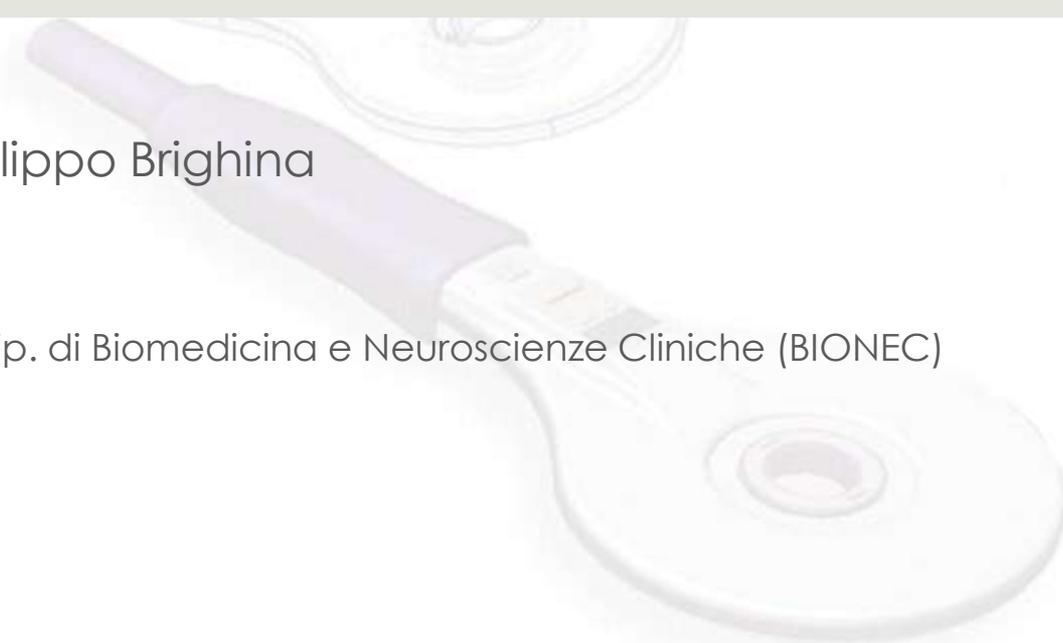


# Neurostimolazione cerebrale non invasiva ed emicrania

Fisiopatologia e prospettive terapeutiche

Filippo Brighina

Dip. di Biomedicina e Neuroscienze Cliniche (BIONEC)



# Il razionale: la TMS



*Snap! I don't feel any pain or notice anything unusual other than the sound, but my arm jumps again, seemingly of its own accord....*

Welcome to transcranial magnetic stimulation (TMS), one of the hottest research tools in neuroscience. Since its invention 15 years ago, TMS has become a relatively simple, noninvasive, and usually painless way to electrically stimulate specific brain regions. It's power tantalizes investigators who want to unravel how the human mind works. More recently, TMS has also grabbed the attention of physicians and psychologists, who predict that it has the potential to treat conditions ranging from epilepsy to stuttering to depression.



# Come funziona?

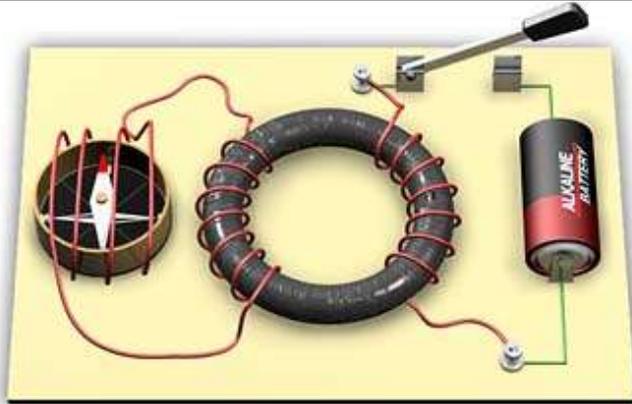
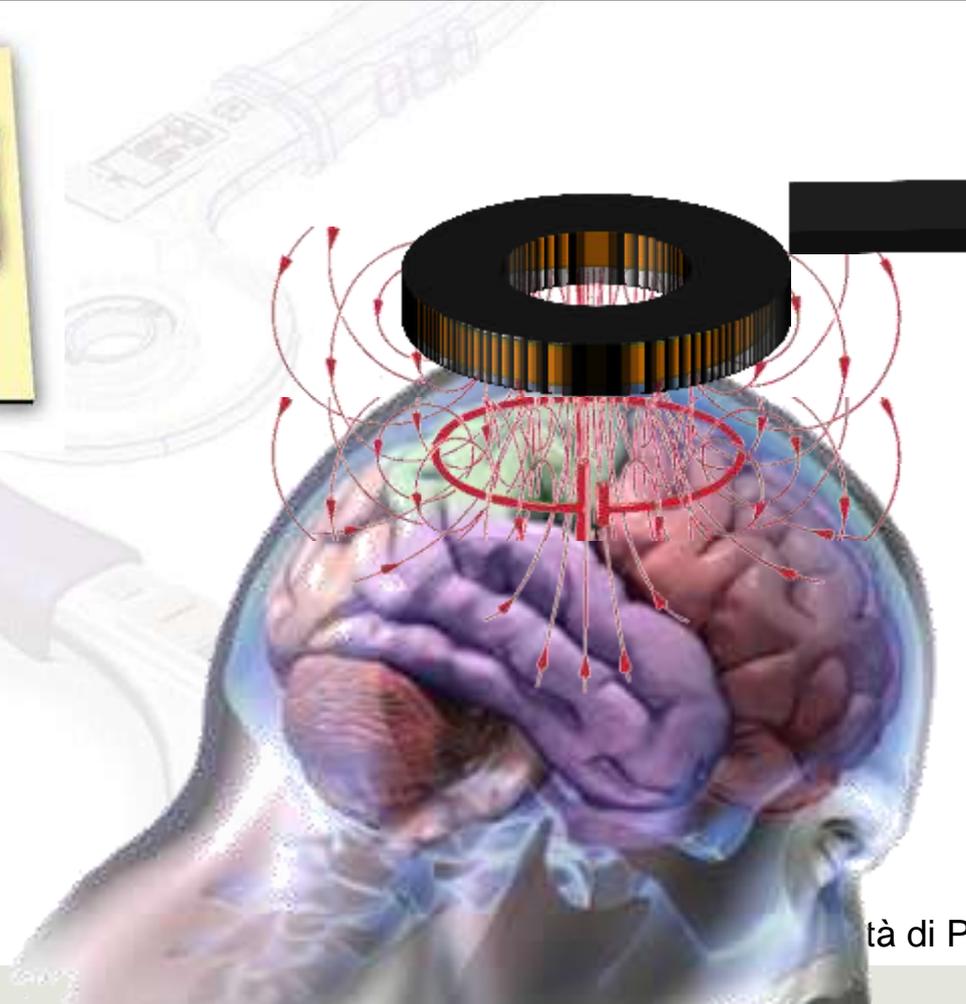
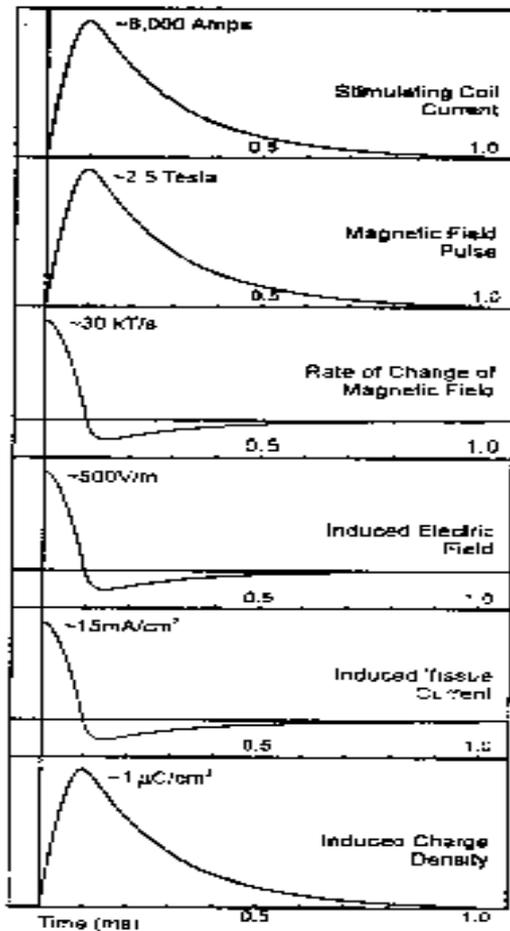


Figure 1



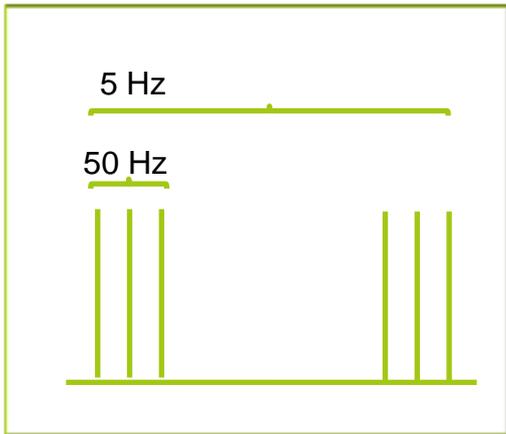
# Come funziona?



