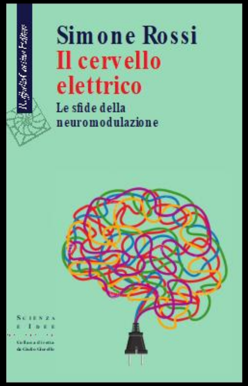
Non-invasive Brain Stimulation

Simone Rossi

Simone.rossi@unisi.it

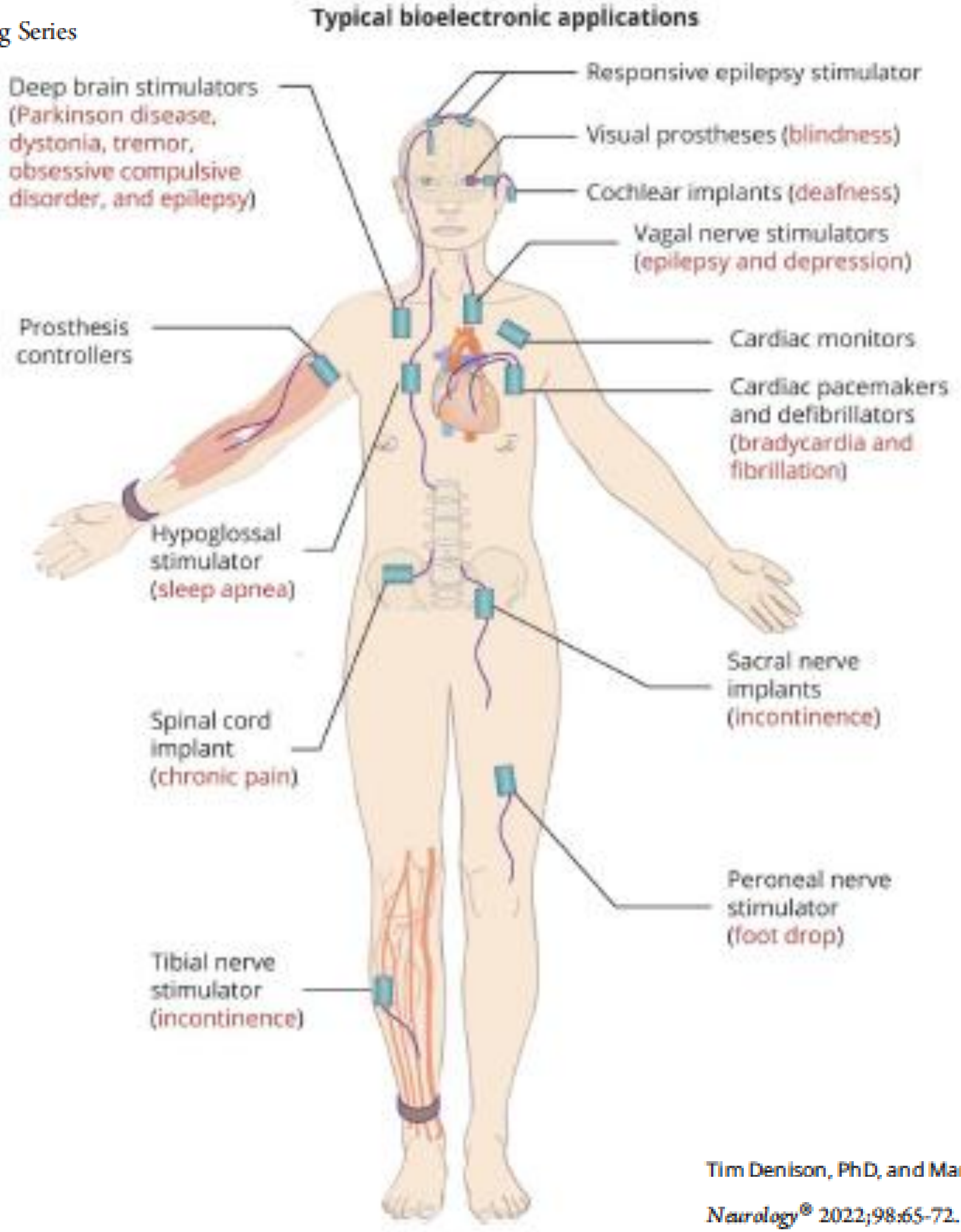
Brain Investigation & Neuromodulation Lab
Univesity of Siena –Italy-

www.sibinlab.it



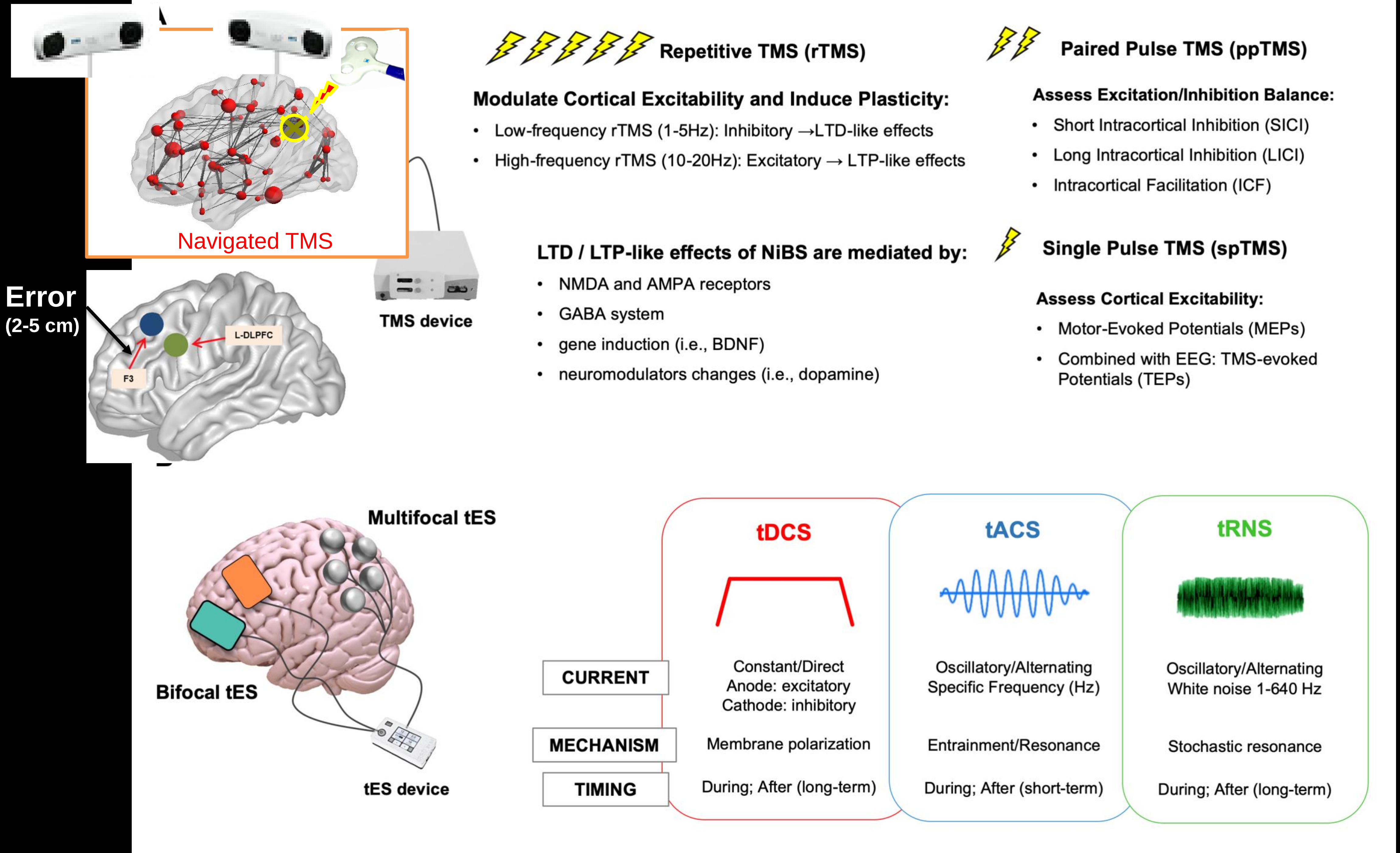
Neuromodulation in 2035

The Neurology Future Forecasting Series

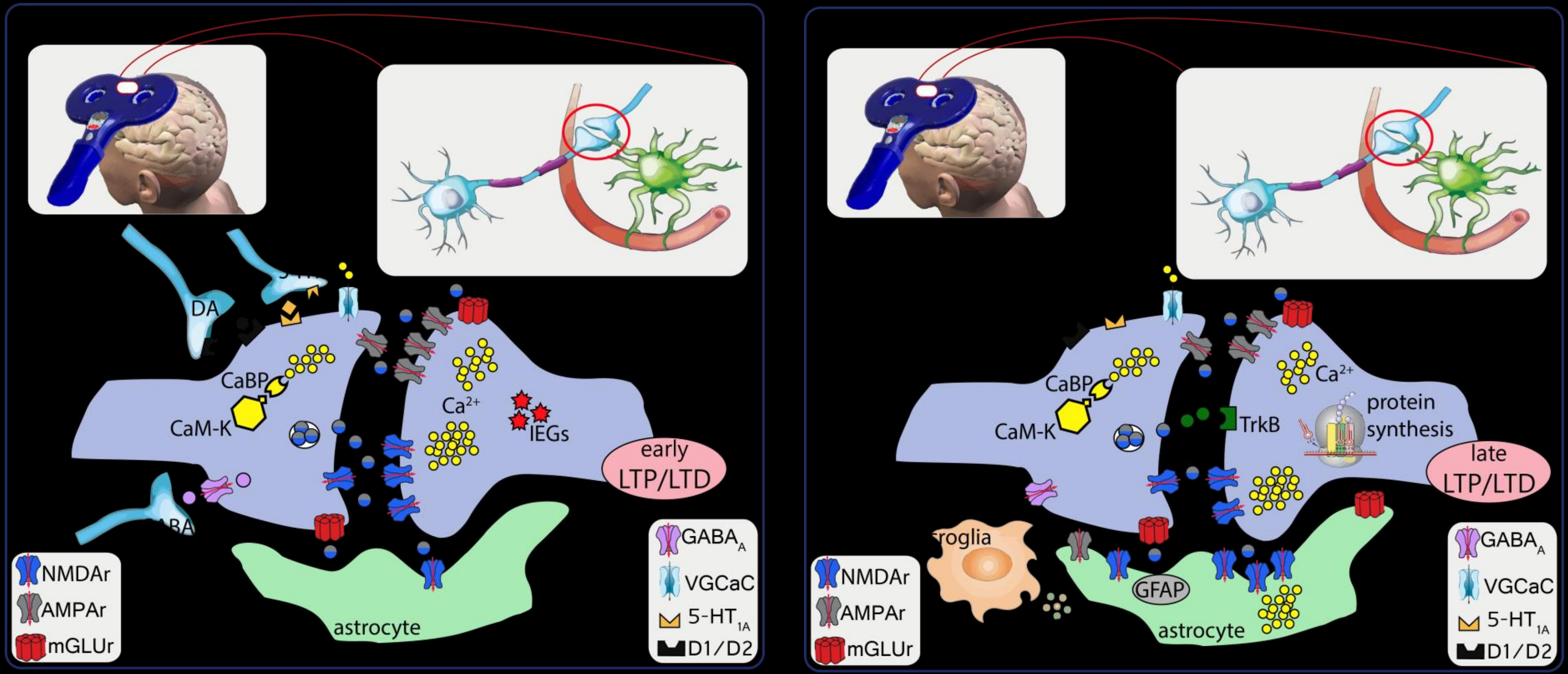


Tim Denison, PhD, and Martha J. Morrell, MD

Neurology® 2022;98:65-72. doi:10.1212/WNL.0000000000013061


Navigated TMS
Error
(2-5 cm)
L-DLPFC
F3
TMS device
Repetitive TMS (rTMS)
Modulate Cortical Excitability and Induce Plasticity:
• Low-frequency rTMS (1-5Hz): Inhibitory →LTD-like effects
• High-frequency rTMS (10-20Hz): Excitatory → LTP-like effects
LTD / LTP-like effects of NiBS are mediated by:
• NMDA and AMPA receptors
• GABA system
• gene induction (i.e., BDNF)
• neuromodulators changes (i.e., dopamine)
Paired Pulse TMS (ppTMS)
Assess Excitation/Inhibition Balance:
• Short Intracortical Inhibition (SICI)
• Long Intracortical Inhibition (LICI)
• Intracortical Facilitation (ICF)
Single Pulse TMS (spTMS)
Assess Cortical Excitability:
• Motor-Evoked Potentials (MEPs)
• Combined with EEG: TMS-evoked Potentials (TEPs)
Multifocal tES
Bifocal tES
tES device
tDCS
tACS
tRNS
CURRENT
Constant/Direct
Anode: excitatory
Cathode: inhibitory
Oscillatory/Alternating
Specific Frequency (Hz)
Oscillatory/Alternating
White noise 1-640 Hz
MECHANISM
Membrane polarization
Entrainment/Resonance
Stochastic resonance
TIMING
During; After (long-term)
During; After (short-term)
During; After (long-term)

Depending on the combination of frequecy/intensity, **the rTMS prodces long-lasting modification of synaptic efficacy** in the stimulated networks……..(LTP-LTD)



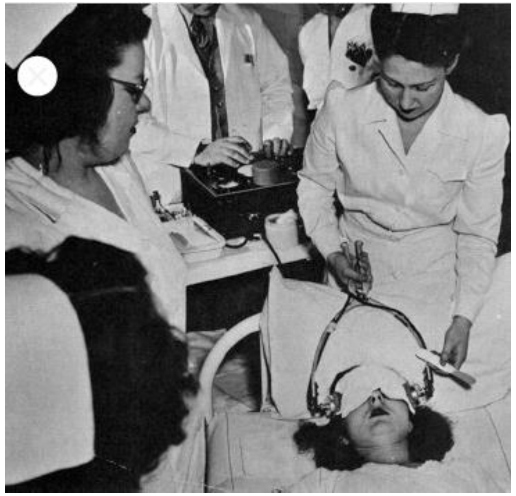
…….thereby restoring a more physiological operating mode (………as a drug)

