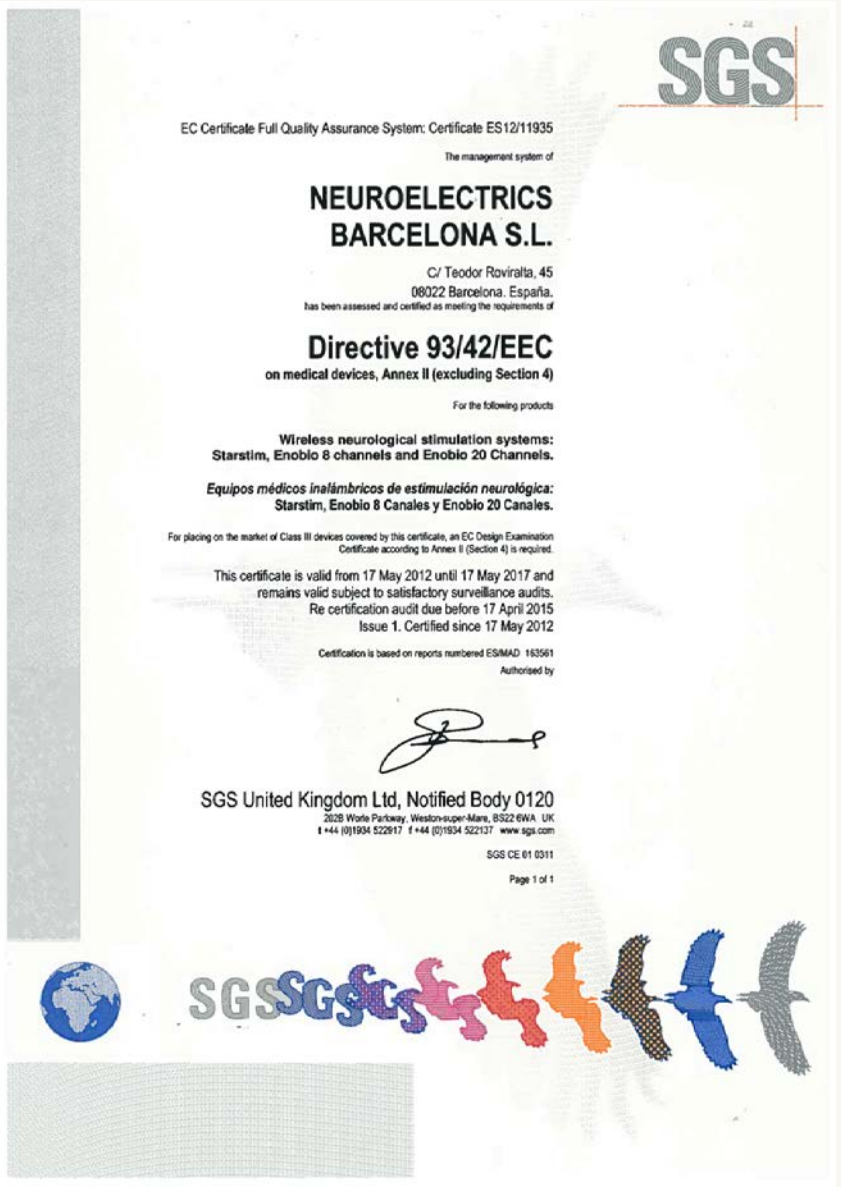


Regulatory & Reimbursement

- Medical device manufacturing license (Spanish Ministry of Health)

- QMS = ISO 13485 (ISO 9001 also included) *FDA uses GMP's*

- CE Mark (93/42/EEC) *Not valid for FDA*
- CLINICAL EVALUATION *Not valid for FDA*
- IEC 60601-1 (international standard on product safety) *Not 100% compatible with FDA*



SGS

EC Certificate Full Quality Assurance System: Certificate ES12/11935

The management system of

NEUROELECTRICS BARCELONA S.L.

C/ Teodor Roviralta, 45
08022 Barcelona. España.

has been assessed and certified as meeting the requirements of

Directive 93/42/EEC
on medical devices, Annex II (excluding Section 4)

For the following products

Wireless neurological stimulation systems:
Starstim, Enobio 8 channels and Enobio 20 Channels.

Equipos médicos inalámbricos de estimulación neurológica:
Starstim, Enobio 8 Canales y Enobio 20 Canales.

For placing on the market of Class III devices covered by this certificate, an EC Design Examination Certificate according to Annex II (Section 4) is required.