# “Coils”



# Potenzialità

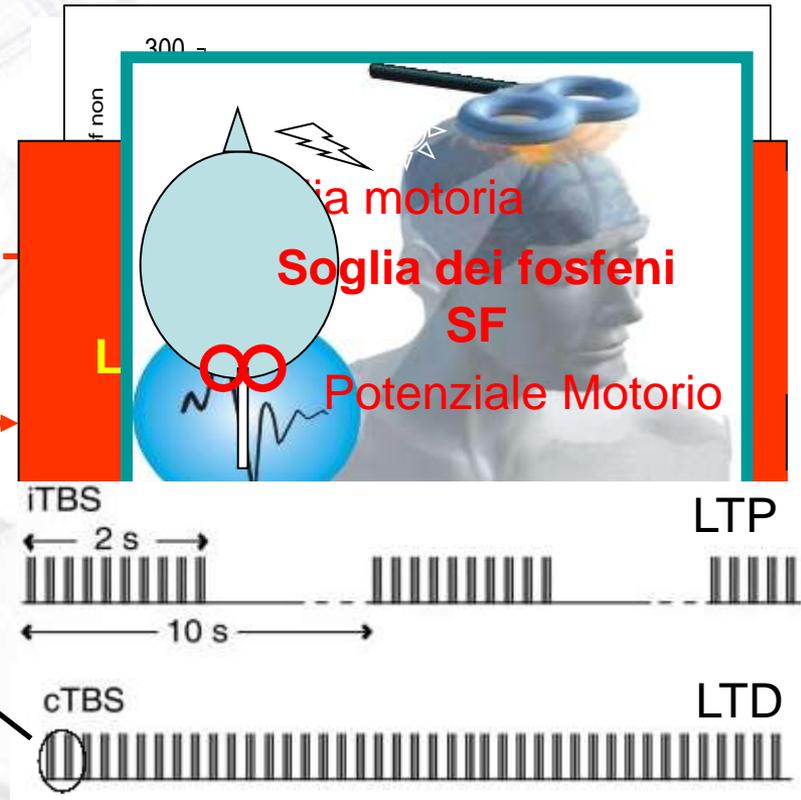


o stimolo

o stimolo

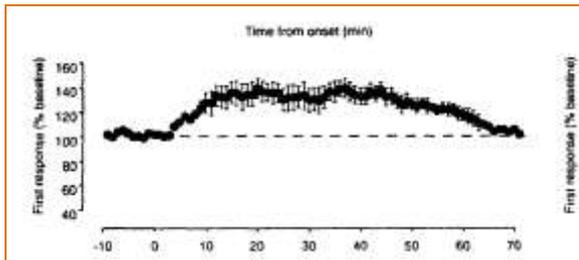
Ripetitivo

Theta burst

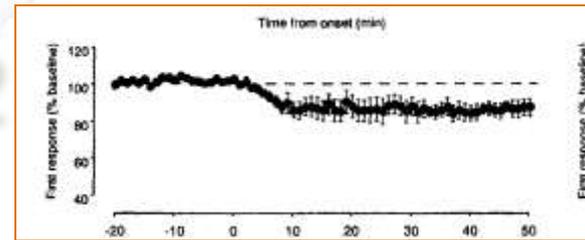


# rTMS: meccanismi elementari della plasticità cerebrale

1



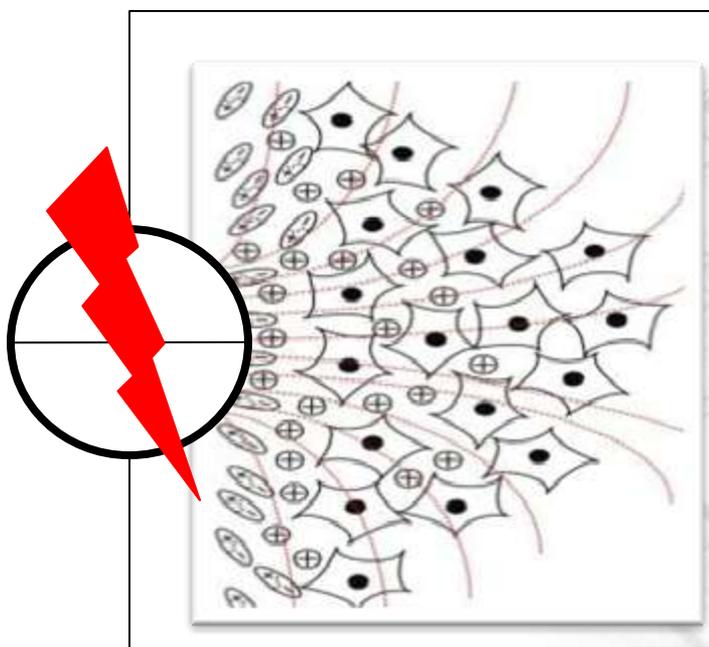
2



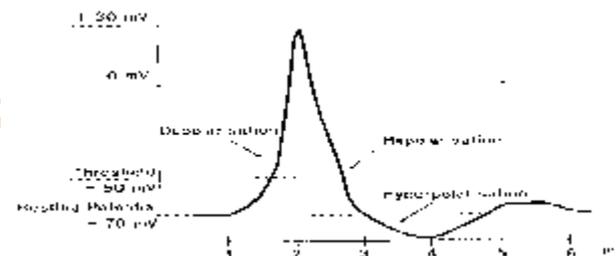
1 Long Term Potentiation (LTP): rTMS  $\geq$  3Hz  
eccitazione neuronale persistente dopo treni ad alta frequenza

2 Long Term Depression (LTD): rTMS  $<$  1Hz  
depressione neuronale persistente dopo treni a bassa frequenza

# Transcranial direct current stimulation (tDCS): principi



Applicazione di una corrente elettrica/campo elettrico al tessuto nervoso



VARIAZIONE DELLO STATO DI ECCITAZIONE DELLE CELLULE

VARIAZIONE DELLA RISPOSTA SINCRONA DI POPOLAZIONI DI NEURONI

# tDCS: caratteri generali

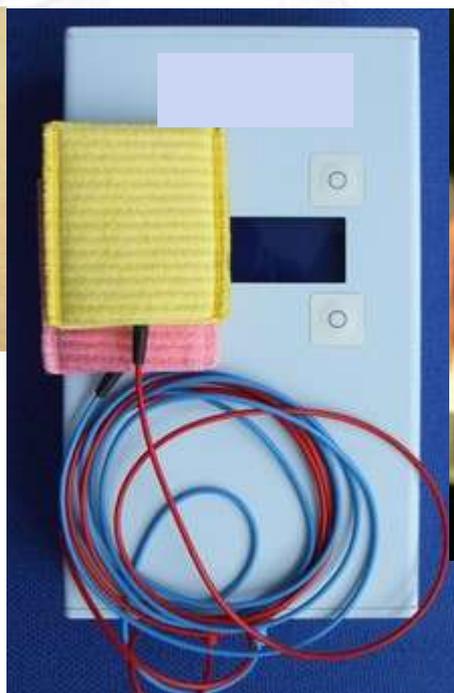
La tDCS è una tecnica di stimolazione cerebrale non invasiva che consiste nell'applicazione di una corrente continua di bassa intensità non percepibile dal soggetto allo scalpo tramite una coppia di elettrodi.

Infatti, la semplicità di tale tecnica, l'assenza di effetti collaterali e la persistenza degli effetti indotti la rendono un'interessante prospettiva per il trattamento di diverse patologie neurologiche e neuropsichiatriche

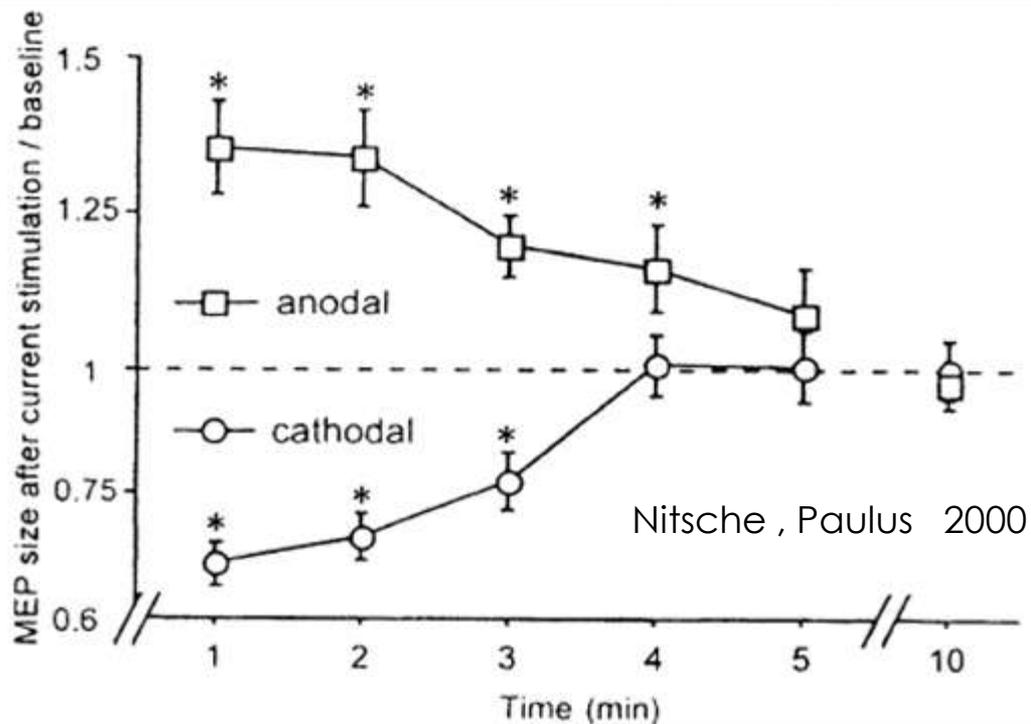
# Transcranial direct current stimulation (tDCS): principi

## Brain Stimulant

Blog focusing on new neurotechnology methods of brain stimulation, neuroscience and artificial intelligence.