Review

One century of healing currents into the brain from the scalp: From electroconvulsive therapy to repetitive transcranial magnetic stimulation for neuropsychiatric disorders

Riccardo Di Iorio [a,*], Simone Rossi [b], Paolo M. Rossini [c]

Clinical Neurophysiology 133 (2022) 145–151



La Neuromodulazione non è una terapia elettroconvulsivante (o Elettroshock)

- No anestesia
- No crisi comiziali
- No effetti avversi (memoria)

	Electroconvulsive Therapy (ECT)	Transcranial magnetic stimulation (TMS)
Mechanism	Electrically induced seizures	Non-convulsive electromagnetic stimulation
Stimulation target	Spread	Personalized (focal target/ individual threshold/ neuronavigation)
Setting	Requires hospitalization	Performed in an outpatient setting
Medical procedure	Requires general anaesthesia	No anaesthesia or sedation
Recovery time after each treatment	Hours	Minutes
Major after-effects	Short- and long-term memory loss	None (seizure very rare)
Minor side-effects	Headaches, muscle and jaw aches, feeling confused, ill and nauseous	Little, transient, discomfort on the stimulation site, headaches, fatigue
Treatment plan	2–3 times a week (max. 15 sessions)	Daily (Monday-Friday) for 4–6 weeks

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)

Jean-Pascal Lefaucheur[a,b,*], André Aleman[c], Chris Baeken[d,e,f], David H. Benninger[g], Jérôme Brunelin[h], Vincenzo Di Lazzaro[i], Saša R. Filipović[j], Christian Grefkes[k,l], Alkomiet Hasan[m], Friedhelm C. Hummel[n,o,p], Satu K. Jääskeläinen[q], Berthold Langguth[r], Letizia Leocani[s], Alain Londero[t], Raffaele Nardone[u,v,w], Jean-Paul Nguyen[x,y], Thomas Nyffeler[z,aa,ab], Albino J. Oliveira-Maia[ac,ad,ae], Antonio Oliviero[af], Frank Padberg[m], Ulrich Palm[m,ag], Walter Paulus[ah], Emmanuel Poulet[h,ai], Angelo Quartarone[aj], Fady Rachid[ak], Irena Rektorová[al,am], Simone Rossi[an], Hanna Sahlsten[ao], Martin Schecklmann[r], David Szekely[ap], Ulf Ziemann[aq]

Clinical Neurophysiology 131 (2020) 474–528

Level A (definite efficacy):

- Depression (DLPFC)
- Chronic neurophatic pain (M1)
- Post-stroke motor hand recovery (M1, acute phase)
- Obsessive-compulsive disorder (FDA-approved; target: SMA)

Level B (probable efficacy):

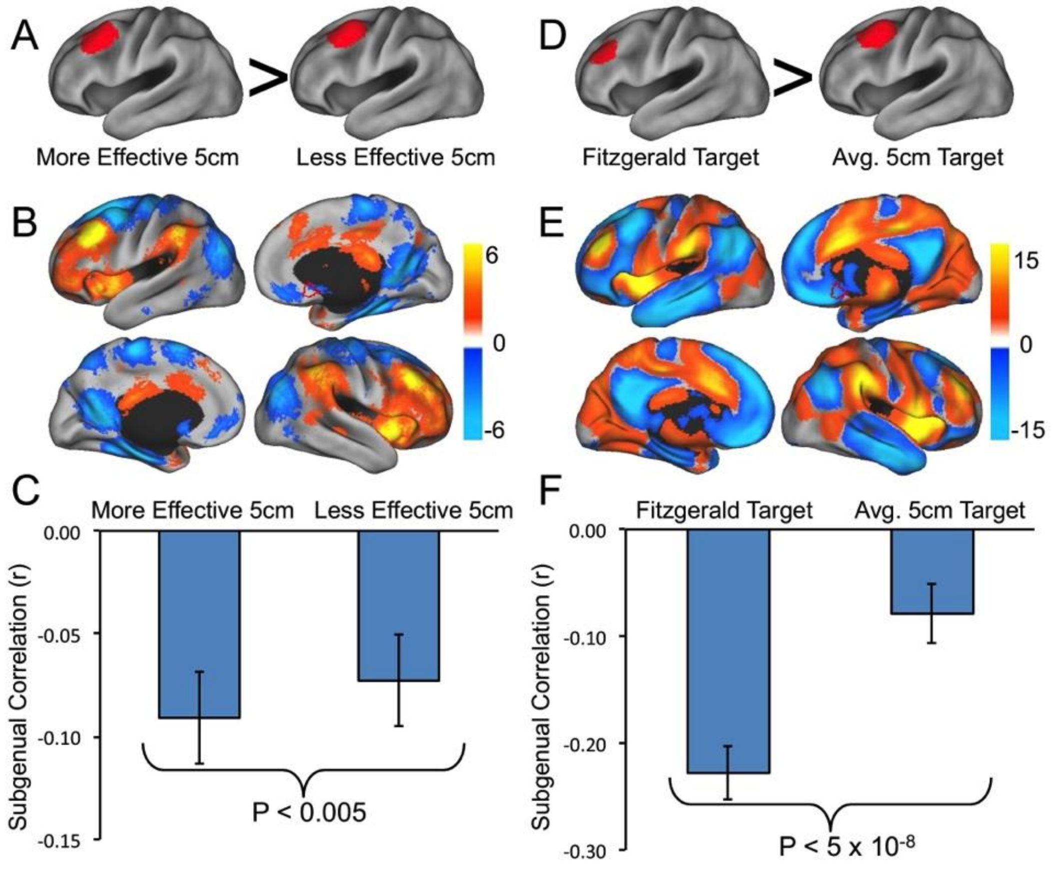
- Lower limbs spasticity in Multiple Sclerosis (M1)
- Depression (DLPFC) and motor symptoms (bilateral M1) in Park
- Quality of life (M1) and pain alleviation (DLPFC) in fibromyalgia
- Post-traumatic stress disorders
- Post-stroke aphasia

Connectivity predicts better efficacy

Efficacy of TMS targets for depression is related to intrinsic functional connectivity with the subgenual cingulate

Michael D. Fox[1,2,3], Randy L. Buckner[3,4,5], Matthew P. White[6], Michael D. Greicius[7], and Alvaro Pascual-Leone[2,8]

- Sites predicted to have better treatment efficacy are "anticorrelated" with subgenual cingulate



Fox et al., 2012

The case of OCD

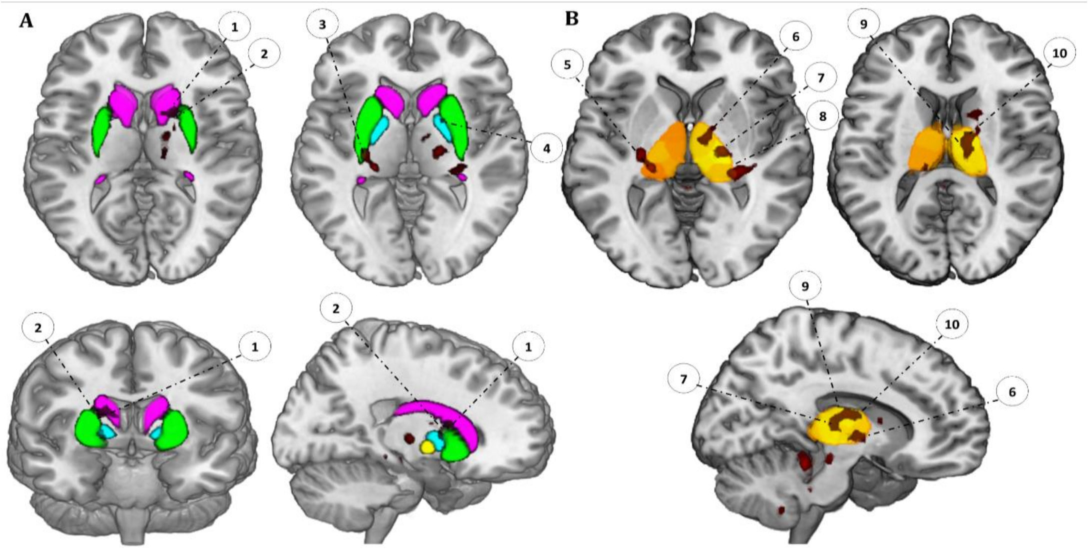
Functional connectivity changes and symptoms improvement after personalized, double-daily dosing, repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: A pilot study

Antonio Mantovani [a,1], Francesco Neri [b,1,*], Giordano D'Urso [c], Lucia Mencarelli [b,d], Elisa Tatti [a], Davide Momi [b,d], Arianna Menardi [b,d], Giulia Sprugnoli [b], Emiliano Santarnecchi [b,d], Simone Rossi [b,e]

Journal of Psychiatric Research 136 (2021) 560–570

High-density, personalized 1 Hz rTMS (7200 stim/day in two sessions) of the SMA in OCD patients

Seed region: bilateral SMA



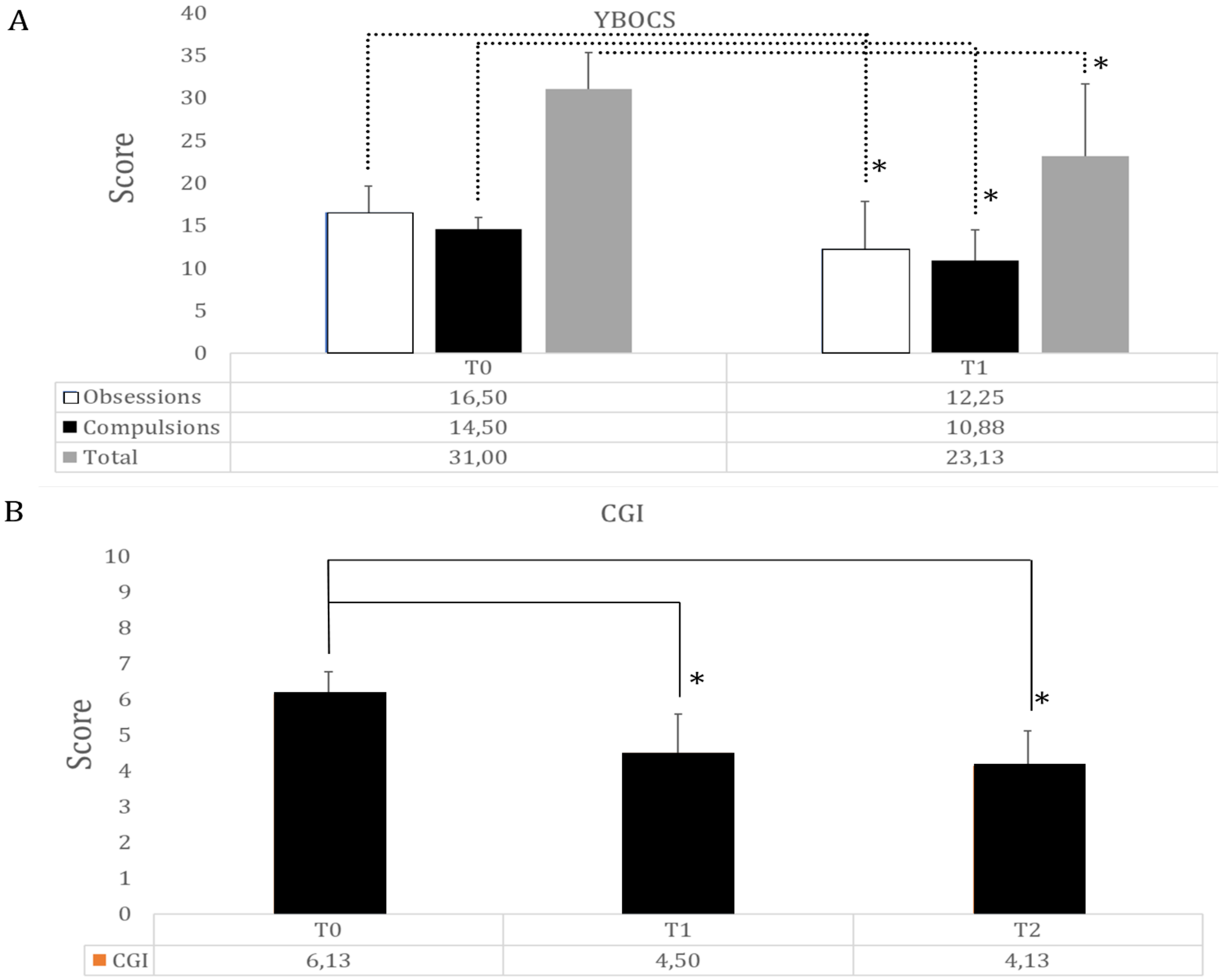
Clinical results:

- 9 OCD patients
- Symptoms improved by 25%
- Up to 3 months

reduction of pathological hyperconnectivity between SMA and certaiin basal ganglia and thalamic regions

