



XXIX CONGRESSO NAZIONALE
PALERMO, 30 SETTEMBRE • 2 OTTOBRE 2021
AULA MAGNA VINCENZO VINDIGNI
UNIVERSITÀ DEGLI STUDI DI PALERMO
BEYOND THE LOCKDOWN OF THE BRAIN



Cortical hyperexcitability and the effect of anti-CGRP antibodies treatment in migraine:

*Evidence by sound induced flash
illusions.*

Filippo Brighina



Department of Biomedicine, Neurosciences
and Advanced Diagnostics (Bi.N.D.)
University of Palermo, Italy.

Disclosures:

- Amgen: clinical trial
- Lilly: onoraria per symposia
- Teva: onoraria per symposia, clinical trials
- Alnylam: onoraria per symposia
- Akcea: onoraria per symposia, clinical trial

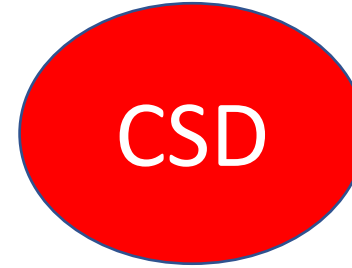
Outline

- Migraine pathophysiology, cortical excitability, glutamate and migraine ground
- Sound induced flash illusions (SIFI) a new reliable technique for assessment of cortical excitability in migraine.
- Plastic modulatory interaction between peripheral and central target and its relevance for treatment
- Evidence about cortical excitability modulation by anti-CGRP MAB treatment (bottom-up)

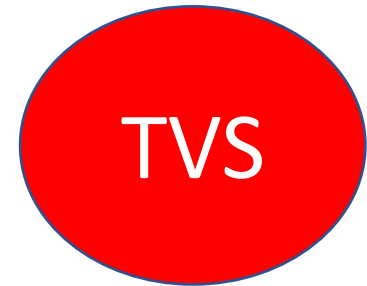
Understanding migraine

Attack

AURA



Headache



Predisposition
to attack

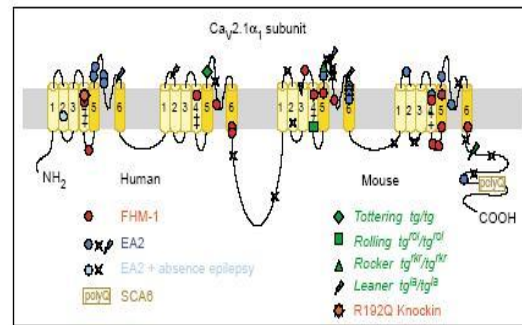
FHM: GLUTAMMATE AND HYPEREXCITABILITY



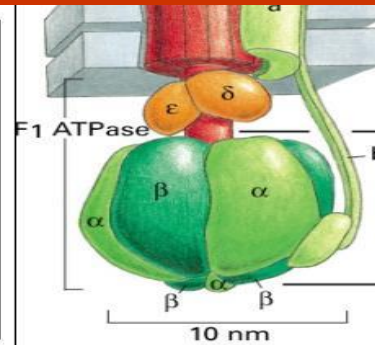
Reduced threshold and increased velocity of CSD in FHM1-2 knock-in rats

