The future of migraine research: the Pavia School continues:

Neuromodulation

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Celebrations of the 50 years of the Pavia Headache Centre
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Disclosure Slide

I have no financial relationships with any commercial interest related to the content of this presentation
Why use non-invasive brain stimulation techniques (NIBS) in migraine research?
• To investigate pathophysiological mechanisms

• For therapeutic reasons
NIBS: main techniques

Transcranial Magnetic Stimulation (TMS)

Transcranial Electrical Stimulation (TES)
### TMS vs TES

**TMS**
- Neuromodulation, **neurostimulation**
- Expensive equipment
- Placebo stimulation: sham coil
- Higher spatial resolution (in relation to the characteristics of the coil)
- Less suited for ‘online’ training / tasks
- Safe but reported seizures with some stimulation parameters
- It induces action potentials at the level of stimulated neurons
- In relation to the stimulation parameters, it can induce reduction or enhancement of cortical excitability, which can last for hours or days

**TES**
- Neuromodulation
- Less expensive and portable
- Reliable placebo stimulation
- Low spatial resolution
- Ideal for ‘online’ protocols
- Excellent safety profile as it does not induce action potentials at the axonal level
- It modulates the firing rate of active neurons
- In relation to polarity, it can induce reduction or enhancement of cortical excitability, which can last for hours or days
Pathophysiology of migraine: what we know...

- Pathogenesis of pain
- Mechanisms responsible for aura symptoms
Pathophysiology of migraine: what we still do not know...

- What mechanisms lead to the activation of the TVS? And why does this happen more frequently in some subjects?
  - What mechanisms underlie the recurrence of attacks?
- How do the many possible triggers of a migraine attack work?
  - What are the mechanisms responsible for the evolution of migraine from an episodic to a chronic form?
The migraine puzzle

Hyperresponsivity

- Low cortical preactivation level (cortical hypoexcitability)
- Cortical hyperexcitability

Hypoexcitability vs Hyperexcitability

Disexcitability

- Glutamatergic hyperactivity
- Impaired intracortical inhibition
Cortical hypoactivation

- 5 Hz rTMS trains (130% MT)
- 5 Hz rTMS sessions

Cortical hyperresponsivity

- 5 Hz rTMS trains (110-120% MT)
- Single pulse TMS: I-O curves
- Intracortical facilitation
  (high stimulation intensity)
- 1 Hz rTMS sessions
- Evoked potentials
  (high stimulation intensity)

Normal cortical activation

- Evoked potentials
  (after the first blocks, low stimulation intensity)
- Intracortical facilitation
  (low stimulation intensity)
- Single pulse TMS: motor and phosphenes threshold
- Evoked potentials
  (first blocks, low stimulation intensity)

Cosentino et al., Clin Neurophysiol. 2014
Cortical hyperresponsivity

- Reduced threshold for inhibitory homeostatic responses
- Glutamatergic hyperactivity
- Reduced intracortical inhibition (relative)
- Reduced cortical preactivation

compensatory mechanisms

Cosentino et al., *Clin Neurophysiol*. 2014
Glutamatergic dysfunction in migraine

Glutamate is involved in the mechanisms of cortical spreading depression, neurogenic inflammation and trigeminal sensitization

(Gorji, 2001; Goadsby and Classey, 2000)

Increased interictal cerebrospinal and plasma glutamate levels in migraine

(Peres et al, 2004; Alam et al., 1998)

Impairment of glutamatergic metabolism in migraine platelets

(Vaccaro et al., 2007)

Animal models of familial hemiplegic migraine (FHM)

(van den Maagdenberg et al., 2004)

Neuroimaging studies showing increased glutamatergic neurotransmission in the migraine visual cortex

(Siniatchkin et al., 2012, Zielman et al., 2017)
Intracortical facilitation within the migraine motor cortex depends on the stimulation intensity. A paired-pulse TMS study

Giuseppe Cosentino, Salvatore Di Marco, Salvatore Felisi, Francesca Valentino, Walter M. Capitano, Brígida Fierro and Filippo Brighina

A. Intracortical facilitation (ICF)

B. Short intracortical inhibition (SICI)

C. Long intracortical inhibition (LICI)
The origin of the attack: the role of the cerebral cortex

Activation of the TVS

Cortical hyperresponsivity

K+ H+ Glutamate Aspartate NO Adenosine Eicosanoids

Cortical spreading depression

Migraine triggers

Bolay, 2012
Susceptibility to migraine attacks cannot be explained by a low activation threshold of the TVS!