# tDCS: tecnica di modulazione



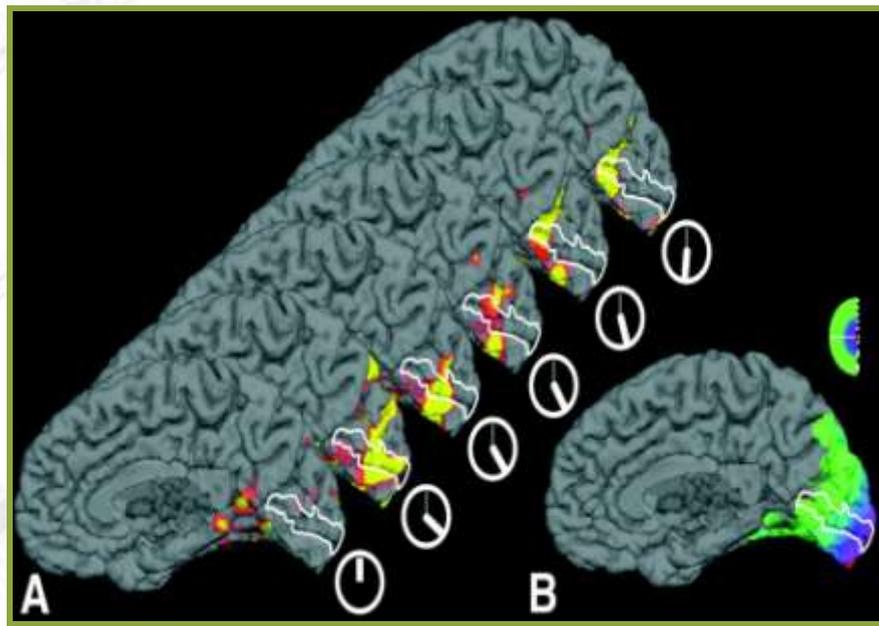
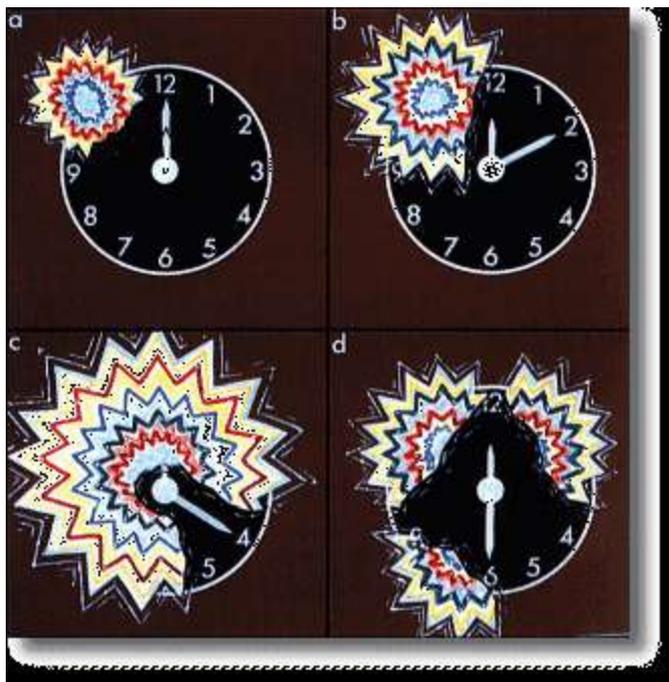
# rTMS, tDCS, emicrania

Applicazioni allo studio dei meccanismi fisiopatologici

Potenziali applicazioni terapeutiche



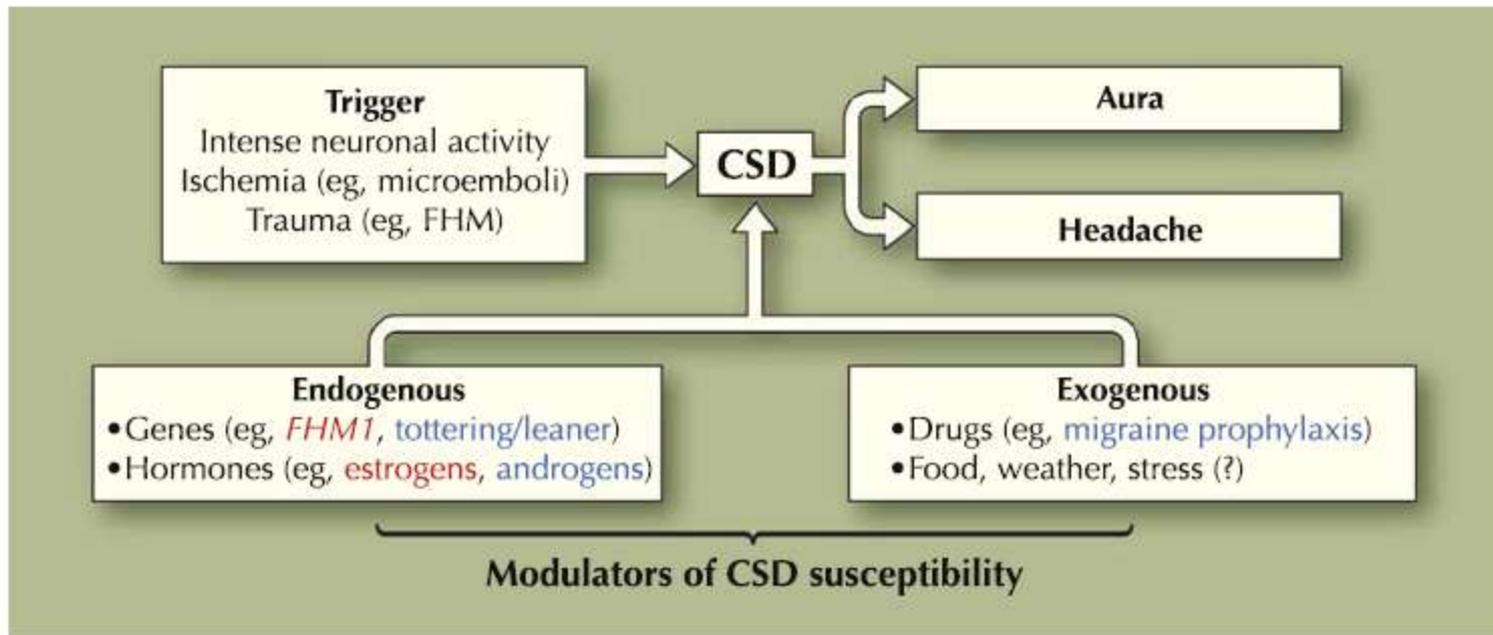
# Aura: modificazioni elettriche?





# Aura → dolore: CSD → Sist. Trig. Vas

Eikermann-Haerter & Ayata, 2010



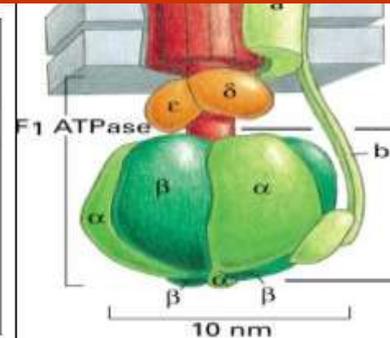
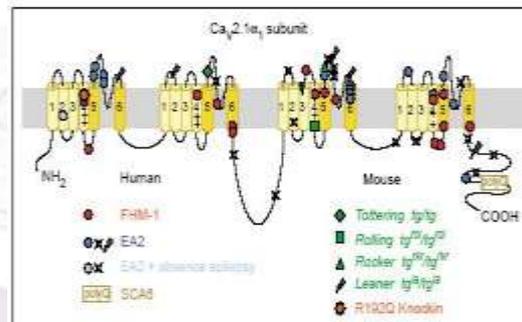
CSD attiva il sistema trigemino-vascolare in modelli animali  
Bolay et al, 2002