Rs Connectvity changes are related to clinical improvement

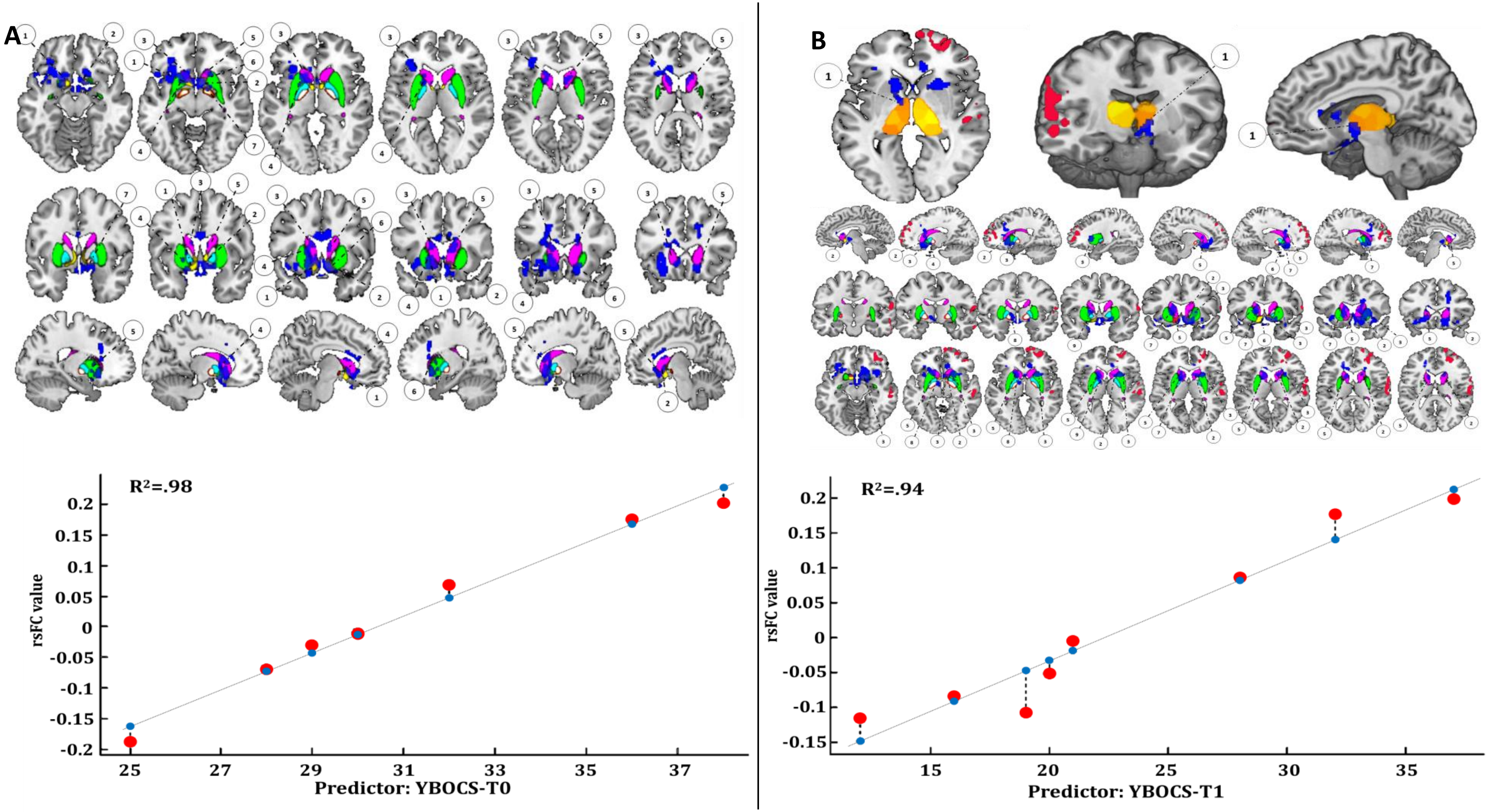
rTMS: therapeutic application for OCD



Mantovani et al., 2021

The case of OCD

Higher YBOCS Total Score correlation with higher connectivity between SMA and subcortical regions



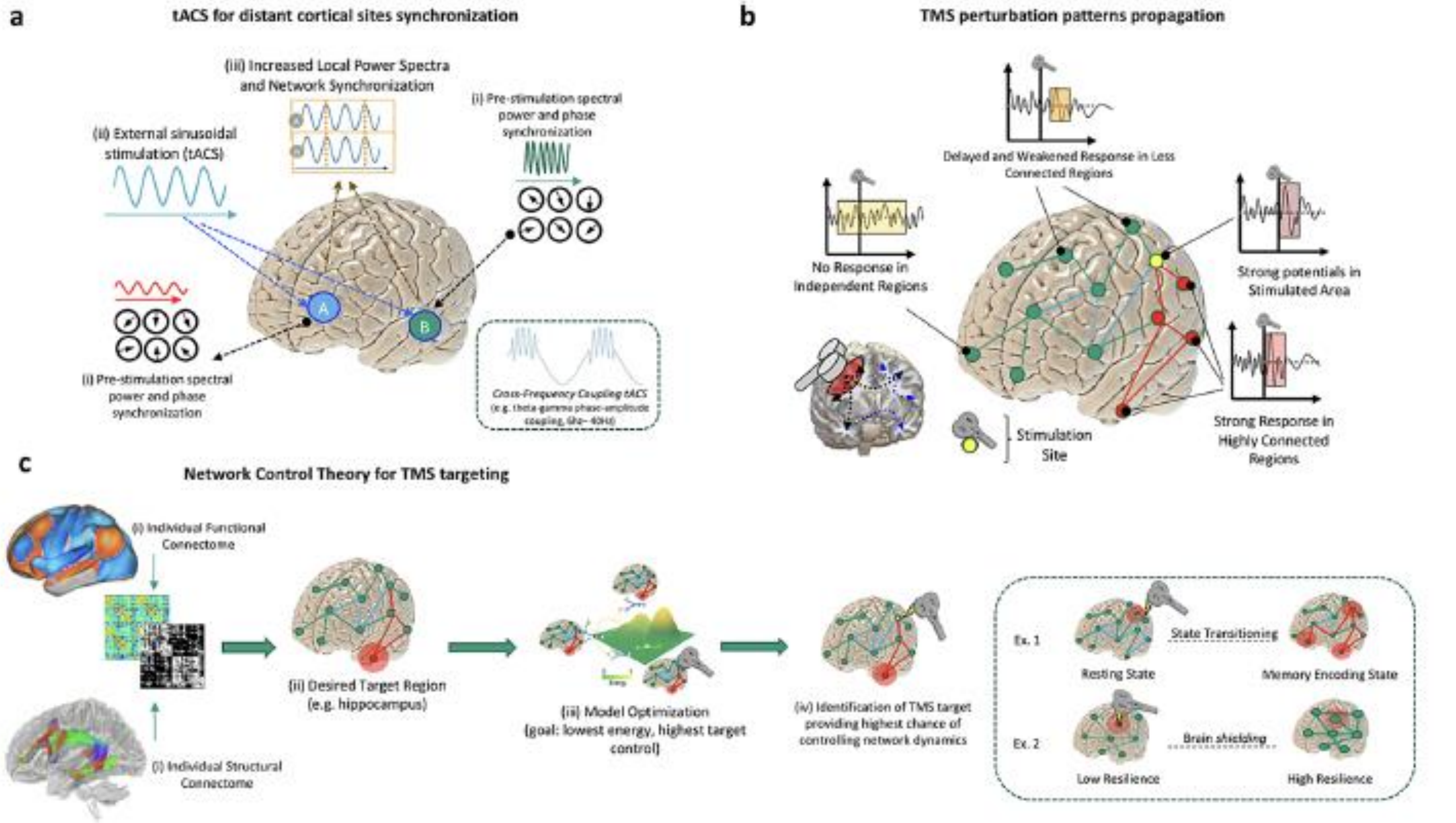
Connectivity might predict rTMS outcome

Journal of Psychiatric Research 136 (2021) 560–570

Toward noninvasive brain stimulation 2.0 in Alzheimer's disease

Arianna Menardi [a,b], Simone Rossi [c], Giacomo Koch [d], Harald Hampel [e], Andrea Vergallo [e], Michael A. Nitsche [f,g], Yaakov Stern [h], Barbara Borroni [i], Stefano F. Cappa [j,k], Maria Cotelli [l], Giulio Ruffini [m], Georges El-Fakhri [n], Paolo M. Rossini [o], Brad Dickerson [p], Andrea Antal [q], Claudio Babiloni [r,s], Jean-Pascal Lefaucheur [t,u], Bruno Dubois [v,w,x], Gustavo Deco [y,z], Ulf Ziemann [aa,ab], Alvaro Pascual-Leone [ac,ad,ae], Emiliano Santarnecchi [a,*,1]

Ageing Research Reviews 75 (2022) 101555



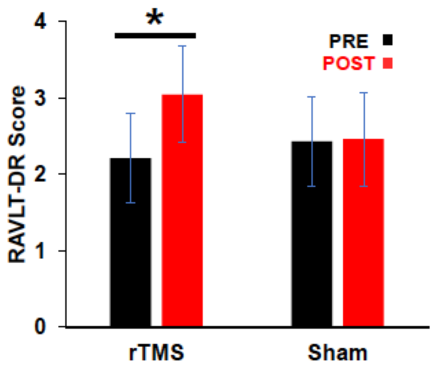
Neuroimage. 2018 Apr 1;169:302-311. doi: 10.1016/j.neuroimage.2017.12.048. Epub 2017 Dec 19.

Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease

Giacomo Koch [1], Sonia Bonnì [2], Maria Concetta Pellicciari [2], Elias P Casula [2], Matteo Mancini [3], Romina Esposito [2], Viviana Ponzo [2], Silvia Picazio [2], Francesco Di Lorenzo [4], Laura Serra [3], Caterina Motta [2], Michele Maiella [2], Camillo Marra [5], Mara Cercignani [6], Alessandro Martorana [4], Carlo Caltagirone [4], Marco Bozzali [7]

20 Hz, 1600 stim/day,
two weeks
RSCT

Delayed Recall



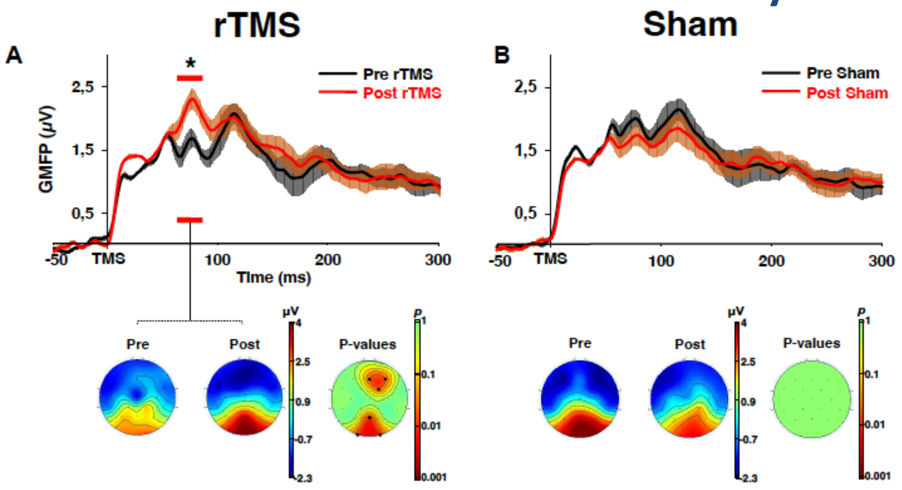
Improved episodic memory
(no other cognitive domains)

TMS-EEG: increase of Parietal neural activity

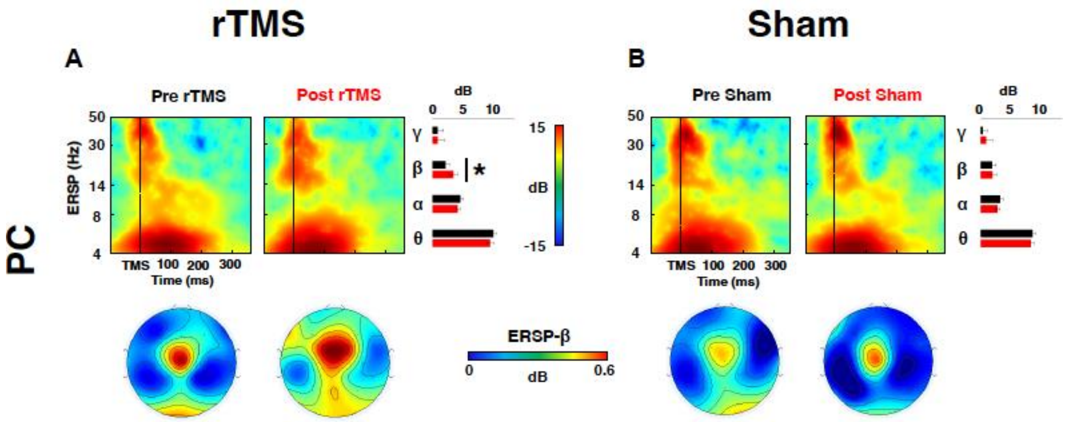
EEG: increase of beta-band

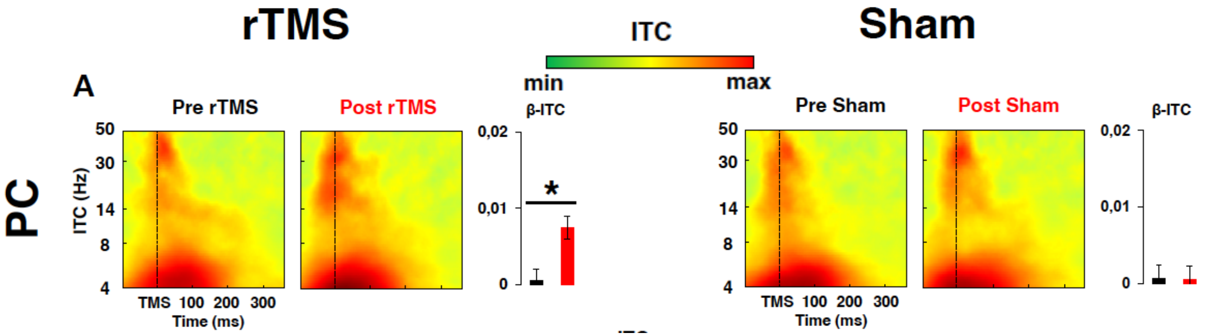
Increase of functional connections within the DMN
(network effect?)