This has been shown to follow to an increased glutamate transmission

FHM 1 FHM 2 FHM 3



Calcium channels
Ophoff et al, 1996

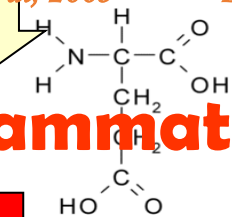


Na/K Pump
De Fusco et al, 2003

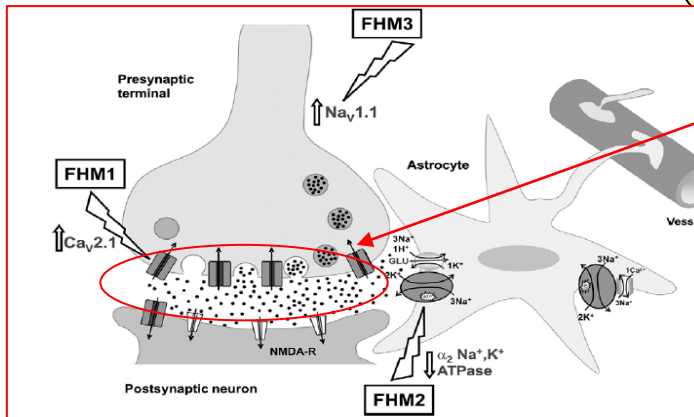


Sodium Channels
Dichgans et al, 2005

glutammate



Cortical hyperexcitability



GLUTAMATE IN MIGRAINEURS

doi:10.1093/brain/awx130

BRAIN 2017; Page 1 of 13 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Cortical glutamate in migraine


Ronald Zielman,¹ Jannie P. Wijnen,^{2,3} Andrew Webb,² Gerrit L. J. Onderwater,¹
Itamar Ronen,² Michel D. Ferrari,¹ Hermien E. Kan,² Gisela M. Terwindt^{1,*} and
Mark C. Kruit^{4,*}

Neurological Sciences (2019) 40:2343–2348

<https://doi.org/10.1007/s10072-019-03973-6>

ORIGINAL ARTICLE

Visuospatial learning is fostered in migraine: evidence by a neuropsychological study

Roberta Baschi¹  · R. Monastero¹ · G. Cosentino^{2,3} · V. Costa¹ · G. Giglia¹ · B. Fierro¹ · F. Brighina¹



Cortical excitability and migraine: new approaches

- Techniques like TMS and tES have been diffusely employed to explore excitability in migraine thanks to their ability to directly modulate cortical neurons. These approaches provided relevant insight in mechanisms of cortical activation in migraine
- However, these techniques, particularly rTMS induce paradoxical inhibitory responses even in condition like chronic migraine where there is general agreement about persistent marked increase in cortical excitability.
- This unwanted responses can be avoided, through a technique based on cross-modal illusion known as Sound induced flash illusions.

rTMS and Paradoxical inhibitory response



PAIN® 155 (2014) 1070–1078

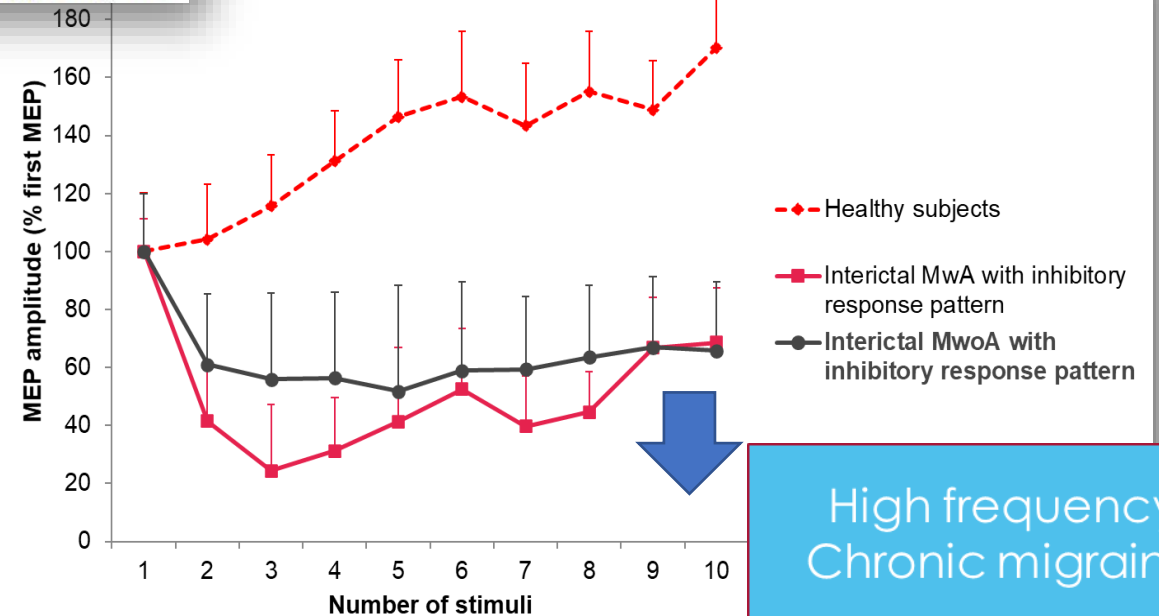
PAIN®

www.elsevier.com/locate/pain

Cyclical changes of cortical excitability and metaplasticity in migraine:
Evidence from a repetitive transcranial magnetic stimulation study