# La lezione delle FHM

*FHM 1*

*FHM 2*

*FHM 3*



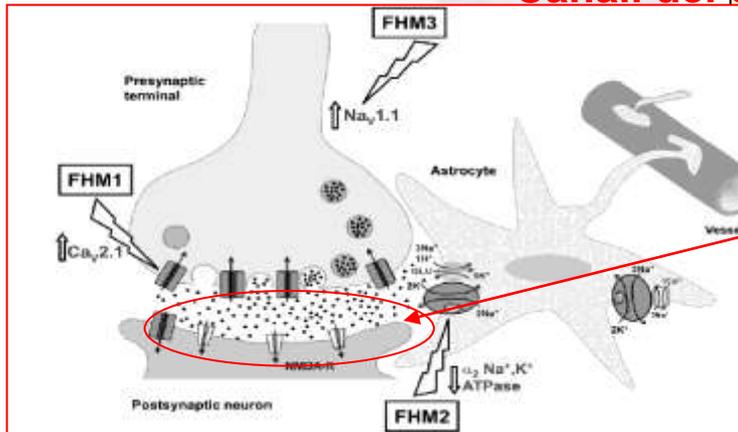
**Canali del calcio**

**Pompa Na/K**

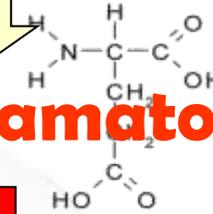
*De Fusco et al, 2003*

**Canali del Sodio**

*Dichgans et al, 2005*



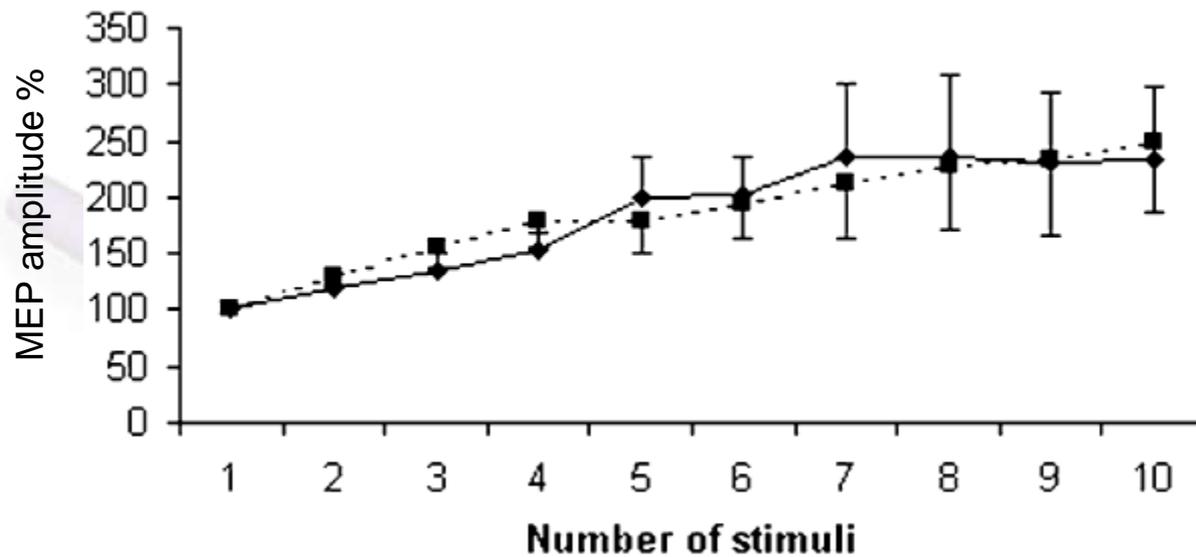
**glutamato**



**Ipereccitabilità corticale**



# 5 Hz rTMS (curva dei MEP)



Pascual.Leone et al, 1994

Berardelli et al, 1998,1999

Romeo et al, 1998,1999

# Metodi

18 emicranici con aura; 18 controlli

**Treni rTMS** : 10 impulsi, 5 Hz frequenza,  
2 Intensità: 110% MT: 9pz/9c  
130% MT: 9pz/9c



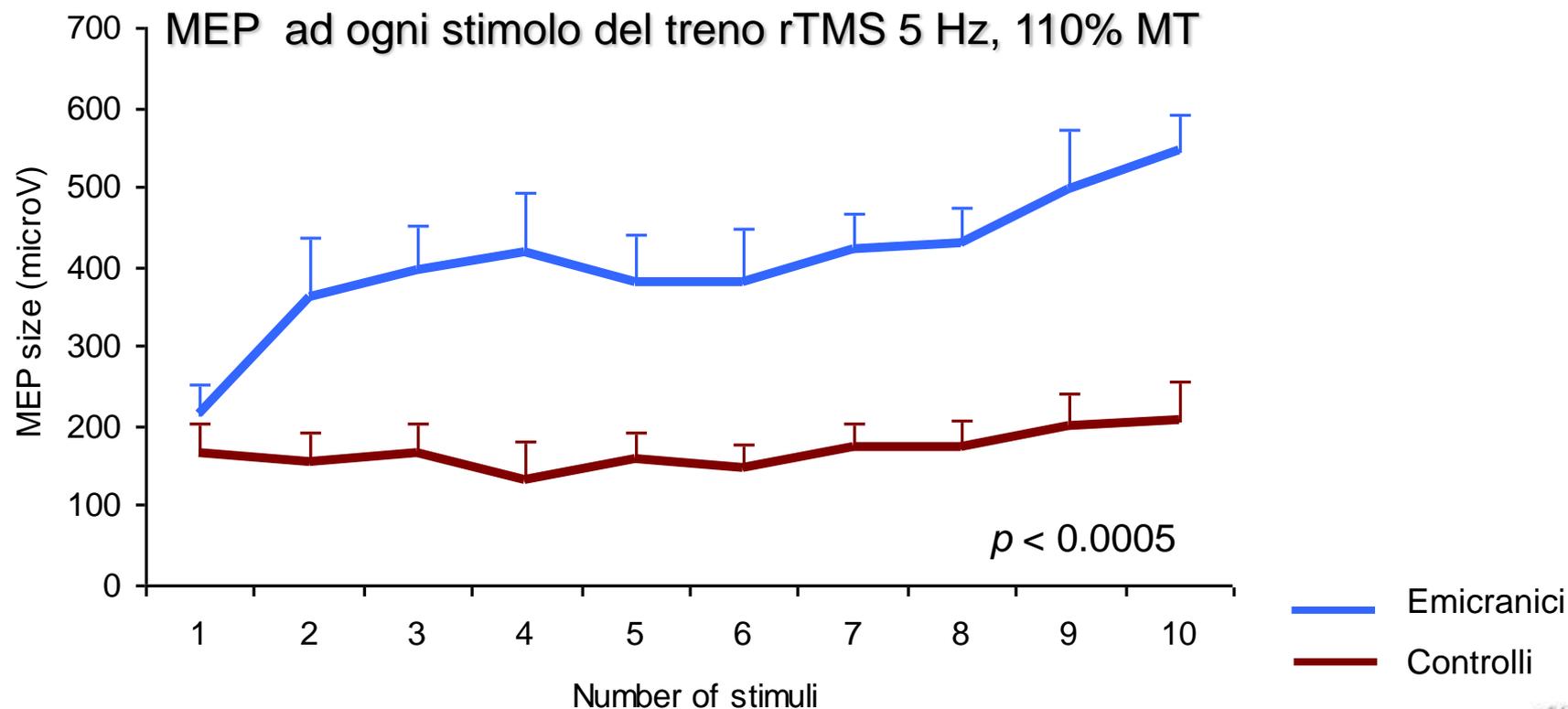
## ***Ampiezza del MEP***

Ampiezza MEP picco-picco ad ogni stimolo del treno

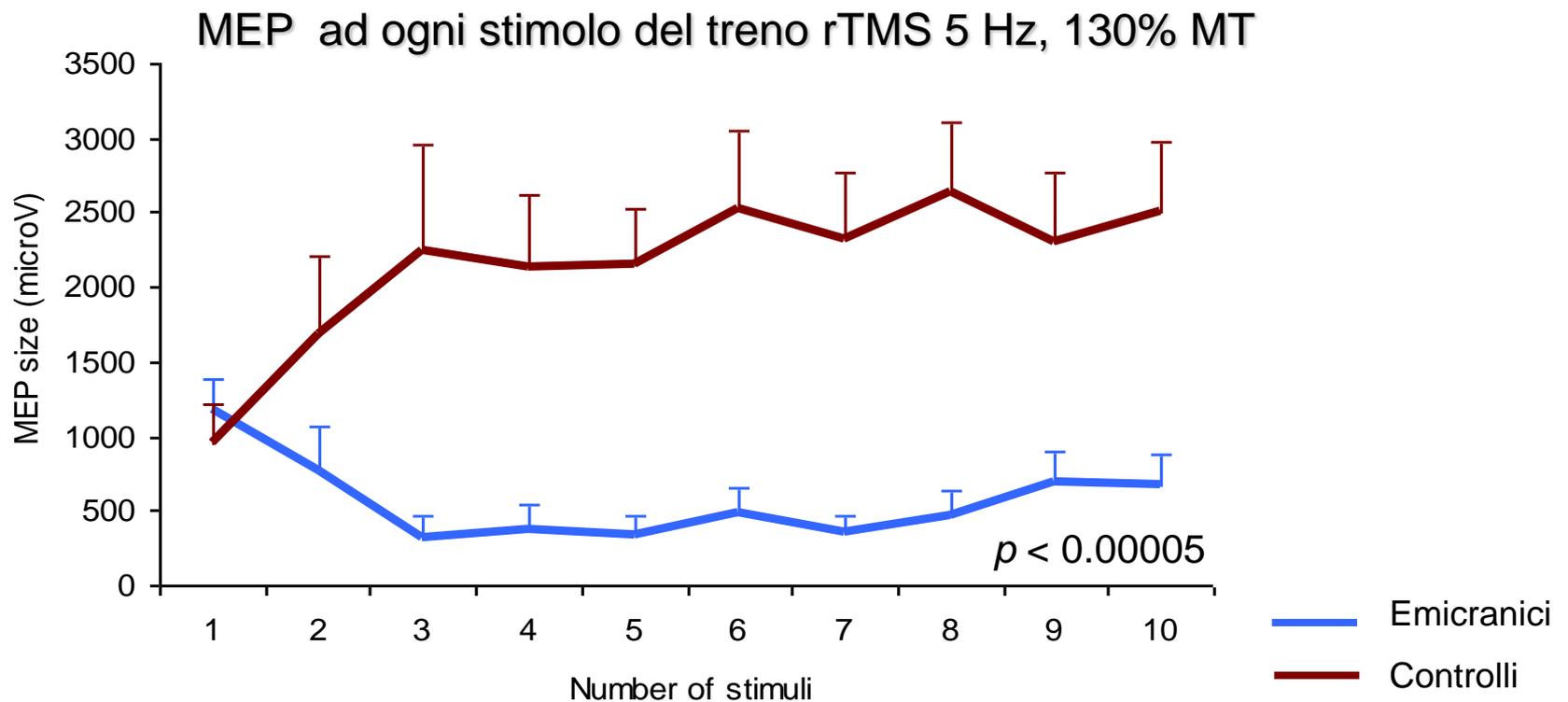
## ***Durata del periodo silente(SP)***

rTMS durante contrazione ABP dx (30% massimale); durata di SP ad ogni stimolo

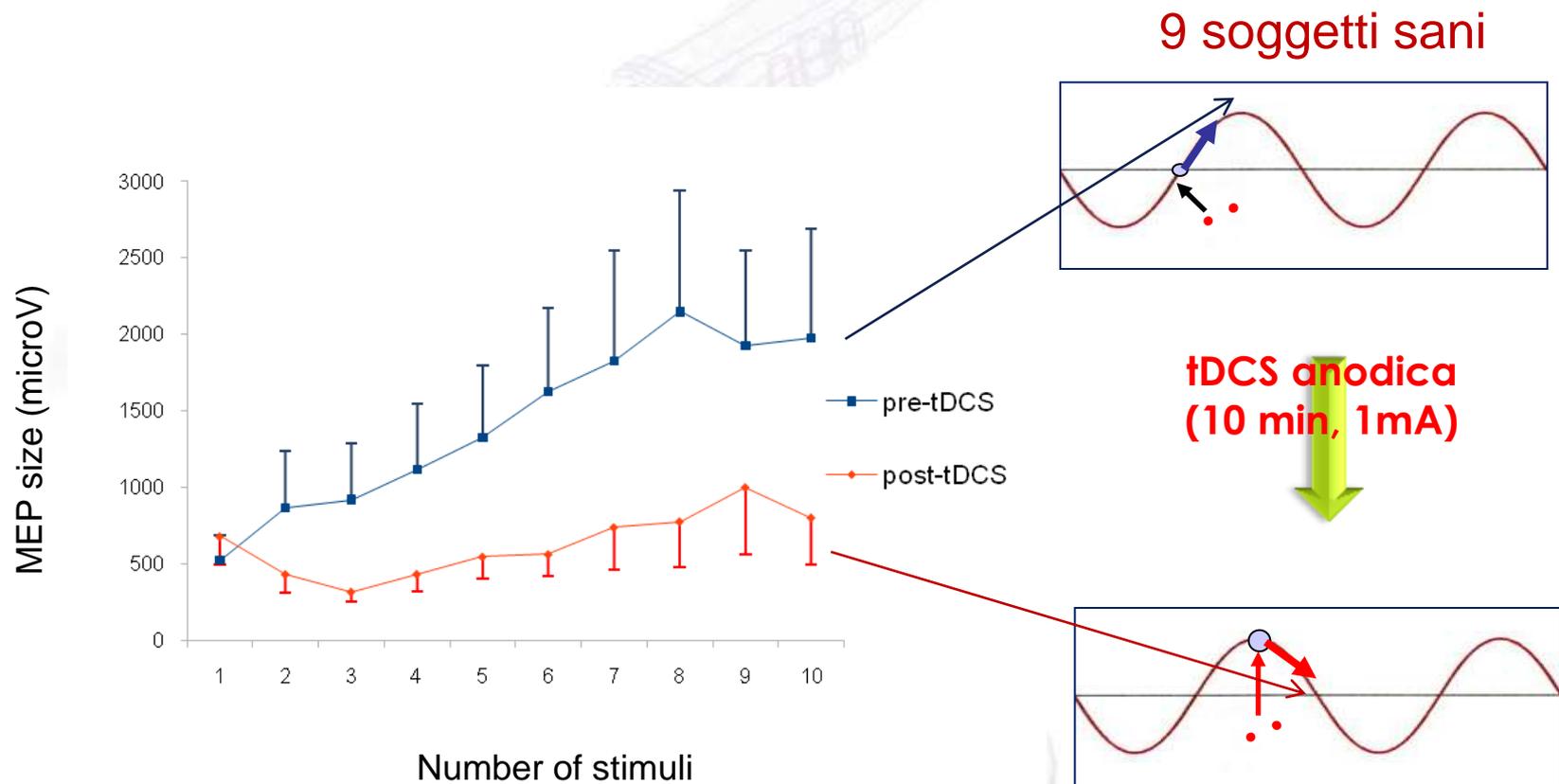
# Effetti di modulazione del MEP in relazione all'intensità: 110%



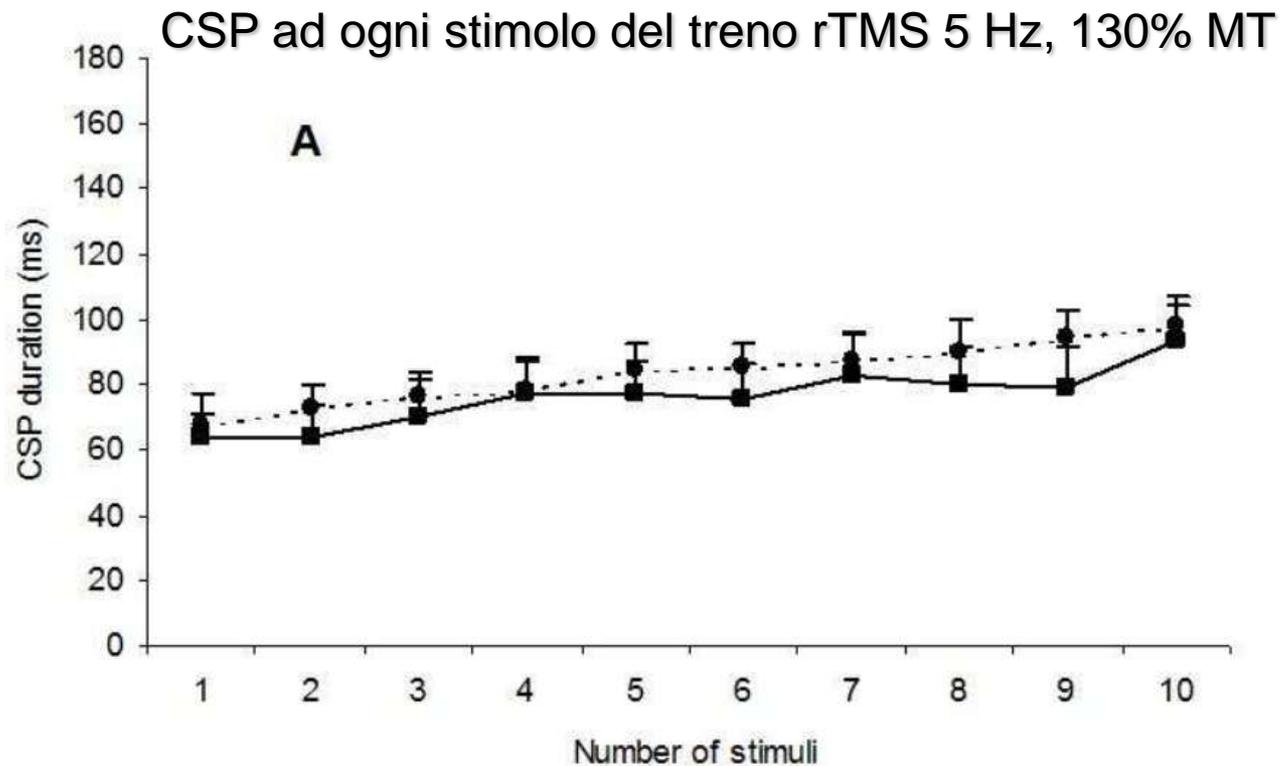
# Effetti di modulazione del MEP in relazione all'intensità: 130%



# Effetti della modulazione con tDCS



# Assenza di modulazione da intensità sul periodo silente



## The Headache of a Hyperactive Calcium Channel

Mingshan Xue<sup>1</sup> and Christian Rosenmund<sup>1,2,\*</sup>

<sup>1</sup>Department of Neuroscience

<sup>2</sup>Department of Molecular and Human Genetics

Baylor College of Medicine, Houston, TX 77030, USA

\*Correspondence: [rosenmun@bcm.tmc.edu](mailto:rosenmun@bcm.tmc.edu)

DOI 10.1016/j.neuron.2009.02.015

Migraine is thought to be triggered by excessive neocortical neuronal excitability that leads to cortical spreading depression. In this issue of *Neuron*, Tottene et al. study a mouse model of familial hemiplegic migraine type 1, and provide evidence for the hyperactivity of P/Q-type calcium channel-mediated cortical glutamatergic synaptic transmission as an underlying mechanism for the susceptibility of cortical spreading depression initiation in migraine disorders.