Increased local neural activity

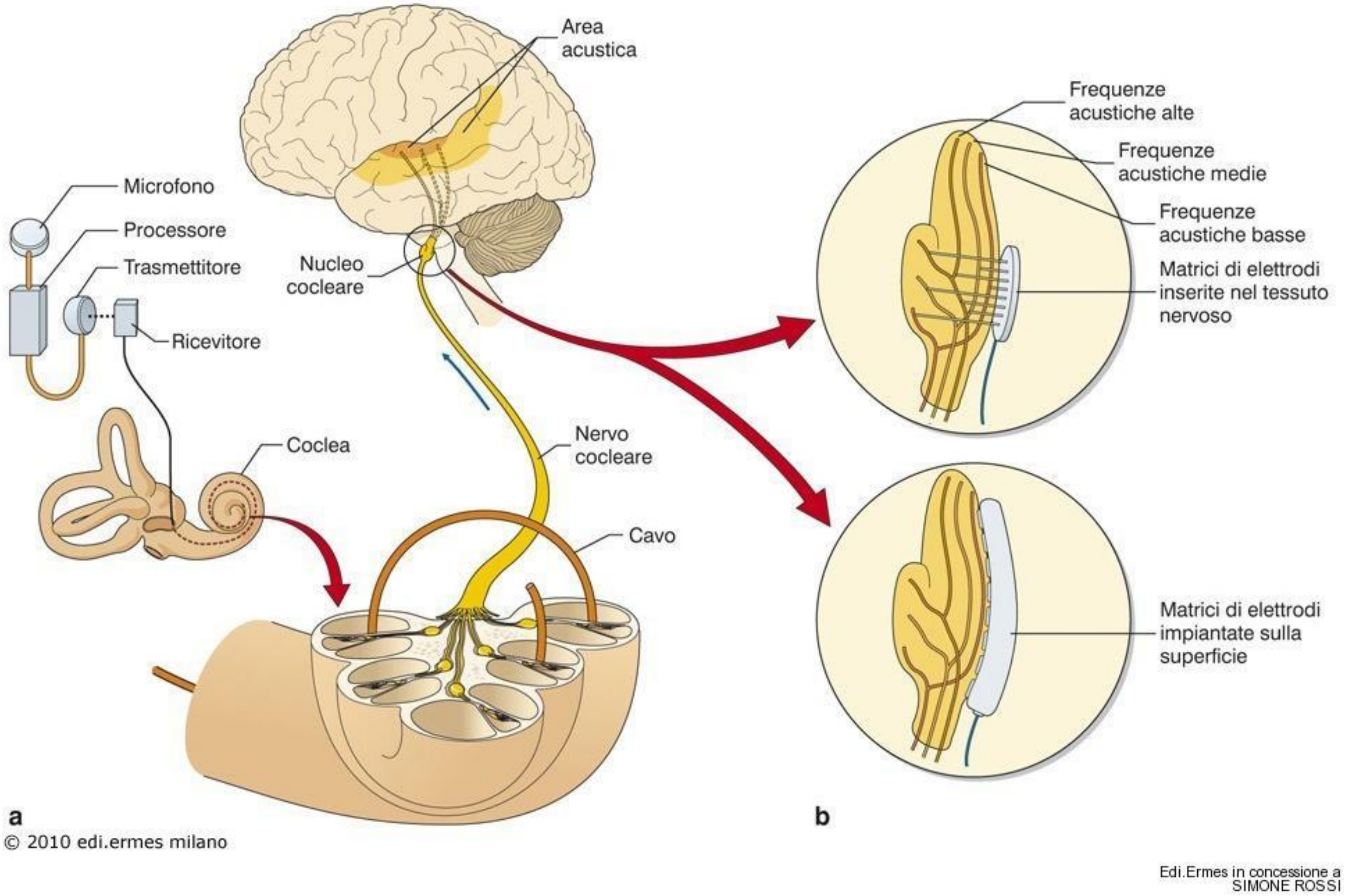


Local beta-band increase





rTMS in patients with Cochlear Implants

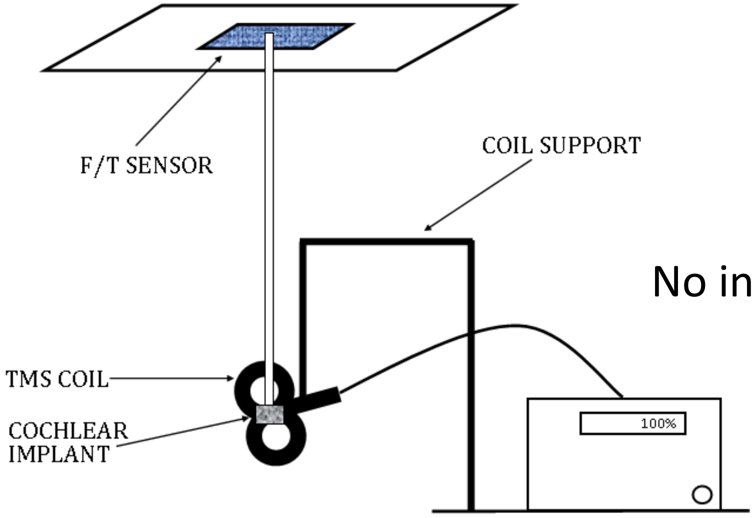


Francesco Neri – PhD student

ELSEVIER
Clinical Neurophysiology
Volume 132, Issue 3, March 2021, Pages 723-729

Feasibility of TMS in patients with new generation cochlear implants

Marco Mandalà [a], Tommaso Lisini Baldi [b], Francesco Neri [c], Lucia Mencarelli [c], Sara Romanella [c], Monica Ulivelli [c], Domenico Prattichizzo [b], Emiliano Santarnecchi [c, d], Simone Rossi [c]



No induced forces

5 titanium housed cochlear implant devices (2 x Mi1000 and 3 x Mi1200 were tested

Stimulation parameters:

- 1 Hz rTMS for 30 minutes (total: 1800 pulses)
- 10 Hz rTMS for 4 seconds trains, with inter-train intervals of 8 seconds (total: 1800 pulses)
- Max stim output

Extreme tests: both combinations of frequency/intensity and length of stimulation exceeded the upper limits of published safety tables thus they have to be considered reasonably unsafe for humans

All the implants resulted completely functioning and with no damages/defections, irrespective to the applied protocols of stimulation.

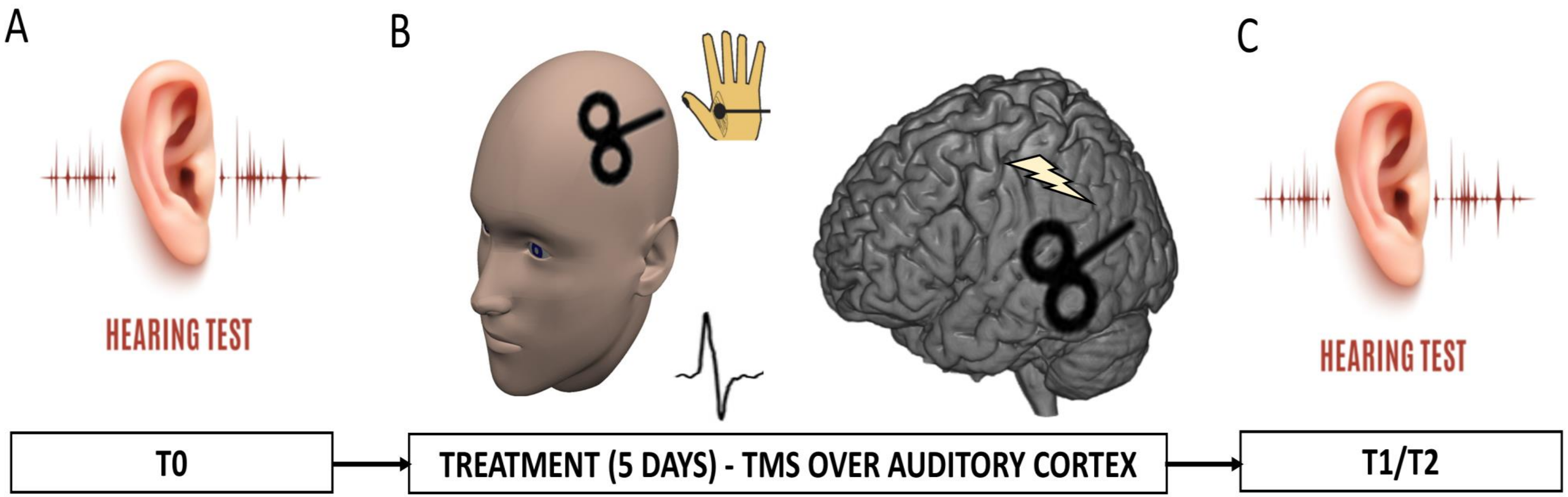
SiBIN LAB

Francesco Neri – PhD student

rTMS for the treatment of age-related hearing loss in patients with wearable hearing aids

Francesco Neri[1*], Chiara Cappello[2*], Francesca Viberti[2], Lucia Burzi[1], Alessandra Cinti[1], Alberto Benelli[1], Carmelo Luca Smeralda[1], Sara Romanella[1], Emiliano Santarnecchi[3], Marco Mandalà[2**], Simone Rossi[1**]

PROTOCOL



Results are under submission

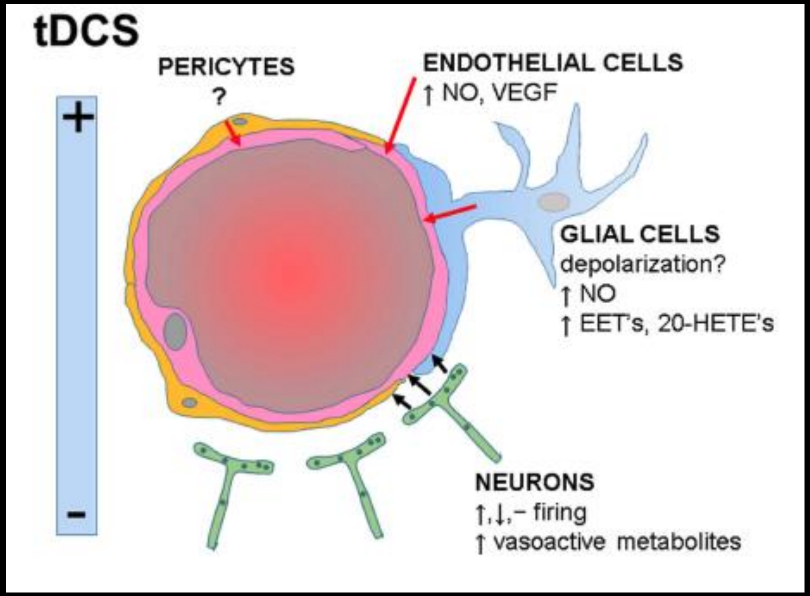
Francesco Neri – PhD student

tDCS and perfusion

Contents lists available at ScienceDirect
Experimental Neurology
journal homepage: www.elsevier.com/locate/yexnr

Transcranial direct current stimulation induces polarity-specific changes of cortical blood perfusion in the rat

Dorothee Wachter [a,*], Arne Wrede [c], Walter Schulz-Schaeffer [c], Ali Taghizadeh-Waghefi [a], Michael A. Nitsche [b], Anna Kutschenko [b], Veit Rohde [a], David Liebetanz [b]

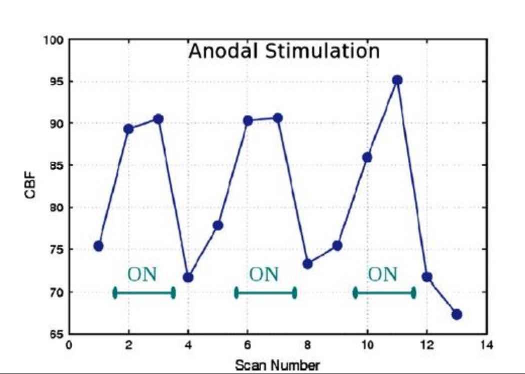


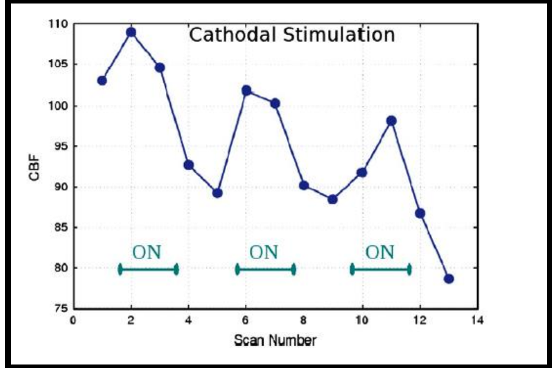
Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

Effects of transcranial direct current stimulation (tDCS) on human regional cerebral blood flow

Xin Zheng [a], David C. Alsop [b], Gottfried Schlaug [a,*]