This certificate is valid from 17 May 2012 until 17 May 2017 and remains valid subject to satisfactory surveillance audits.
Re certification audit due before 17 April 2015
Issue 1. Certified since 17 May 2012

Certification is based on reports numbered ES/MAD 163561

Authorised by

SGS United Kingdom Ltd, Notified Body 0120
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t +44 (0)1934 522917 f +44 (0)1934 522137 www.sgs.com

SGS CE 01 0311

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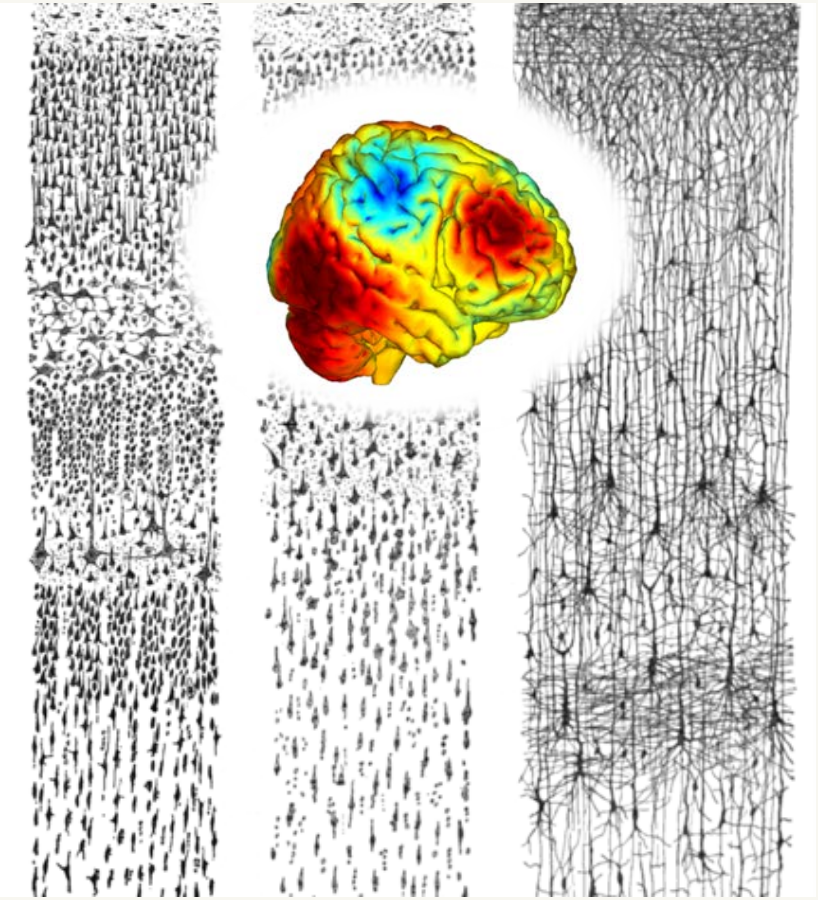
Conclusions

- tCS holds great potential for therapy in ways not possible before. We focus on EEG + multielectrode tCS solutions to help patients (clinic & home).
- Excellent scientific work (many KOL here today) and safety record. Need to keep funding more scientific/clinical longitudinal studies
- Regulatory agencies should carefully take a look into therapeutic and non therapeutic devices
- Create specific frameworks for novel start up companies willing to approach novel treatments combining medical devices & telemedicine services
- We are eager to help to push the field forward!



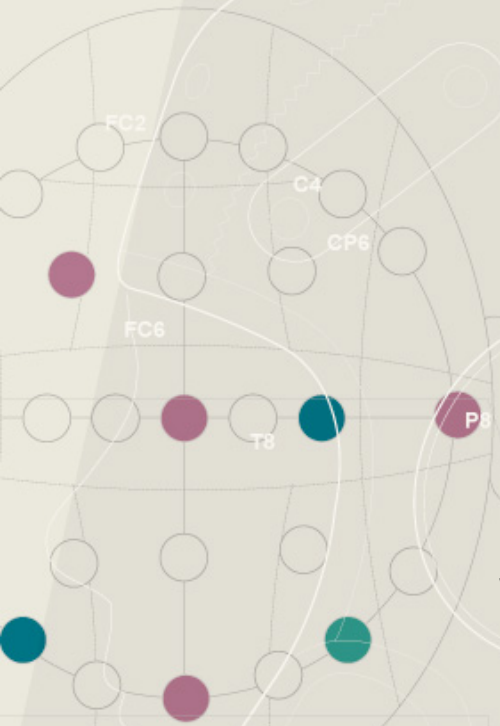
Ramon y Cajal (1899)

Thank you for your attention

ana.maiques@neuroelectrics.com

For more info, visit :

www.neuroelectrics.com



A new paradigm to monitor and stimulate the brain

We are committed to change the way in which we monitor and stimulate our brains, providing innovative and affordable diagnosis and treatment technologies for all patients in need.