Facilitazione diretta per maggiore responsività dei canali ed incremento del Glu

Facilitazione indiretta per ridotta efficienza inibitoria da ridotta attività G protein da squilibrio P/Q vs N ed R Ca canali : ridotta inibizione !

L'iperattivazione dei canali Ca non modifica però la trasmissione GABA nei neuroni inibitori:  
assenza di effetti short term sul periodo silente

# Contribution of calcium-dependent facilitation to synaptic plasticity revealed by migraine mutations in the P/Q-type calcium channel

Paul J. Adams<sup>a</sup>, Ravi L. Rungta<sup>b</sup>, Esperanza Garcia<sup>a</sup>, Arn M. J. M. van den Maagdenberg<sup>c</sup>, Brian A. MacVicar<sup>b</sup>, and Terrance P. Snutch<sup>a,b,1</sup>

<sup>a</sup>Michael Smith Laboratories, University of British Columbia, Vancouver, BC, Canada V6T 1Z4; <sup>b</sup>Brain Research Centre, Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada V6T 2B5; and <sup>c</sup>Department of Human Genetics, Leiden University Medical Centre, 2300 RC, Leiden, The Netherlands

Ipereccitabilità basale da aumentato ingresso del calcio

Possibili effetti inibitori per successive stimolazioni per innesco meccanismi di plasticità omeostatica



# Usi terapeutici della rTMS

- Depressione maggiore
- Schizofrenia, DOC, allucinazioni
- Tinnitus
- Afasie
- Riabilitazione post-stroke
- ...

# The Migraine Zapper



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## Migraine Headache Study

*Treatment of Migraine Headache by Non-Invasive Transcranial Magnetic Stimulation*

A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of Transcranial Magnetic Stimulation (TMS) for the treatment of migraine headache. The purpose of this study is to evaluate the treatment following TMS pulses, an alteration of the sympathetic and parasympathetic autonomic activity which showed alteration in previous trials.



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# Stato dell'arte

*Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*

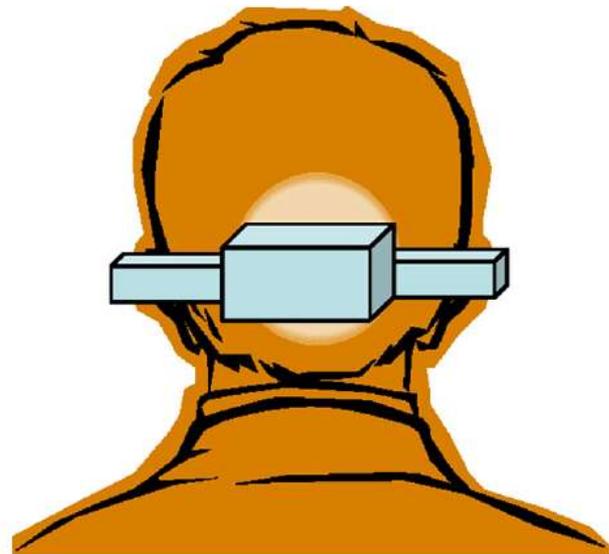
## Transcranial Magnetic Simulation in the Treatment of Migraine

Richard B. Lipton\* and Starr H. Pearlman†

*\*Departments of Neurology, Epidemiology and Population Health and the Montefiore Headache Center, Albert Einstein College of Medicine, Bronx, New York 10461; and the †Department of Biology, Armstrong Atlantic State University, Savannah, Georgia 31419*



# Attacco emicranico



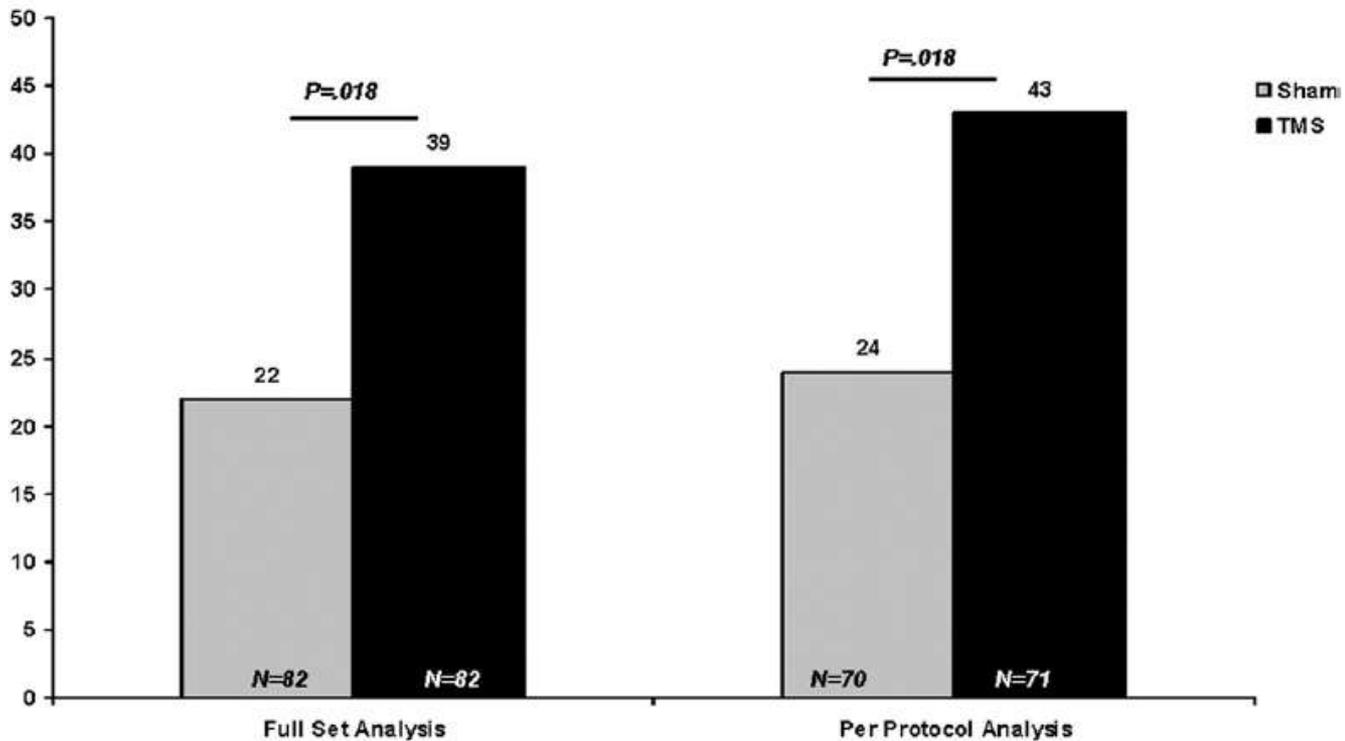
**Table 1. Efficacy of sTMS for Acute Migraine Treatment**

sTMS—Acute Tx	Study Design	Number of Patients	Device/Site of Application	Dose and Frequency	Response/Primary Endpoint
Lipton et al., <sup>25</sup> 2010 Migraine with aura 30% of attacks; <8 attacks/mo	Randomized, sham-controlled, double blind	n = 201	Portable sTMS over occiput	2 pulses; 30 s interval	2 H pain-free response rates: TMS = 39%; sham = 22%; $p = 0.0179$
Clarke et al., <sup>27</sup> 2006 Episodic migraine	Randomized to high- or low-impulse group	n = 42	Tabletop clinic-based sTMS over area of brain generating pain or aura	2 pulses, 5 s interval	69% reported improvement; 32% reported pain-free at 24 h.
Mohammad et al., <sup>55</sup> 2006 Migraine with aura 75% of the time; <7 attacks/mo	Randomized, double blind, parallel group, sham-controlled	n = 42 (50 attacks)	Tabletop Clinic-based sTMS over occiput	2 pulses, 30 s interval	69% reported mild pain or no pain at 2-h <i>versus</i> 48% sham ( $p = 0.1$ )
Mohammad et al., <sup>54</sup> 2006 Migraine with aura 75% of the time; 2–4 attacks/mo	Open label, 3-month	n = 12	Portable sTMS; over occiput	2 pulses, onset of aura	81% of attacks pain-free at 2 h after treatment

sTMS = single-pulse transcranial magnetic stimulations; TMS = transcranial magnetic stimulation; Tx = treatment.

# Attacco emicranico

% of subjects pain free at 2 hours after sTMS treatment



# Trattamento preventivo

rTMS-Preventive Tx	Study Design	Number of Patients	Device/Site of Application	Dose and Frequency	Response/Primary Endpoint
Teepker et al., <sup>57</sup> 2009 Migraine >4 attacks per month	Pre-post design	n = 27	Tabletop	500 pulses; 1 Hz for 5 days	27.5% reduction in number of migraine attacks <i>versus</i> baseline ( $p = 0.007$ ; NS vs sham $p = 0.216$ )
Brighina et al., <sup>56</sup> 2004 Chronic migraine	Randomized, double-blind, sham control	n = 11	Tabletop/ dorsolateral prefrontal cortex	10 trains or 2 s duration; 30 s intervals; 12 sessions on alternate days	Improvement over baseline in attack frequency, acute treatment use, headache index; NS <i>versus</i> sham

rTMS = repetitive transcranial magnetic stimulations; NS = not significant; Tx = treatment.