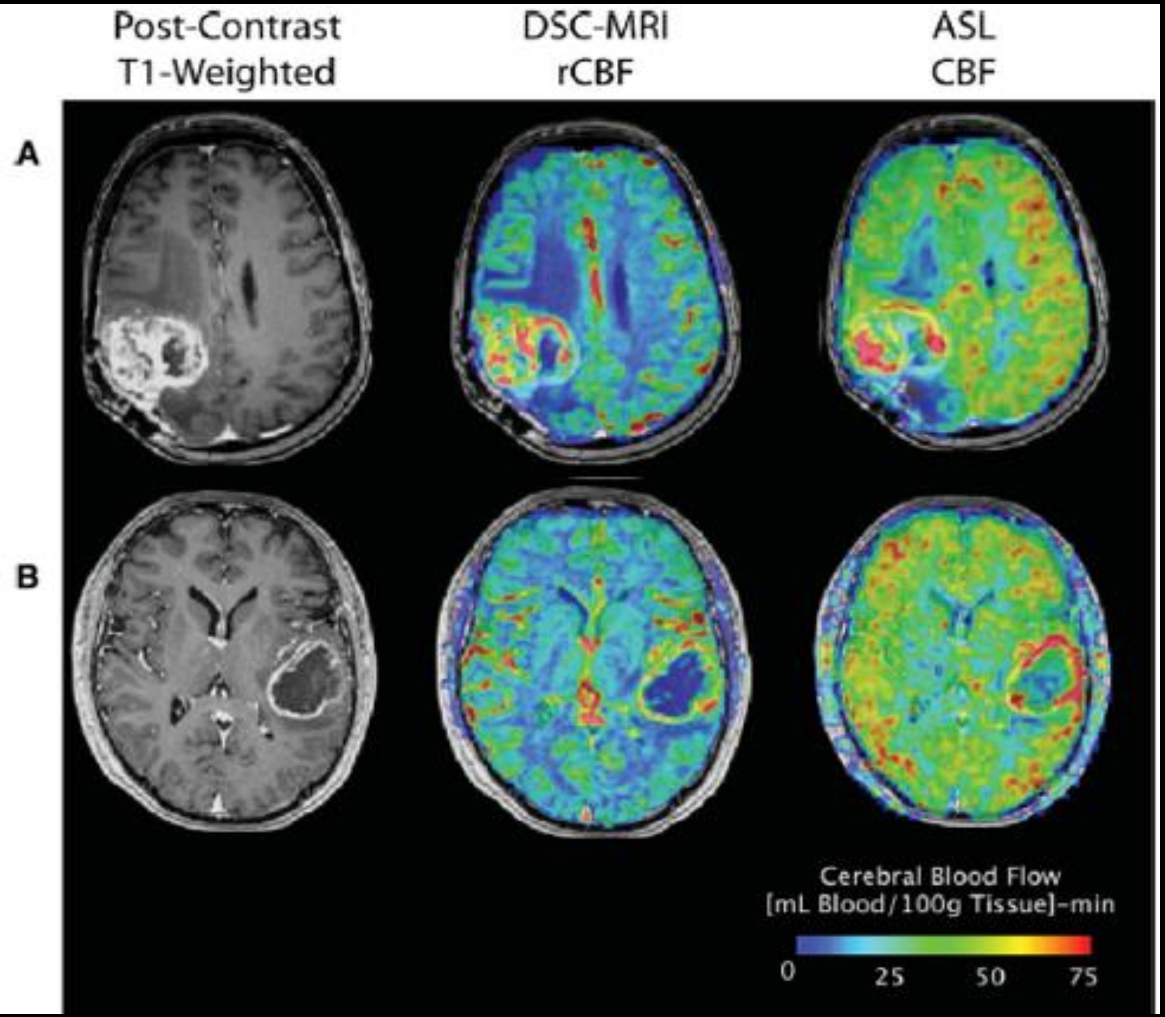
[a] Dept. of Neurology, Neuroimaging and Stroke Recovery Laboratories, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
[b] Dept. of Radiology, Division of MRI Research, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA





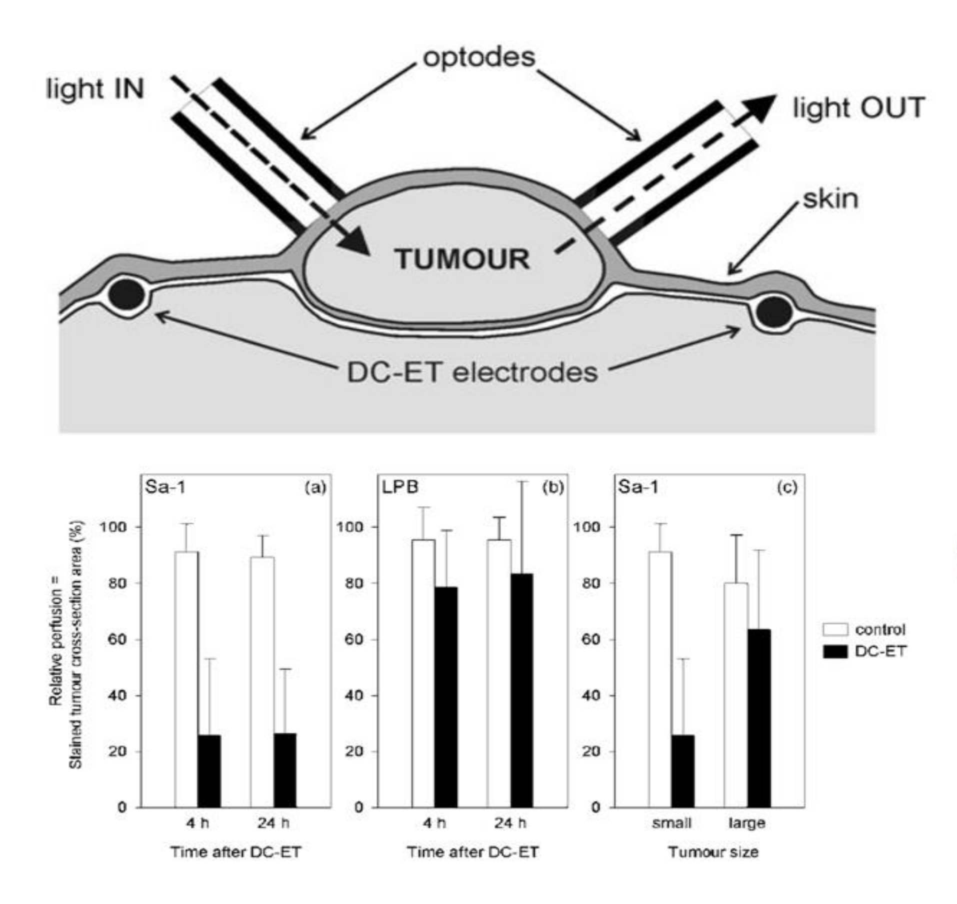
HGG and Perfusion

Arterial Spin Labeling

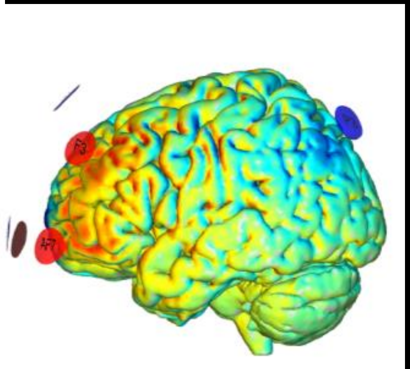


Perturbation of blood flow as a mechanism of anti-tumour action of direct current electrotherapy

Tomaž Jarm[1], Maja Čemažar[2], Fritz Steinberg[3,4], Christian Streffer[3,5], Gregor Serša[2] and Damijan Miklavčič[1]



tDCS on brain tumors?

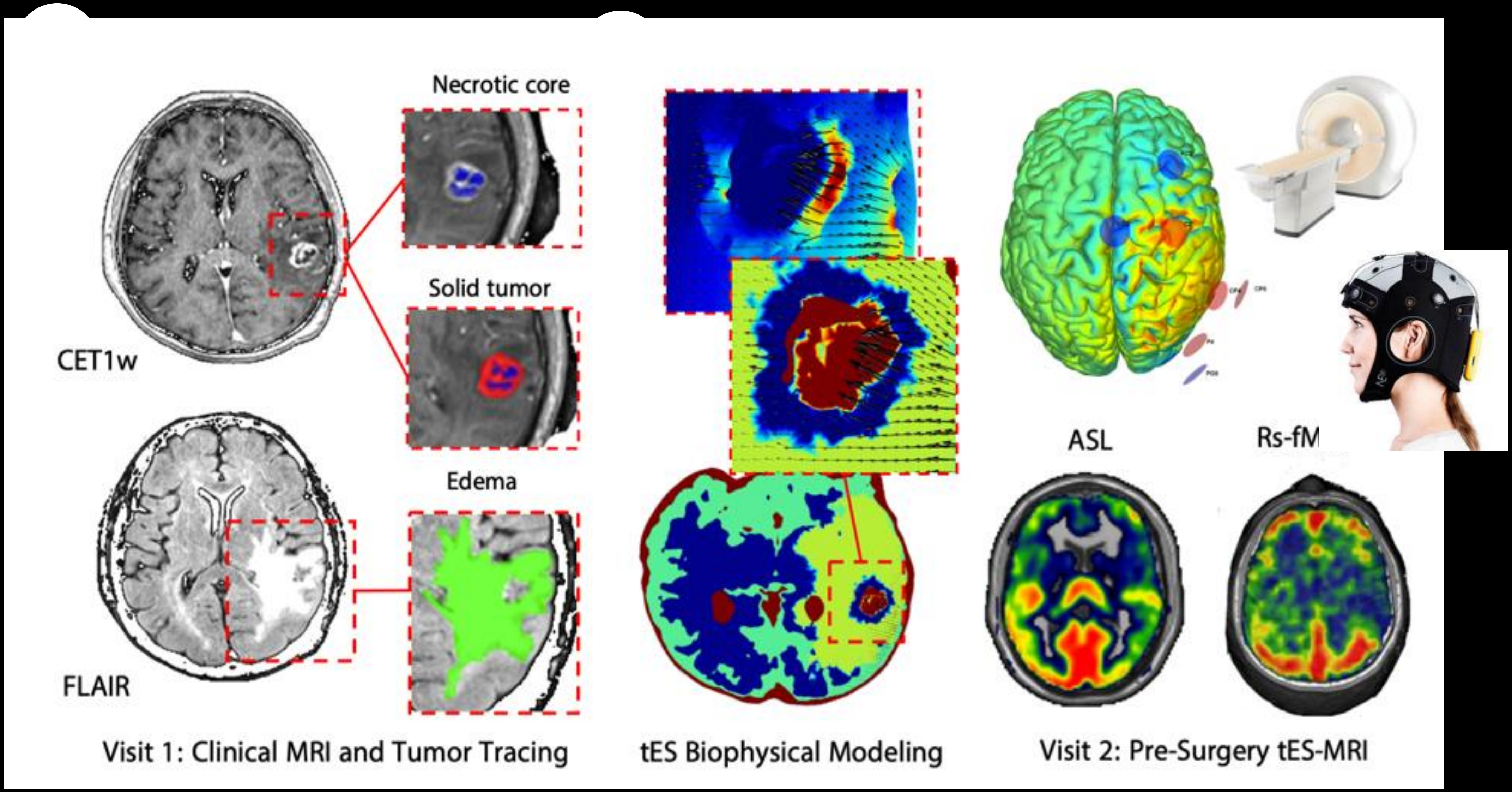


Experimental Protocol

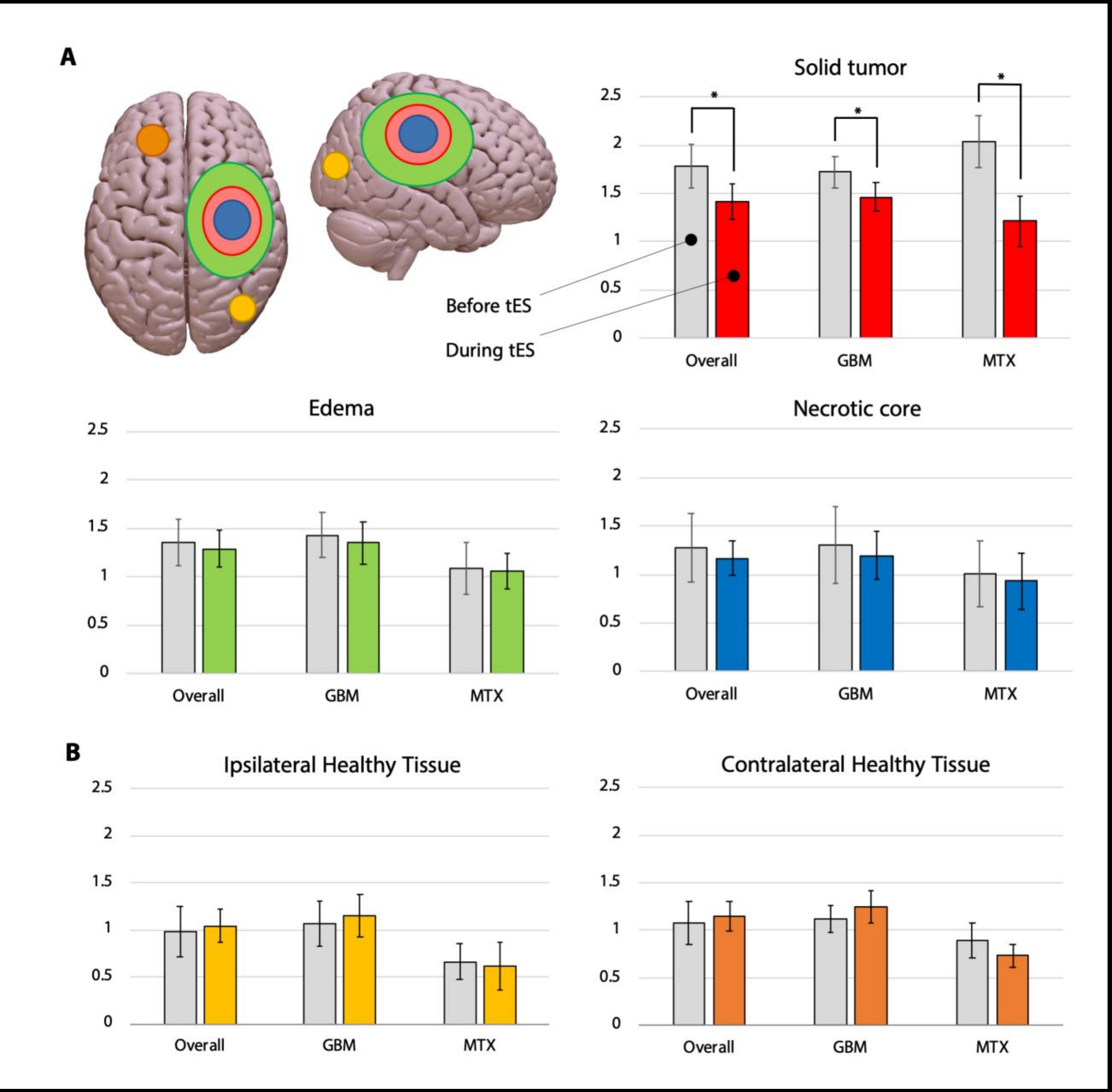
Lesion definition

Modeling

Personalized tDCS



Results



- pilot study
- no sham
- long term effects?
- repetitive sessions?