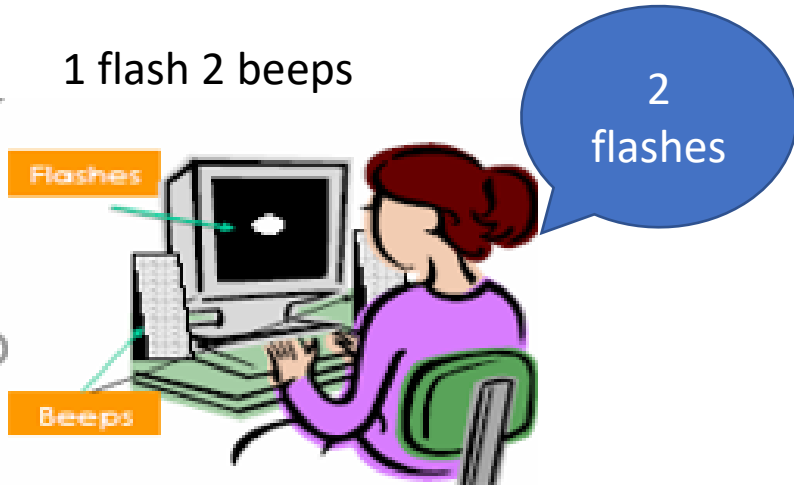


Giuseppe Cosentino*, Brigida Fierro, Simone Vigneri, Simona Talamanca, Piera Paladino, Roberta Baschi, Serena Indovino, Simona Maccora, Francesca Valentino, Enrico Fileccia, Giuseppe Giglia, Filippo Brighina



Sound Induced Flash illusions

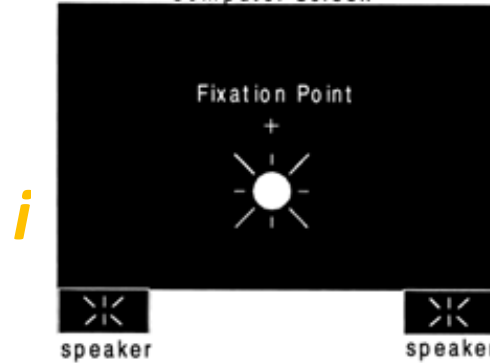
1 flash 2 beeps



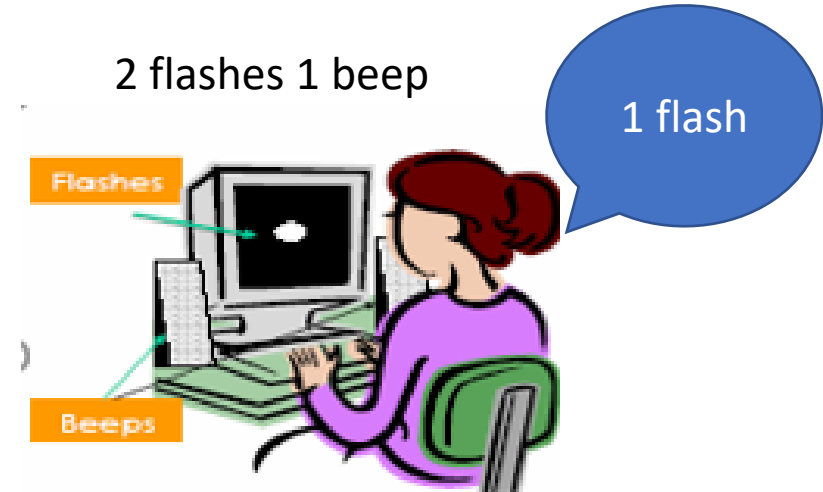
FISSION ILLUSIONS

When a single flash is given with 2 beeps, the visual stimulus it is perceived as 2 flashes