Journal of the Neurological Sciences 227 (2004) 67–71

Journal of the  
**Neurological  
Sciences**

[www.elsevier.com/locate/jns](http://www.elsevier.com/locate/jns)

## rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study

Filippo Brighina, Aurelio Piazza, Gaetano Vitello, Antonina Aloisio, Antonio Palermo,  
Ornella Daniele, Brigida Fierro\*

*Neurophysiological Unit, University of Palermo, Palermo, Italy*

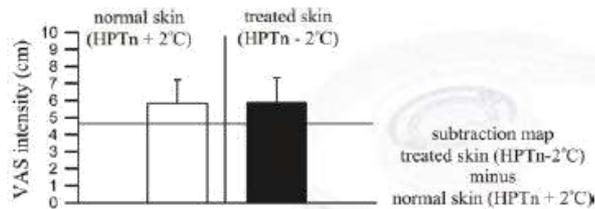
Received 14 May 2004; received in revised form 10 August 2004; accepted 11 August 2004  
Available online 23 September 2004

# rTMS nelle cefalee: la nostra esperienza

Effetti della rTMS sull'emicrania cronicizzata



# rTMS nell'e. cronica background

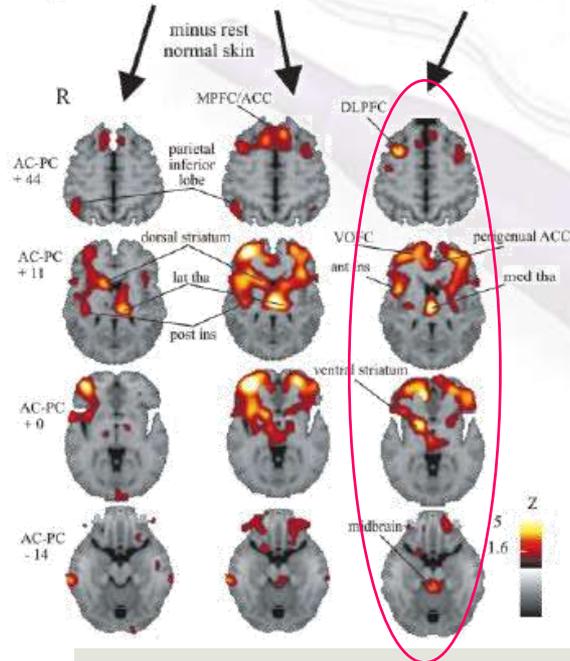


DOI: 10.1093/brain/hwg102

Brain (2003), 126, 1079-1091

## Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation

J. Lorenz,<sup>1,3,5</sup> S. Minoshima<sup>4</sup> and K. L. Casey<sup>1,2,3</sup>



Attivazione della DLPFC



Inibizione vie del dolore



Ridotta sensazione dolorifica

Università di Palermo

Lorenz et al, Brain 2003



# rTMS nell'e. cronica

## Soggetti e metodi

- 11 pazienti (7 F/ 4 M) età media:  $47 \pm 7$ , range: 33-56 anni
- Diagnosi: Emicrania cronica
- Almeno tre tentativi di profilassi inefficaci.
- Punteggio al test di Hamilton  $< 7$

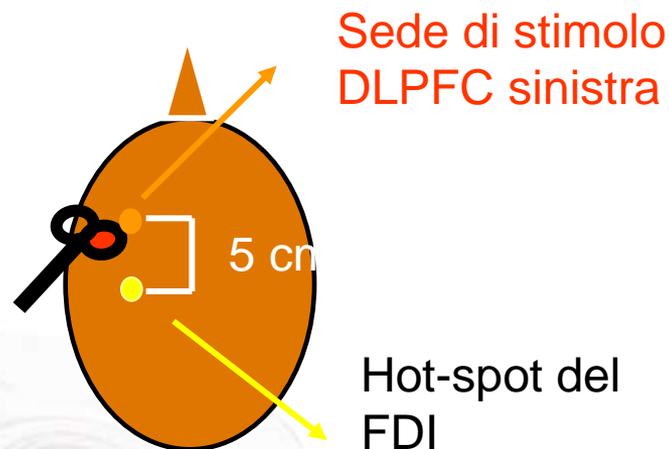
# rTMS nell'e. cronica

## TMS

- Il trattamento consisteva di 12 sedute di stimolazione a giorni alterni

- In ogni seduta:

10 treni di 2 sec.  
20 Hz frequenza  
90% soglia motoria  
Pause intertreno : 30 sec.



Sham rTMS: medesima procedura con coil a 90

# rTMS nell'e. cronica

## Disegno dello studio

- 2 gruppi di trattamento:

rTMS: 6 pazienti

Sham (placebo): 5 pazienti

### Tempi dello studio

Mese 1 (T0)

Mese 2 (T1)

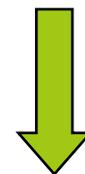
Mese 3 (T2)