SCIENCE ADVANCES | RESEARCH ARTICLE

HEALTH AND MEDICINE

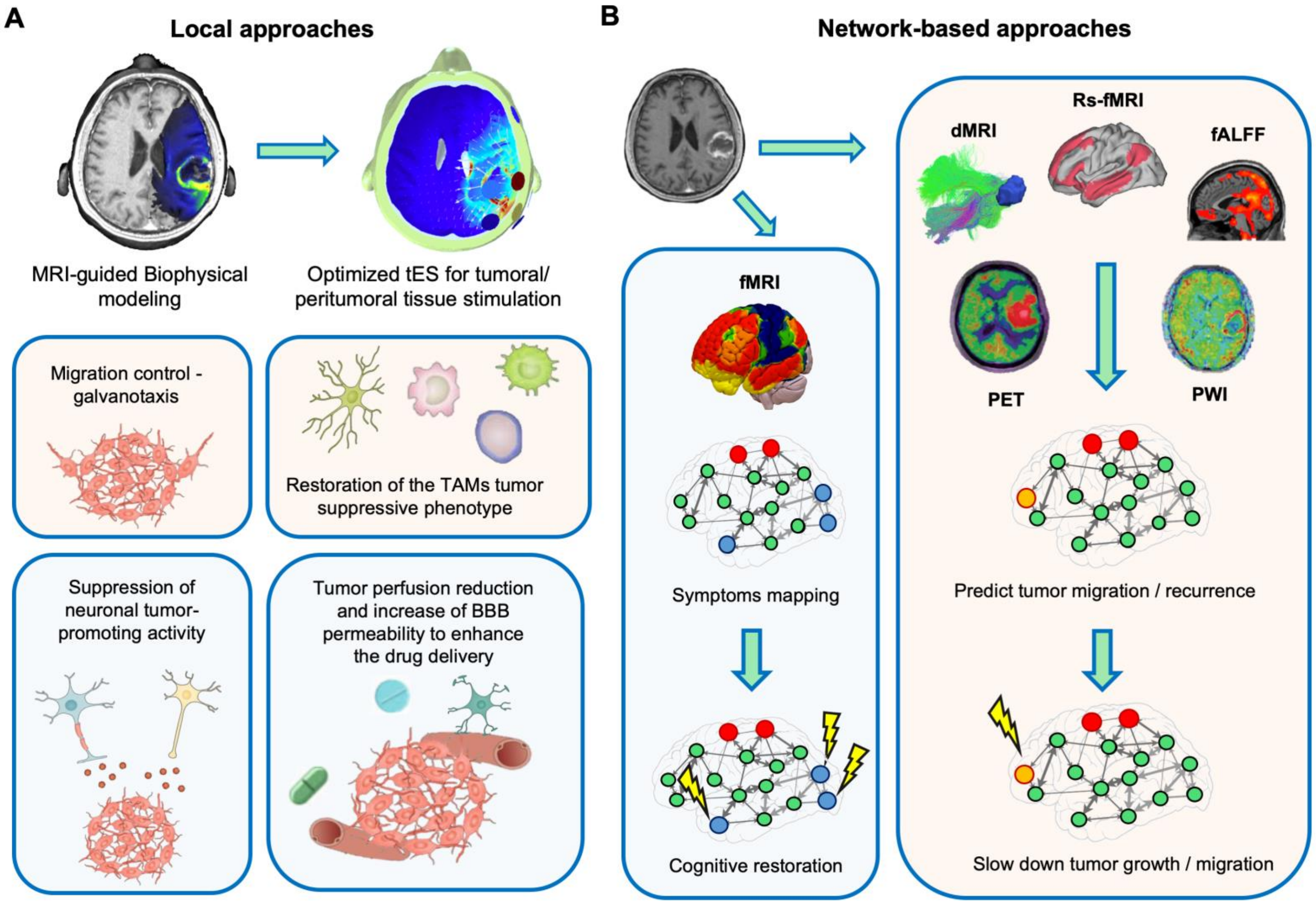
Reduction of intratumoral brain perfusion by noninvasive transcranial electrical stimulation

G. Sprugnoli[1]*, L. Monti[2]*, L. Lippa[3], F. Neri[1], L. Mencarelli[1], G. Ruffini[4], R. Salvador[4], G. Oliveri[3], B. Batani[3], D. Momi[1], A. Cerase[2], A. Pascual-Leone[5,6], A. Rossi[1,7], S. Rossi[1,7], E. Santarnecchi[1,5,6]†

1) No Adverse Events or Side Effects, neither Pre- nor Post- surgery

2) Selective Decrease of Intratumoral perfusion during stimulation (-36%)

Neuromodulation for HHG?



Future Directions:

Tumor-network connectivity as a survival biomarker

Personalized neuromodulatory interventions on tumor's electrical properties?

Personalised, image-guided, noninvasive brain stimulation in gliomas: Rationale, challenges and opportunities

Giulia Sprugnoli[a,b,c,d], Simone Rossi[d], Alexander Rotenberg[e], Alvaro Pascual-Leone[f,g], Georges El-Fakhri[h], Alexandra J. Golby[c,i], Emiliano Santarnecchi[a,1,*]

EBioMedicine 70 (2021) 103514

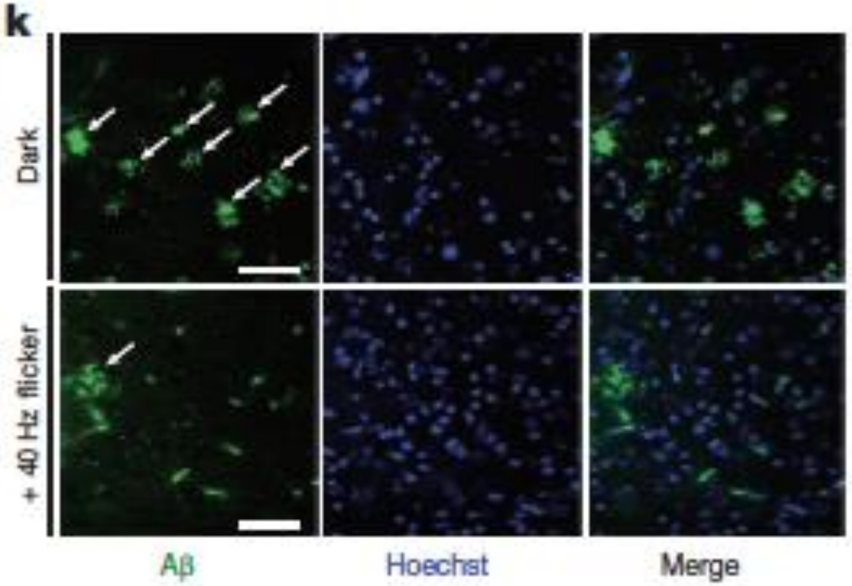
Gamma frequency entrainment attenuates amyloid load and modifies microglia

Hannah F. Iaccarino[1,3*], Annabelle C. Singer[2,3,4*], Anthony J. Martorell[1,3], Andrii Rudenko[1,3], Fan Gao[1,3], Tyler Z. Gillingham[1,3], Hansruedi Mathys[1,3], Jinsoo Seo[1,3], Oleg Kritskiy[1,3], Fatema Abdurrob[1,3], Chinnakkaruppan Adaikkan[1,3], Rebecca G. Canter[1,3], Richard Rueda[1,3], Emery N. Brown[1,3,5,6], Edward S. Boyden[2,3,4] & Li-Huei Tsai[1,3,7]

230 | NATURE | VOL 540 | 8 DECEMBER 2016

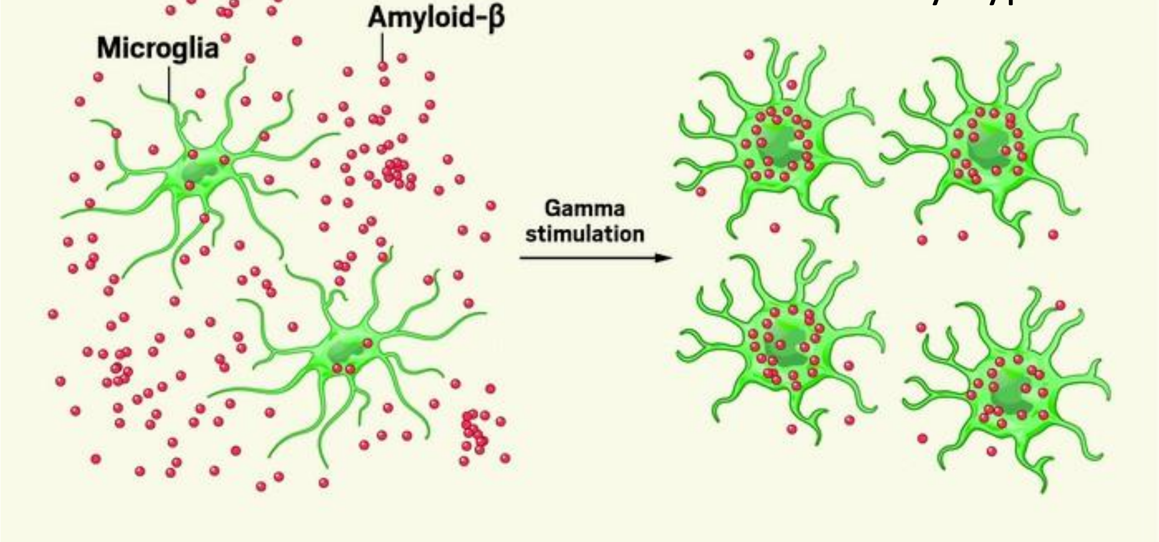
Changes in gamma oscillations (20–50 Hz) have been observed in several neurological disorders. However, the relationship between gamma oscillations and cellular pathologies is unclear. Here we show reduced, behaviourally driven gamma oscillations before the onset of plaque formation or cognitive decline in a mouse model of Alzheimer's disease. Optogenetically driving fast-spiking parvalbumin-positive (FS-PV)-interneurons at gamma (40 Hz), but not other frequencies, reduces levels of amyloid-β (Aβ)$_{1-40}$ and Aβ$_{1-42}$ isoforms. Gene expression profiling revealed induction of genes associated with morphological transformation of microglia, and histological analysis confirmed increased microglia co-localization with Aβ. Subsequently, we designed a non-invasive 40 Hz light-flickering regime that reduced Aβ$_{1-40}$ and Aβ$_{1-42}$ levels in the visual cortex of pre-depositing mice and mitigated plaque load in aged, depositing mice. Our findings uncover a previously unappreciated function of gamma rhythms in recruiting both neuronal and glial responses to attenuate Alzheimer's-disease-associated pathology.

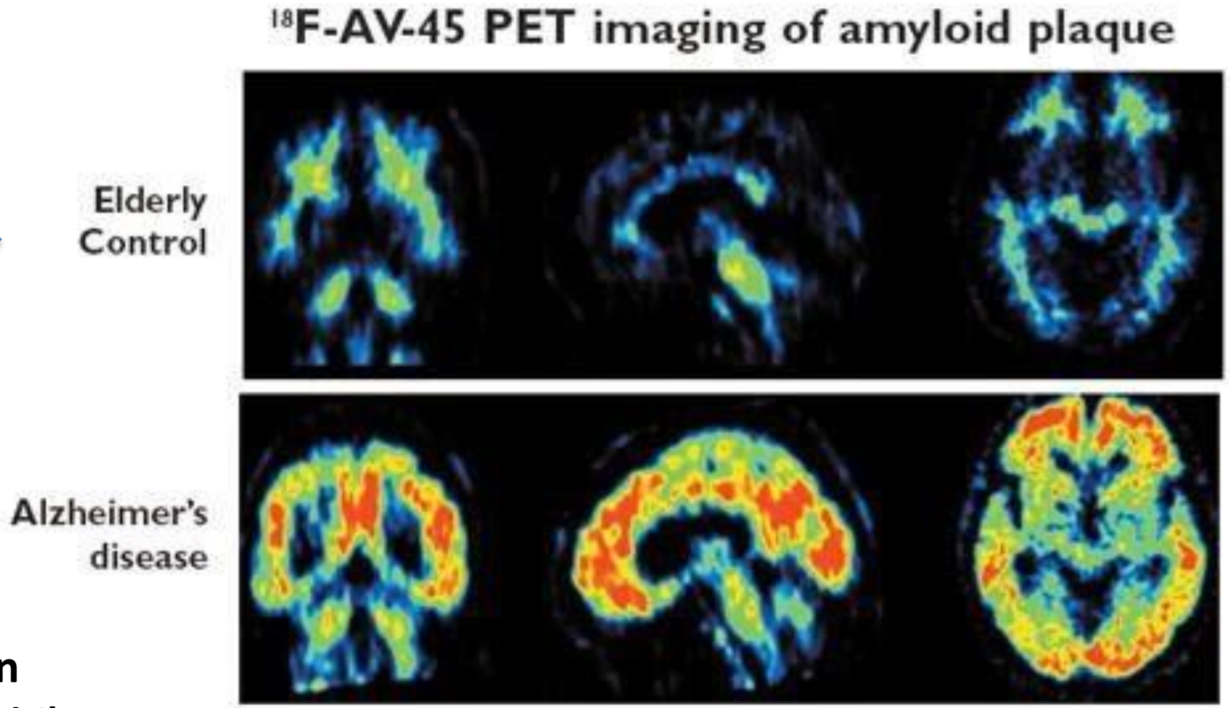
Figure 4 | Driving 40 Hz oscillations in VC via light flicker redu Aβ and amyloid plaques in 5XFAD mice.



k, Immunohistochemistry with anti-Aβ (D5452, green) antibody in 6-month-old VC of 5XFAD mice after 7 days of 1 h per day dark or 40 Hz flicker showing plaques (white arrows; scale bar, 50 μm).