Computer Screen



2 flashes 1 beep

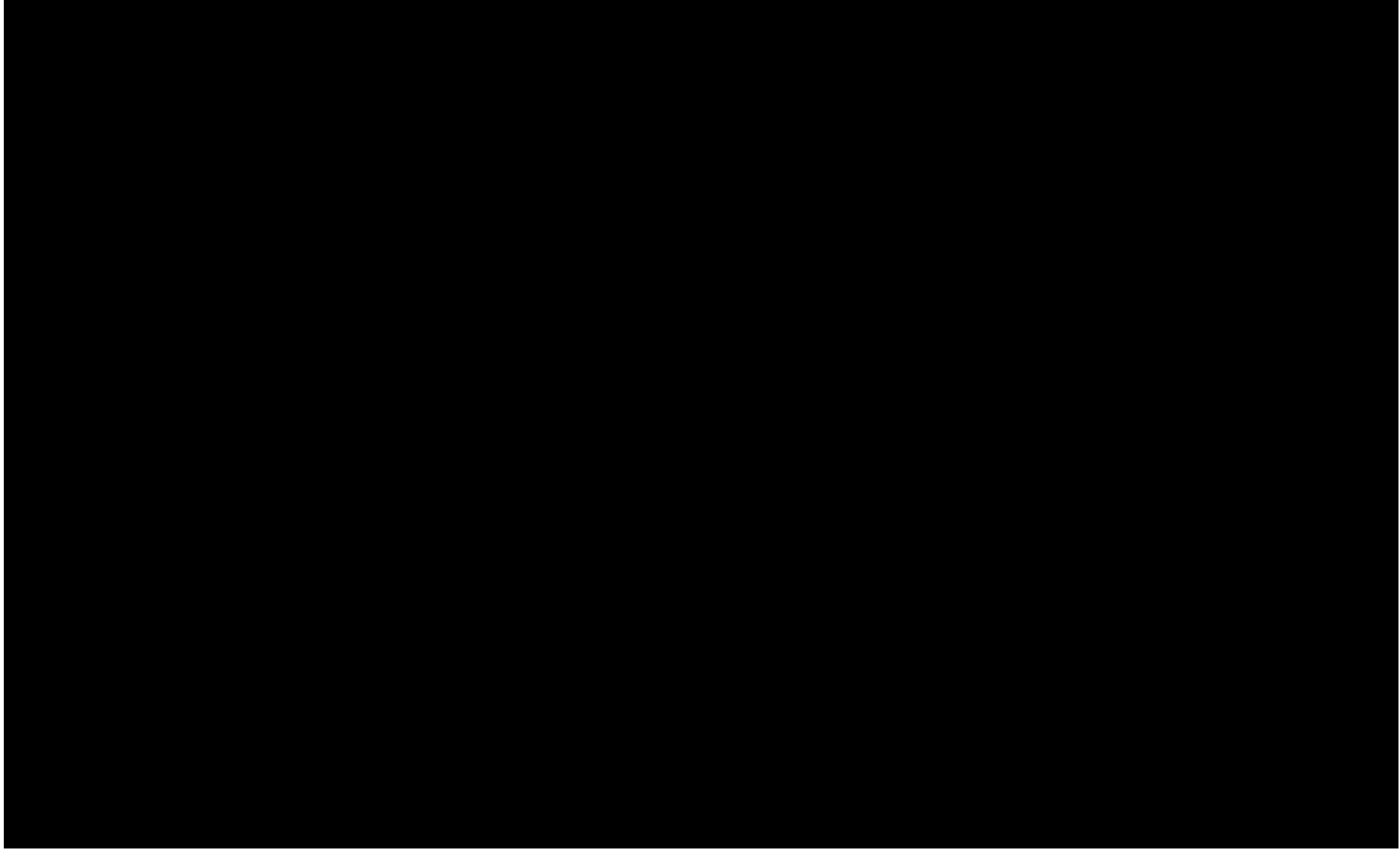


FUSION ILLUSIONS

When 2 flashes are presented together with 1 beep, they are seen as a single flash