Inclusione



Trattamento



Follow-up

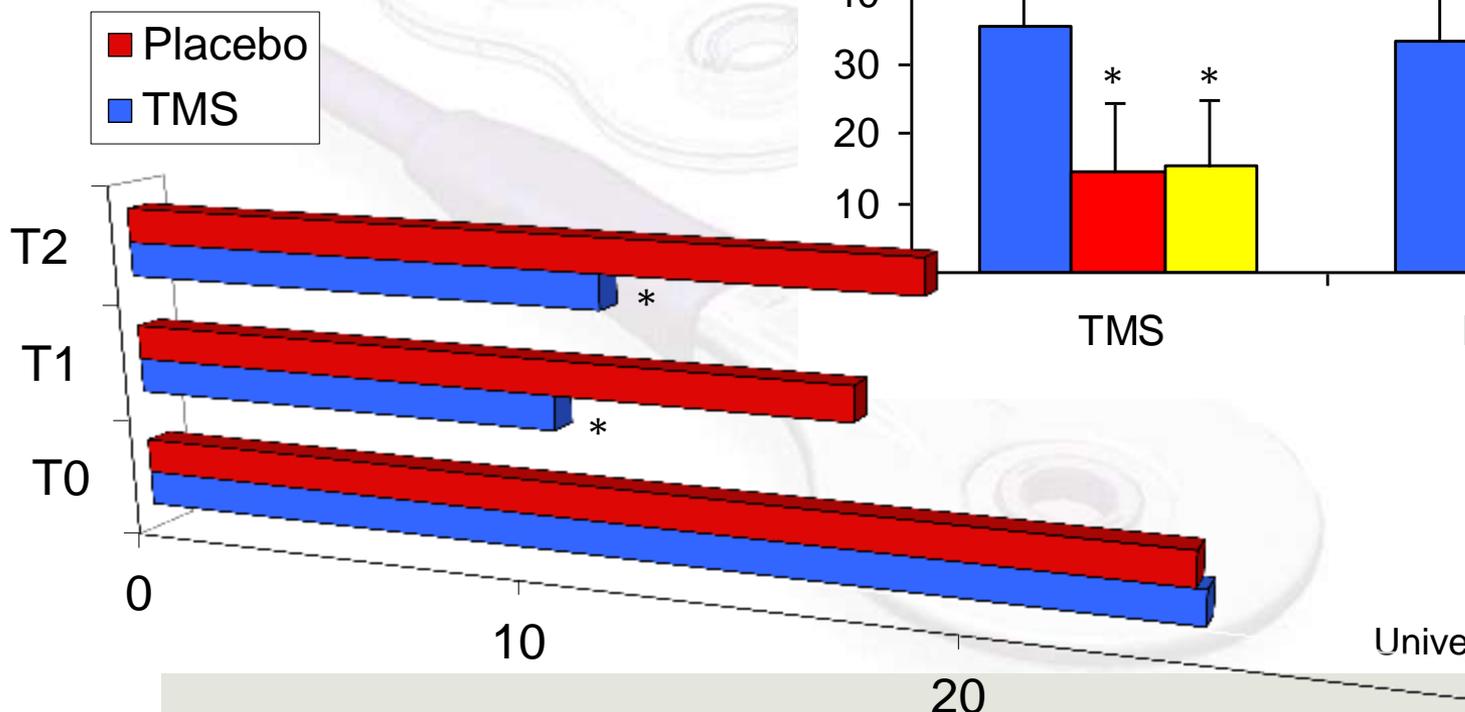
# rTMS nell'e. cronica

## Risultati

### Frequenza attacchi

Interazione tempi x trattamento:  $F(2,18)=13.86, p<.0002.$

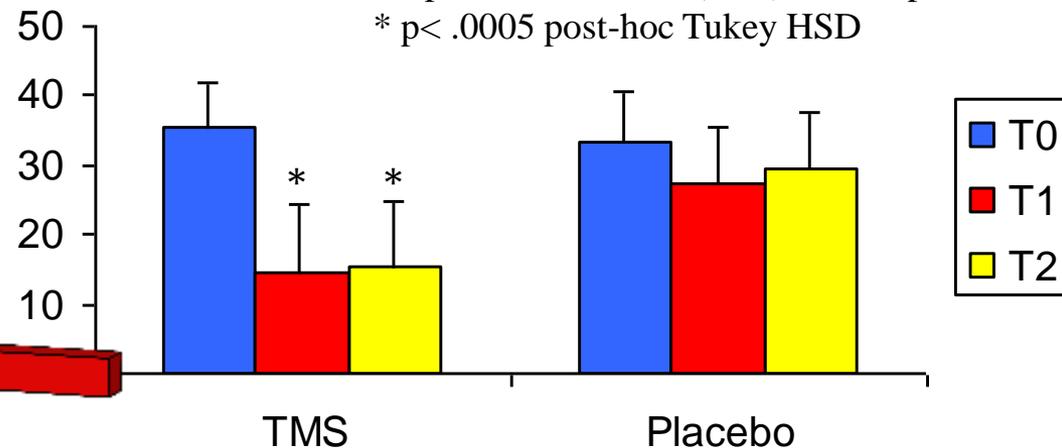
\*  $p<.001$  post-hoc Tukey HSD



### N° farmaci sintomatici

Interazione tempi x trattamento  $F(2,18)=16.83, p<.0001.$

\*  $p<.0005$  post-hoc Tukey HSD



# rTMS nell'e. cronica

## Discussione

- L'rTMS sull'area DLPFC di sinistra sembra in grado di migliorare il quadro clinico in pazienti affetti da emicrania cronica:
  - Riduzione degli attacchi
  - Riduzione del numero di farmaci sintomatici

# †DCS?

*Original Article*

**Cephalalgia**  International  
Headache Society  
An International Journal of Headache

## **Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine**

**Andrea Antal<sup>1</sup>, Naomi Kriener<sup>1</sup>, Nicolas Lang<sup>2</sup>, Klara Boros<sup>1</sup>  
and Walter Paulus<sup>1</sup>**

*Cephalalgia*

31 (7) 820–828

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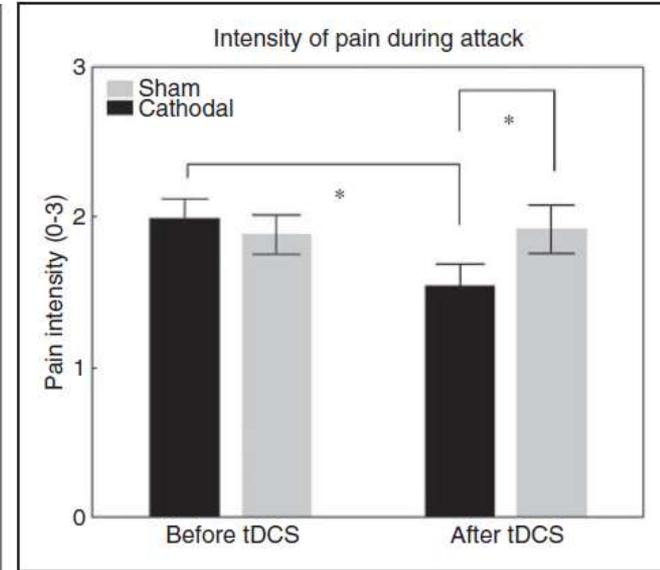
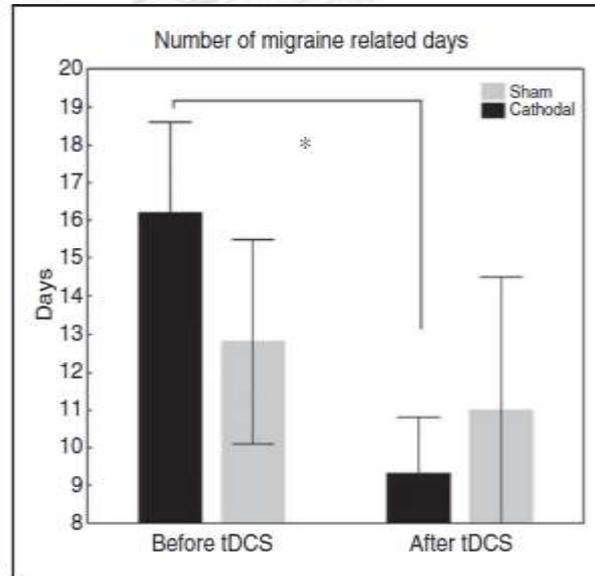
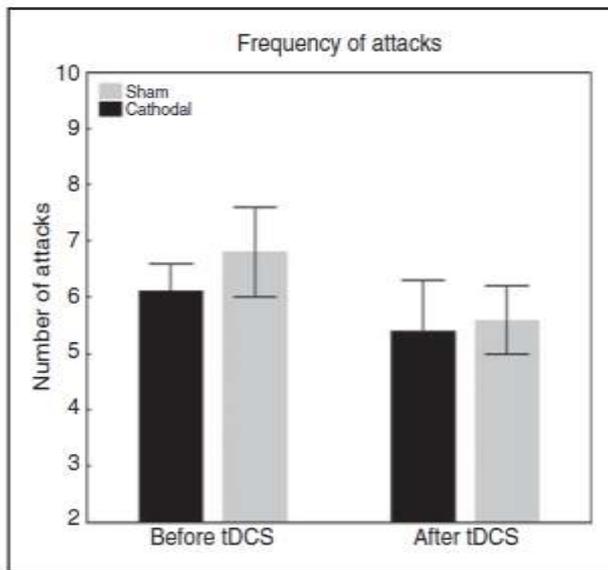
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DOI: 10.1177/0333102411399349

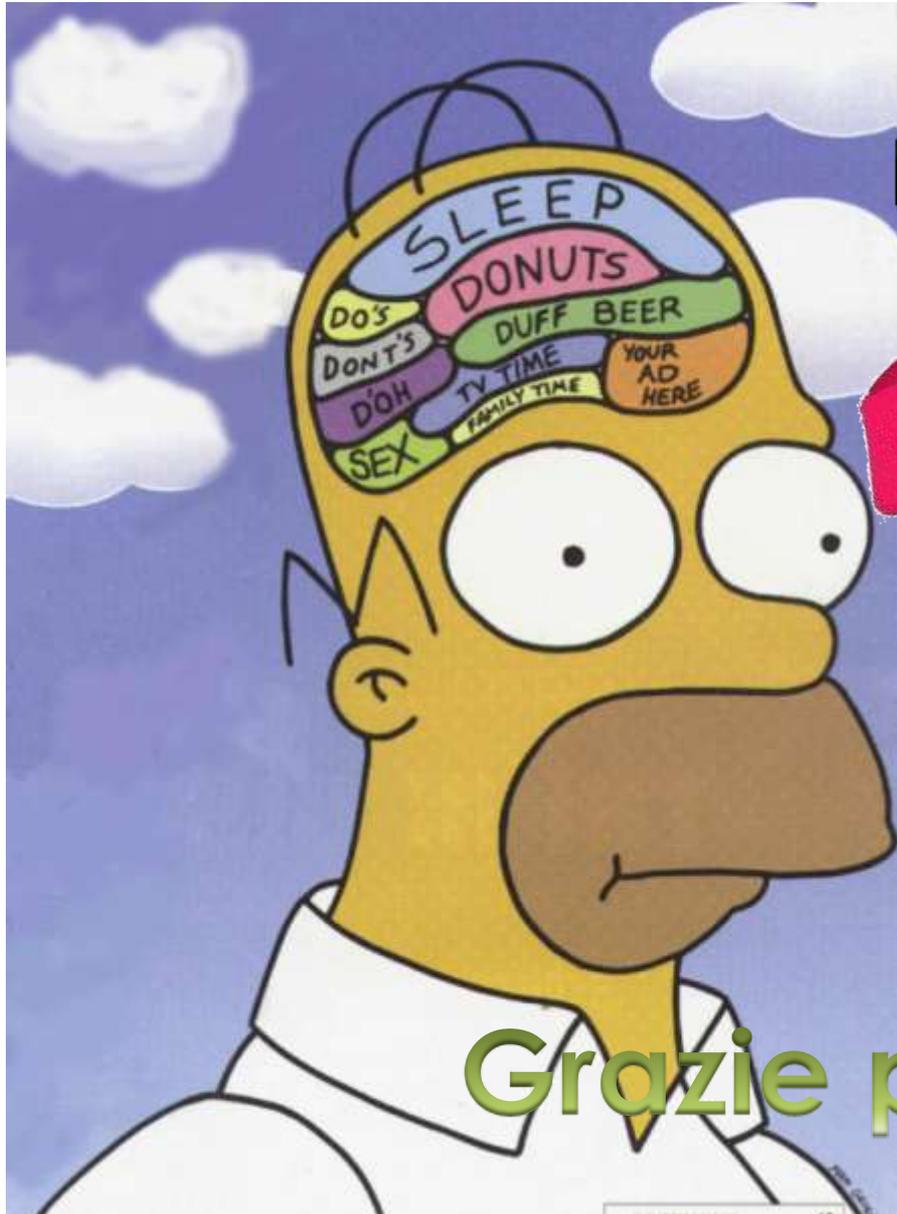
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In futuro....





Grazie per l'attenzione!