Nature 2016 study hypothesis





A trial is ongoing in Boston
(Prof. Emiliano Santarnecchi)

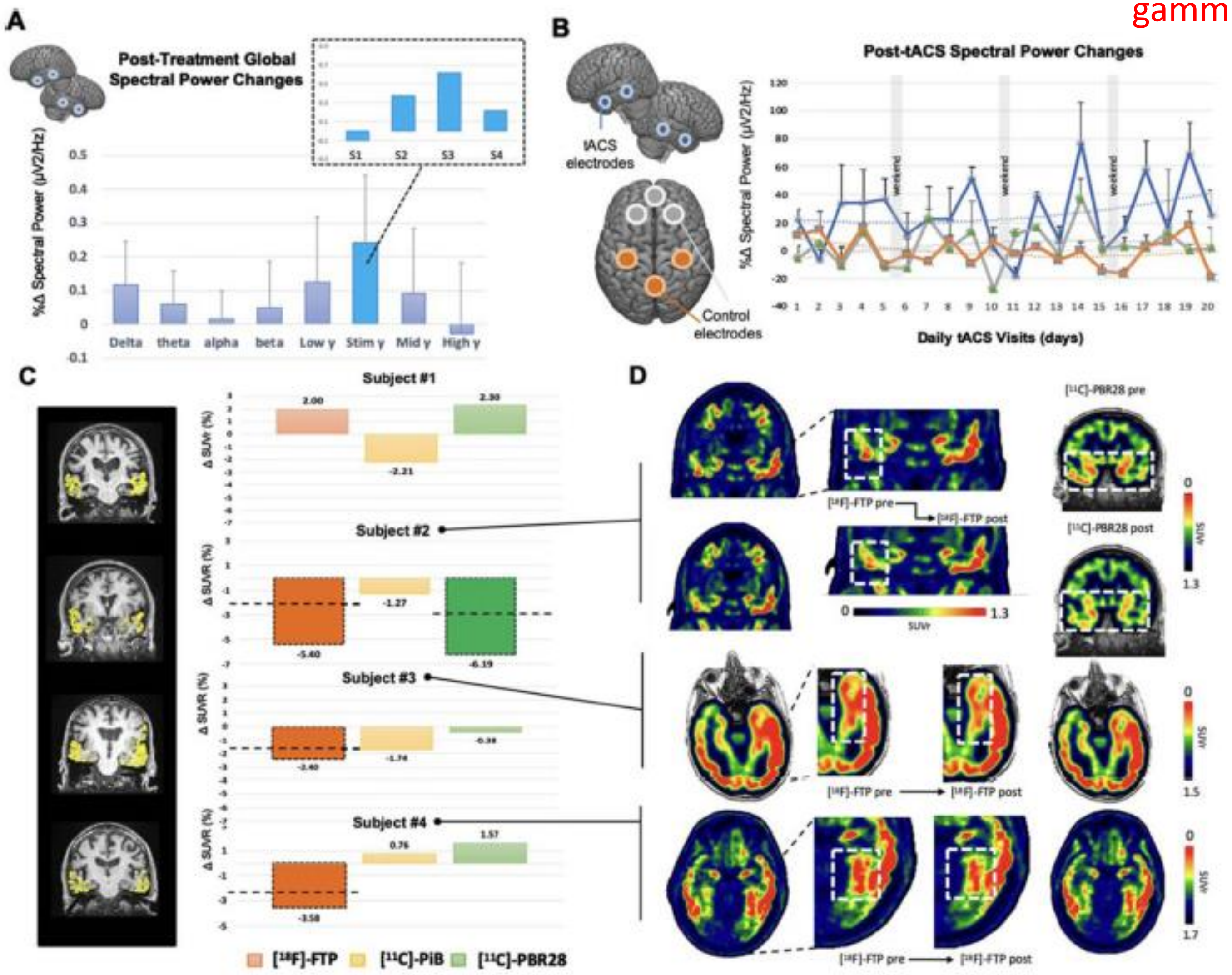
Impact of 40 Hz Transcranial Alternating Current Stimulation on Cerebral Tau Burden in Patients with Alzheimer's Disease: A Case Series

J Alzheimers Dis. Author manuscript. 2022

Maeva Dhaynaut[a,1], Giulia Sprugnoli[b,1], Davide Cappon[b], Joanna Macone[b], Justin S. Sanchez[a,c], Marc D. Normandin[a], Nicolas J. Guehl[a], Giacomo Koch[d], Rachel Paciorek[b], Ann Connor[b], Daniel Press[b], Keith Johnson[a,c], Alvaro Pascual-Leone[e,f], Georges El Fakhri[a,1,*], Emiliano Santarnecchi[a,b,1,*]

1 hour tACS daily
for 4 weeks

Daily increase of
gamma power



= p-Tau

= micorglia activation

= beta-amyloid

2% reduction of p-Tau in ¾ patients (enthorinal cortex)

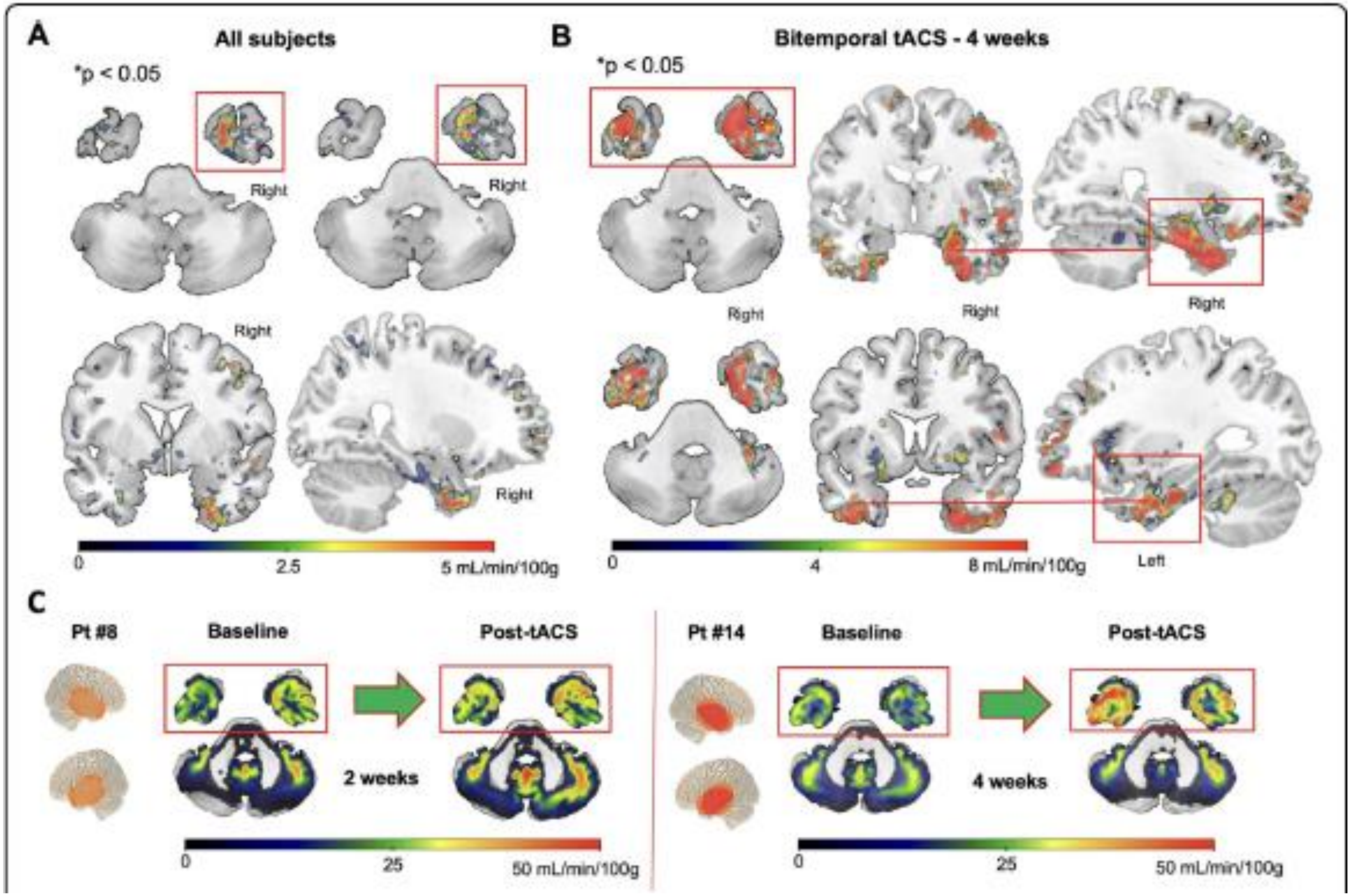
Beta amyloid unchanged

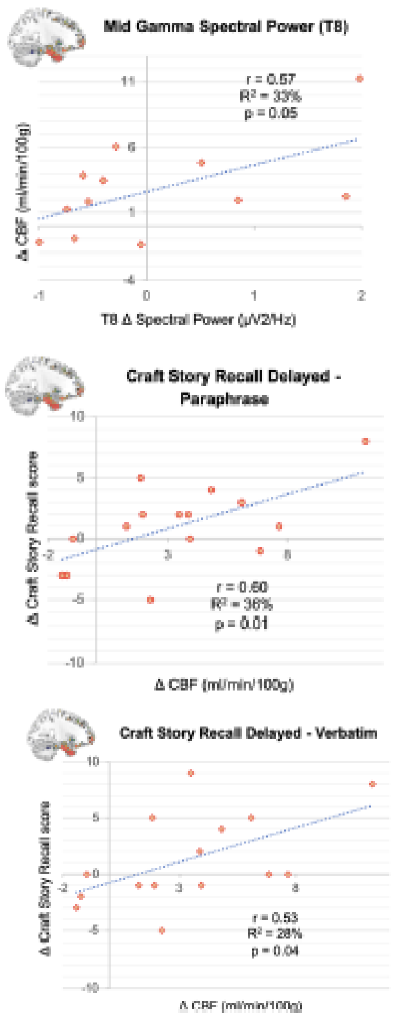
¼ decrease of microglia activation

Impact of multisession 40Hz tACS on hippocampal perfusion in patients with Alzheimer's disease

Giulia Sprugnoli[1,2], Fanny Munsch[3], Davide Cappon[1], Rachel Paciorek[1], Joanna Macone[1], Ann Connor[1], Georges El Fakhri[4], Ricardo Salvador[5], Giulio Ruffini[5], Kevin Donohoe[4], Mouhsin M. Shafi[1], Daniel Press[1], David C. Alsop[3], Alvaro Pascual Leone[6,7,8] and Emiliano Santarnecchi[9*]

Sprugnoli *et al.*
Alzheimer's Research & Therapy (2021) 13:203
https://doi.org/10.1186/s13195-021-00922-4





Review
TRENDS in Neurosciences Vol.27 No.11 November 2004
Full text provided by www.sciencedirect.com
ELSEVIER

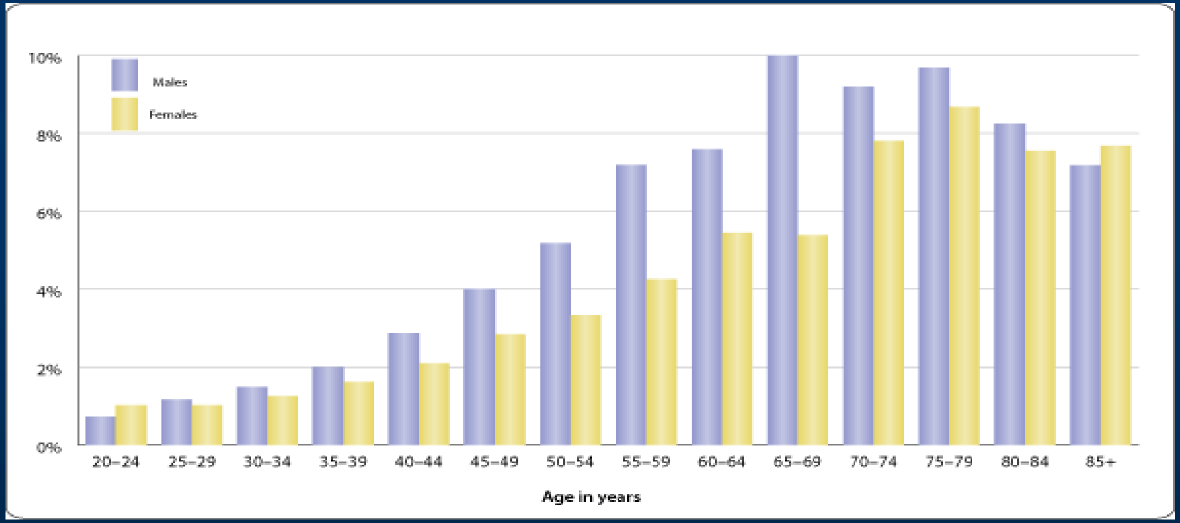
The neuroscience of tinnitus

Jos J. Eggermont[1] and Larry E. Roberts[2]

[1]Department of Physiology and Biophysics, and Department of Psychology, University of Calgary, Alberta, Canada, T2N 1N4
[2]Department of Psychology, McMaster University, Hamilton, Ontario, Canada, L8S 4K1