Prodromal symptoms

Osmophobia

Changes in serotonergic metabolism before the attack
(Demarquay et al., 2011)

HYPERRESPONSIVITY OF THE MIGRAINE CORTEX AT THE BASIS OF THE SUSCEPTIBILITY TO MIGRAINE ATTACK?
5-Hz repetitive Transcranial Magnetic Stimulation (5-Hz rTMS)

2 sec

10 magnetic stimuli at 5 Hz (≥ 120%RMT)
5-Hz repetitive Transcranial Magnetic Stimulation (5-Hz rTMS)

Facilitation of MEPs mainly depends on glutamate neurotransmission mechanisms

(Berardelli et al. 1998; Richards et al., 2010)
Abnormal facilitatory mechanisms in motor cortex of migraine with aura

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Cortical hyperresponsivity

Hyporesponsivity due to activation of homeostatic inhibitory mechanisms
Homeostatic plasticity mechanisms

Bienenstock-Cooper-Munro (BCM) theory of bidirectional synaptic plasticity

The threshold for the induction of synaptic plasticity mechanisms as long-term potentiation (LTP) or long-term depression (LTD) is not constant, but changes according to the basal activity level of the neuronal circuit.
Homeostatic plasticity mechanisms

Bienenstock-Cooper-Munro (BCM) theory of bidirectional synaptic plasticity

The threshold for the induction of synaptic plasticity mechanisms as long-term potentiation (LTP) or long-term depression (LTD) is not constant, but changes according to the basal activity level of the neuronal circuit.
Conditioning effects of tDCS on motor cortical response to rTMS

Preconditioning with "facilitatory" anodal tDCS reverses the normally "facilitatory" effects of high frequency rTMS (5 Hz)

(Siebner et al., 2004)

Preconditioning with cathodal "inhibitory" tDCS reverses the normally "inhibitory" effects of low frequency (1 Hz) rTMS

(Lang et al., 2004)
5 Hz-rTMS trains induce inhibitory homeostatic responses under conditions of experimental hyperexcitability.
Preconditioning with "inhibitory" cathodal tDCS normalizes the facilitatory response to suprathreshold 5 Hz-rTMS trains (130% RMT) in migraine patients with and without aura
What is the role played by fluctuations in the level of cortical activation and in the threshold for the activation of homeostatic inhibitory responses of cortical excitability in the recurrence of attacks and in the chronification of migraine?
Cyclical changes of cortical excitability and metaplastcity in migraine: Evidence from a repetitive transcranial magnetic stimulation study

Giuseppe Cosentino, Brígida Fierro, Simone Vigneri, Simona Talamanca, Piera Paladino, Roberta Baschi, Serena Indovino, Simona Maccora, Francesca Valentino, Enrico Fileccia, Giuseppe Giglia, Filippo Brighina
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15 healthy controls
- 50 MwA pts
- 49 MwoA pts
8 patients with chronic migraine

Phase of the migraine cycle
- Inter-ictal
- Pre-ictal
- Ictal
- Post-ictal

Stimulation paradigm
- 6 rTMS trains of 10 stimuli with 2 min inter-train interval applied to the left M1

Stimulation intensity: 120% RMT
Stimulation frequency: 5 Hz
Interictal period

Increased facilitatory response in patients with lower attack frequency (MwA: 1.4 a / mo; MwoA: 1.6 a / mo) compared to control subjects.

Inhibitory response in patients with higher attack frequency (MwA: 4.3 a / mo; MwoA: 5.9 a / mo) compared to control subjects.
Cortical response to a migraine trigger

Control

Low frequency

Migraine patient

Hyperresponsivity to the rTMS trains in patients with a low attack frequency

Interictal period
Interictal period

Cortical response to a migraine trigger

Control | Low frequency | High frequency

Migraine patient

Attacks threshold

Peripheral and central sensitization
Threshold for inhibitory homeostatic responses

Inhibitory response to 5 Hz rTMS trains in migraine patients with high frequency of attacks
Chronic migraine

- MEP amplitude (microV)
- Number of stimuli
- MwoA interictal
- Chronic migraineurs

* p<.05
Marked inhibitory response to 5 Hz rTMS trains in chronic migraine patients
Pathophysiological mechanisms of recurrence of attacks

How to explain the origin of the attack in patients with a higher frequency of attacks?

Patient with high attack frequency

Cortical response to a migraine trigger

Attack threshold

Threshold for inhibitory homeostatic responses
Preictal period

* p<.01
Pathophysiological mechanisms of recurrence of attacks

How to explain the origin of the attack in patients with a higher frequency of attacks?

Patient with high attack frequency

Trigger factor

Predisposing condition

Threshold for inhibitory homeostatic responses

Cortical response to a migraine trigger
Cortical Excitability / Activity

TRIGGER FACTORS

PREDISPOSING FACTORS
Pathophysiological mechanisms of recurrence of attacks

![Graph showing MEP amplitude over the number of stimuli for different conditions: MwoA interictal, MwoA ictal, and MwoA postictal. The graph includes annotations for significant differences (*p<0.05) between conditions.]
Pathophysiological mechanisms of recurrence of attacks

**Graph**

- MEP amplitude (microV) vs. Number of stimuli
- Lines for MwA interictal, MwA ictal, and MwA postictal
- *p<0.05
Pathophysiologica mechanisms of recurrence of attacks

Patient with high attack frequency

Possible role of homeostatic inhibitory mechanisms in stopping the attack and preventing early relapses?
What are the possible molecular mechanisms?
genetic studies have failed to identify mutations in the Ca\(^{2+}\) and Na\(^{+}\) channels. Could an altered modulation of the presynaptic Ca\(^{2+}\) HVA channels explain the observed effects?
Thank you!