Subject are presented with visual (flashes) and auditory (beeps) stimuli and have to report the number of the flashes seen

Shams L, Kamitani Y. Shimojo, S. (2000). Illusions. What you see is what you hear. Nature, 408, 788





Contents lists available at ScienceDirect

Neuropsychologia

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



Neuromodulation of multisensory perception: A tDCS study of the sound-induced flash illusion

Nadia Bolognini^{a,b,*}, Angela Rossetti^a, Carlotta Casati^{a,b}, Flavia Mancini^{a,b}, Giuseppe Vallar^{a,b}

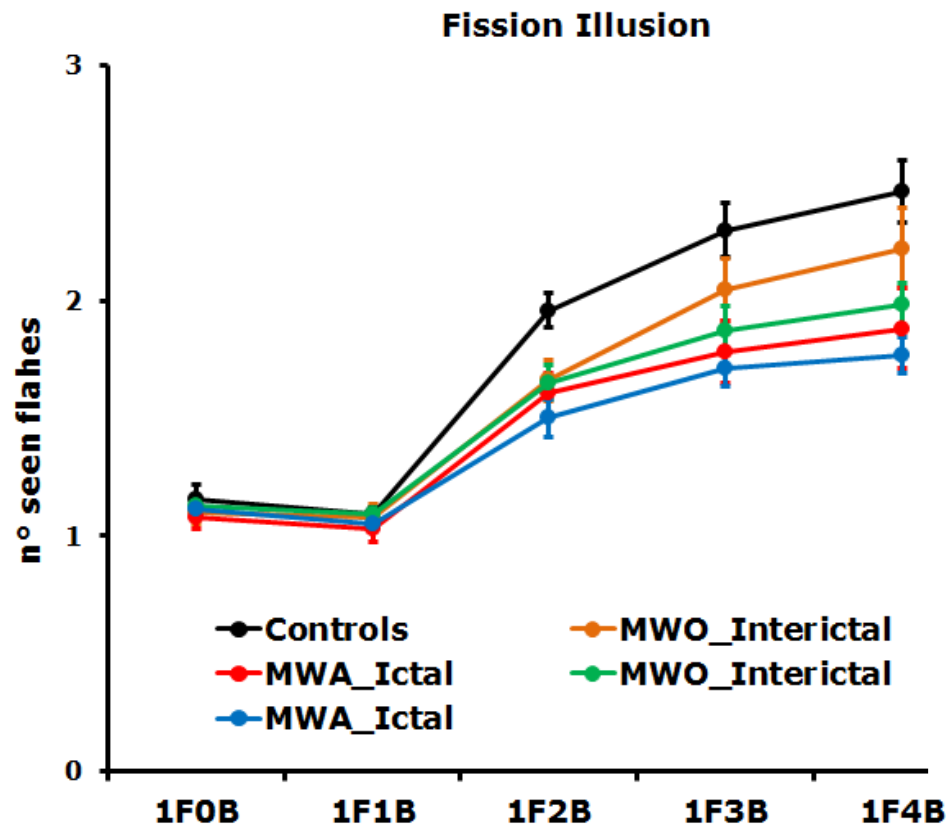
^a Department of Psychology, University of Milano-Bicocca, Milano, Italy

^b Neuropsychological Laboratory, IRCCS Italian Au

Sound induced flash illusion are critically dependent on visual cortical excitability. Less illusions occur when visual excitability increases, so making visual area less prone to auditory input

Visual cortex hyperexcitability in migraine in response to sound-induced flash illusions

Filippo Brighina, MD*
 Nadia Bolognini, PhD*
 Giuseppe Cosentino, MD
 Simona Maccora, MD
 Piera Paladino, MD
 Roberta Baschi, MD
 Giuseppe Vallar, MD
 Brigida Fierro, MD