- In 5–15% of the general population, the tinnitus sensation is unremitting

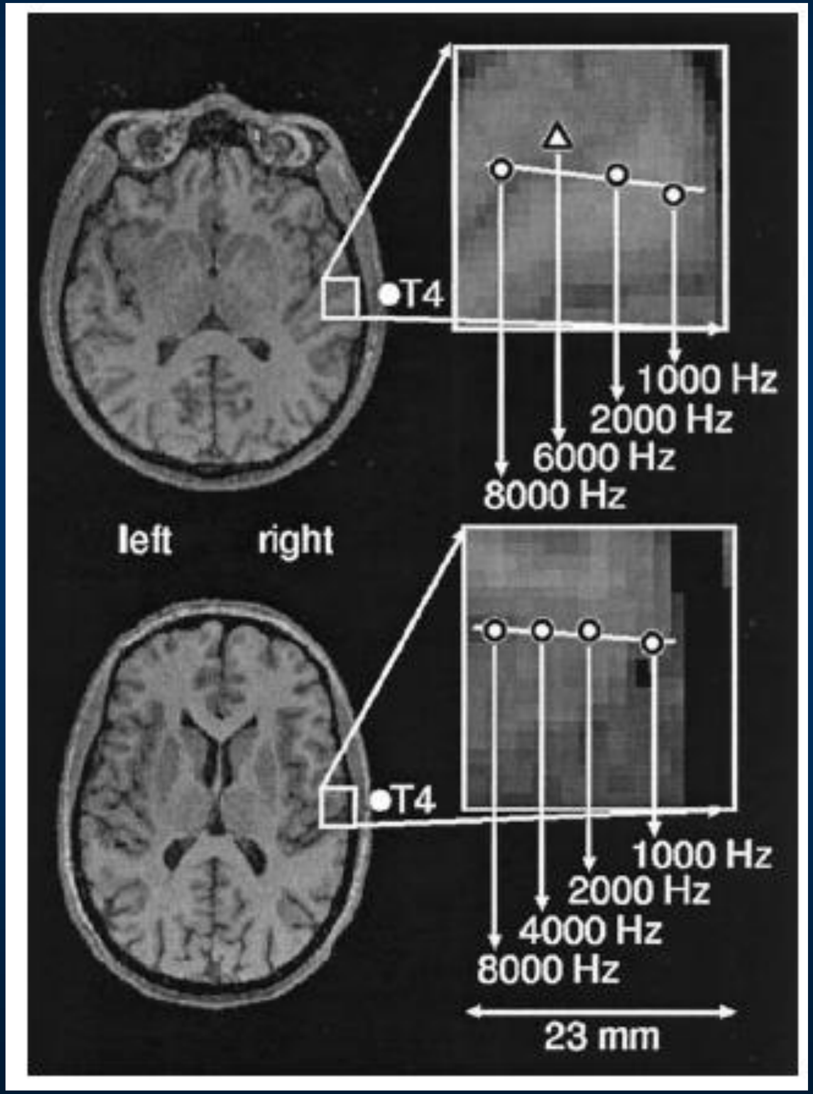
Prevalance of chronic tinnitus



- In 1–3% of the general population, tinnitus affects the quality of life of patients, since it is associated with sleep disturbances, work impairment and psychiatric distress or depression

Maladaptive plastic reorganization of auditory cortex in patients with tinnitus

W.Muhlnickel, T.Elbert, E.Taub, H.Flor, PNAS 1998



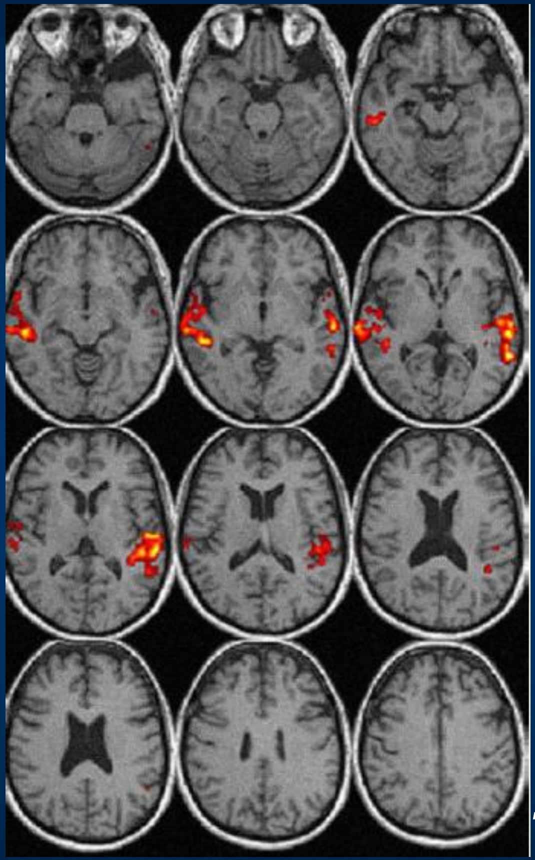
Tonotopy studies by MEG

Anterior shift of the cortical epresentation of certain frequencies in patients with tinnitus

Neurons in a de-afferented cortical region shift their tuning to represent frequencies near the edge of the lesion, thus giving rise to an expanded representation of these frequencies and to the sensation of tinnitus

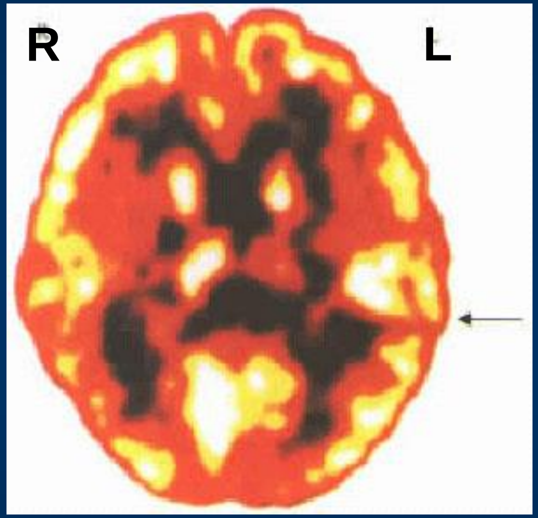
Brain areas involved in tinnitus perception

Increased CBF/metabolism



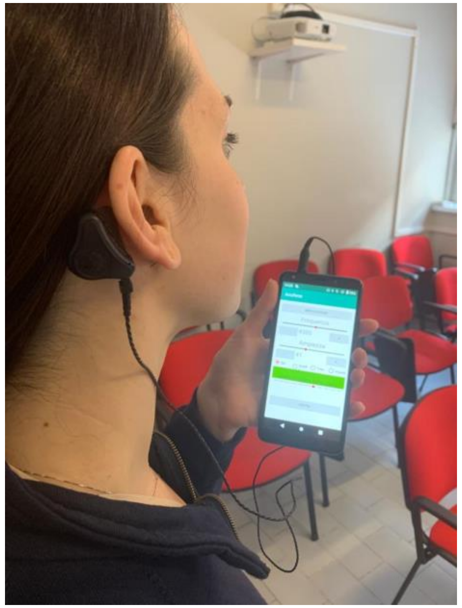
Generally in the left hemisphere, independently by the side where tinnitus is perceived

Sometimes only contralateral to tinnitus

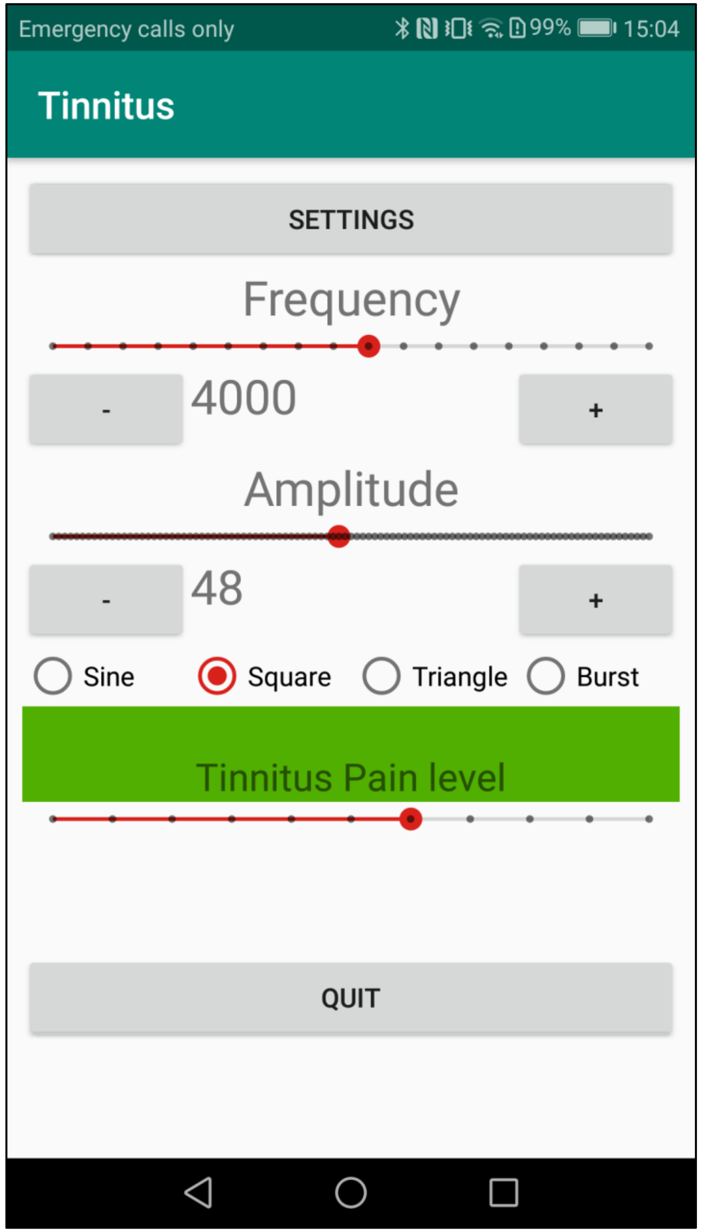


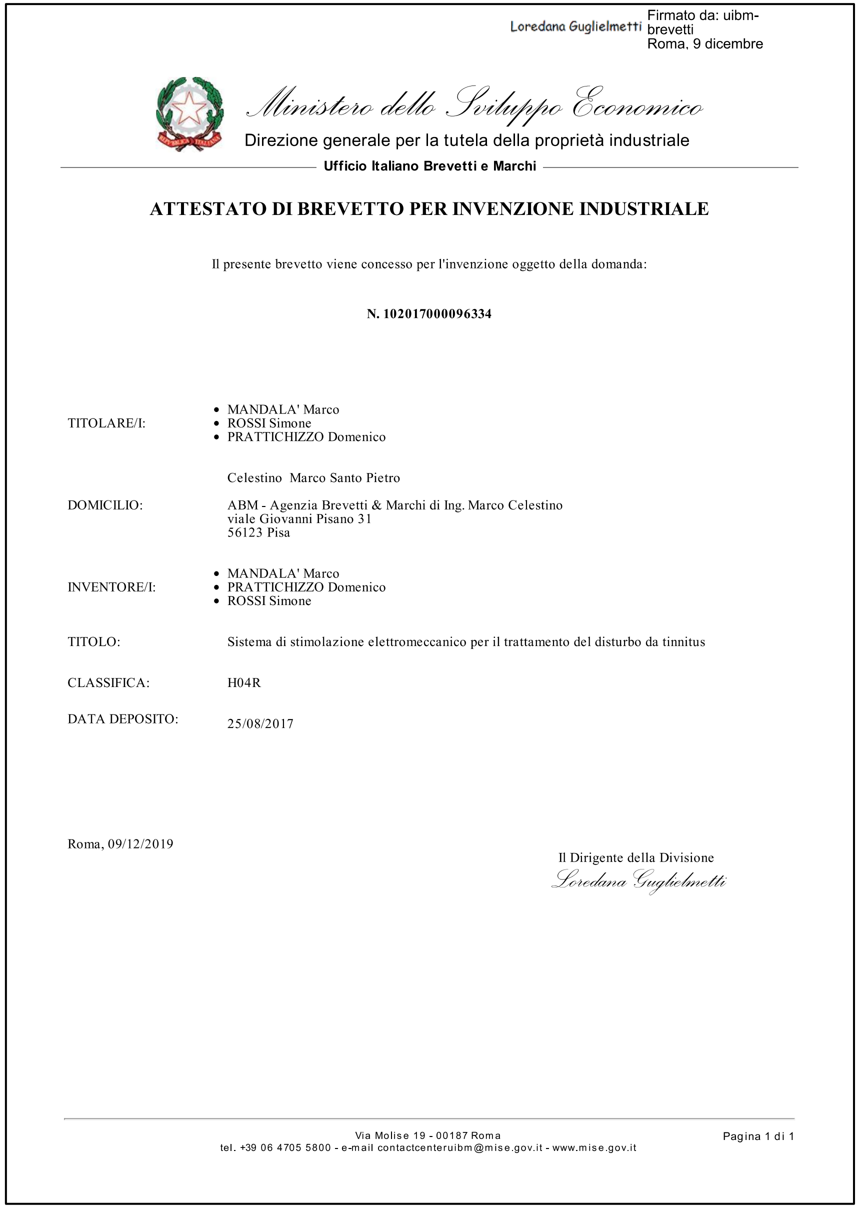
Transverse temporal gyrus (BA41)
Superior temporal gyrus (BA42,22)
Anterior temporal gyrus (BA38)
Hippocampal region

TINNITUS TREATMENT BY WEARABLE MULTISENSORY STIMULATION



Auditory
Vestibular
Somatosensory
(cutaneous and
proprioceptive)





Loredana Guglielmetti Firmato da: uibm-brevetti
Roma, 9 dicembre

Ministero dello Sviluppo Economico
Direzione generale per la tutela della proprietà industriale
Ufficio Italiano Brevetti e Marchi

ATTESTATO DI BREVETTO PER INVENZIONE INDUSTRIALE

Il presente brevetto viene concesso per l'invenzione oggetto della domanda:

N. 102017000096334

TITOLARE/I:	• MANDALA' Marco • ROSSI Simone • PRATTICHIZZO Domenico
DOMICILIO:	Celestino Marco Santo Pietro ABM - Agenzia Brevetti & Marchi di Ing. Marco Celestino viale Giovanni Pisano 31 56123 Pisa
INVENTORE/I:	• MANDALA' Marco • PRATTICHIZZO Domenico • ROSSI Simone
TITOLO:	Sistema di stimolazione elettromeccanico per il trattamento del disturbo da tinnitus
CLASSIFICA:	H04R
DATA DEPOSITO:	25/08/2017

Roma, 09/12/2019

Il Dirigente della Divisione
Loredana Guglielmetti

Via Molise 19 - 00187 Roma
tel. +39 06 4705 5800 - e-mail contactcenteruibm@mise.gov.it - www.mise.gov.it

Pagina 1 di 1

DATA ARE BEING COLLECTED