Cortical excitability

Healthy controls

Interictal migraine without aura

Ictal migraine without aura

Interictal migraine with aura

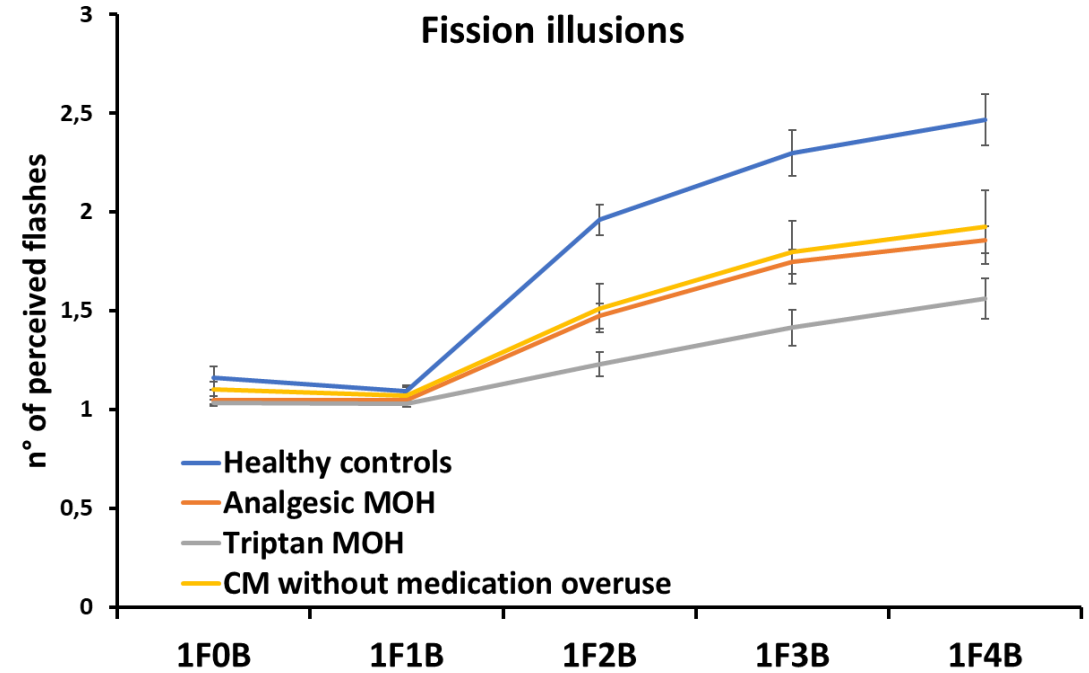
Ictal migraine with aura

**fission illusions
 are reduced in migraine
 with and without aura
 especially
 during attacks**

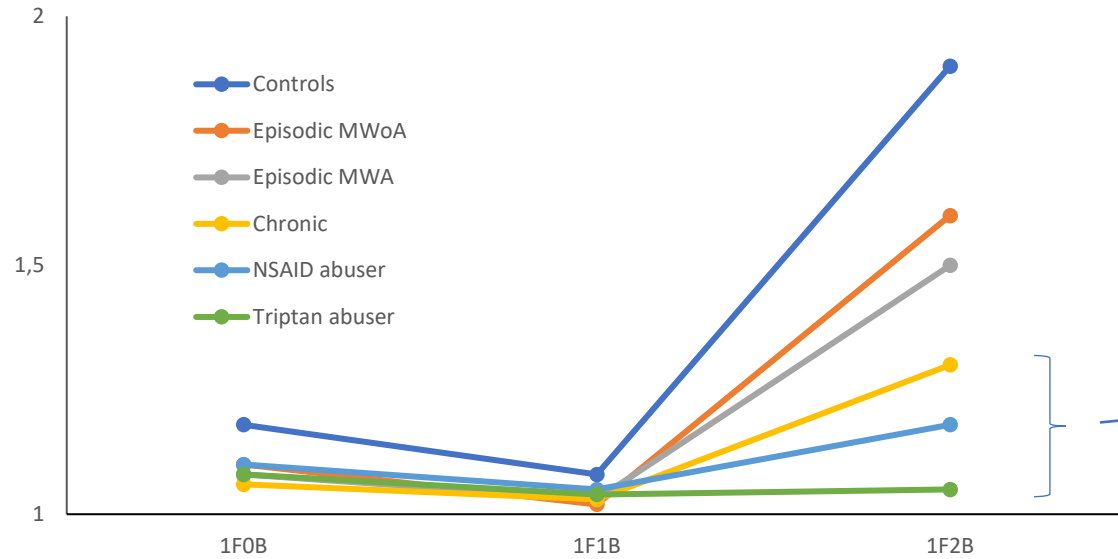


Multisensorial Perception in Chronic Migraine and the Role of Medication Overuse

Simona Maccora,^{*} Nadia Bolognini,^{†,‡} Giuseppe Cosentino,^{§,||} Roberta Baschi,^{*}
Giuseppe Vallar,^{†,‡} Brigida Fierro,^{*} and Filippo Brighina^{*}



Fission illusions in episodic vs chronic migraine



Fission illusions are markedly reduced in all migraine with respect to controls ($p < .001$)

Fission illusions are significantly reduced in chronic as respect to episodic migraine ($p < .005$)

Peripheral-central interaction in migraine

- Are peripheral level, ie trigeminal structures and TVS, and central cortical connected?
- Do exist reciprocal plastic interaction between the two?
- If so can drugs affecting one of two levels indirectly induce changes in the other, through top-down or inversely bottom-up mechanism
- Could this be important when evaluating global effects of drugs and their ability to induce persistent plastic modulation, that could be regarded a disease modifying ability?

Our study - Objective



Using Sound-Induced
Flash Illusions (SIFI)

To explore whether drug anti-CGRP MAB, that act at peripheral TGS level, can modulate **visual cortical excitability** in migraine patients:

Bottom-up effect

Subjects enrolled

Population	
Total	66
Age	51 yrs \pm 3.5
Sex	♀ 24 F 6 M ♂
Diagnosis	Chronic migraine
Previous prophylaxis	3.5 \pm 0.3
Headache days	24.1 \pm 1.2
Abortive drugs/month	18.7 \pm 2



Anti-CGRP:

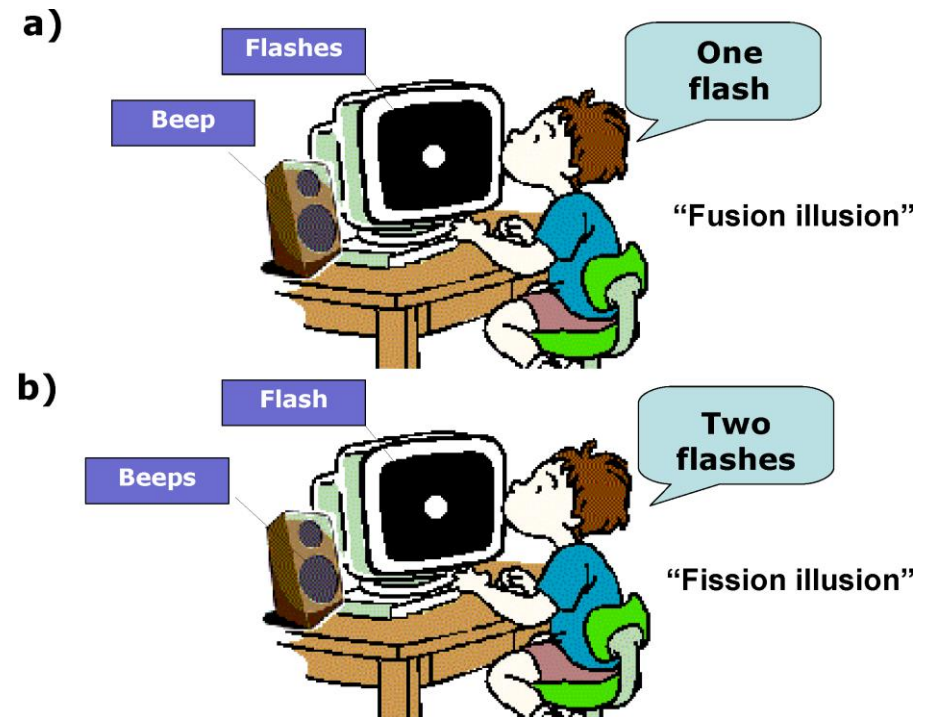
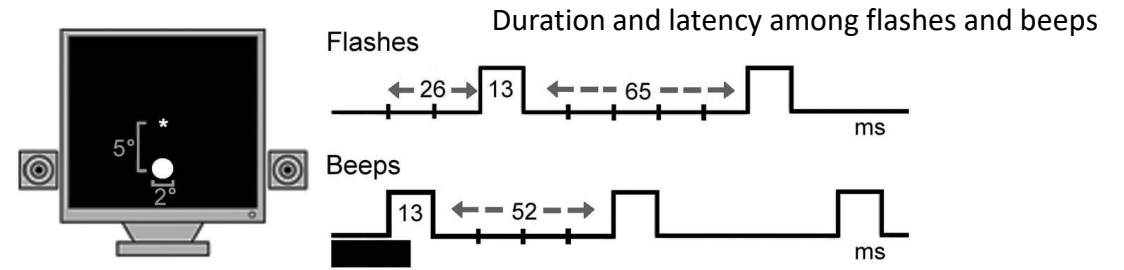
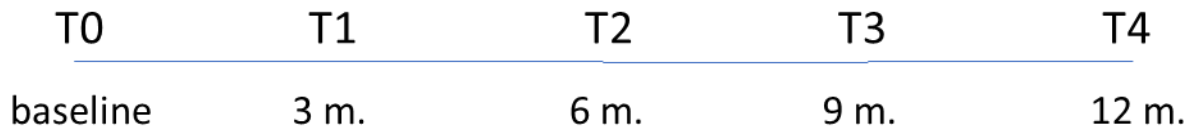
30 Erenumab
20 Fremanezumab
16 Galcanezumab



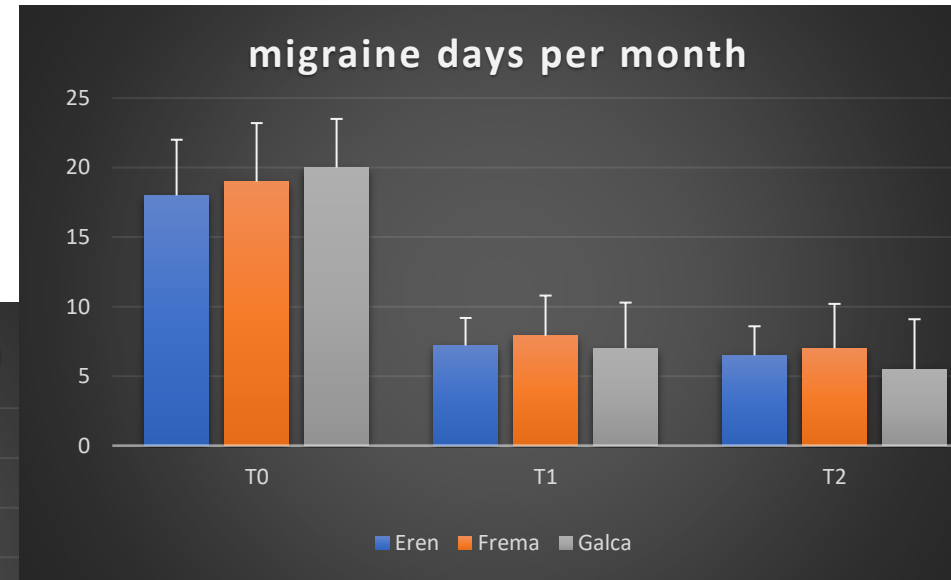
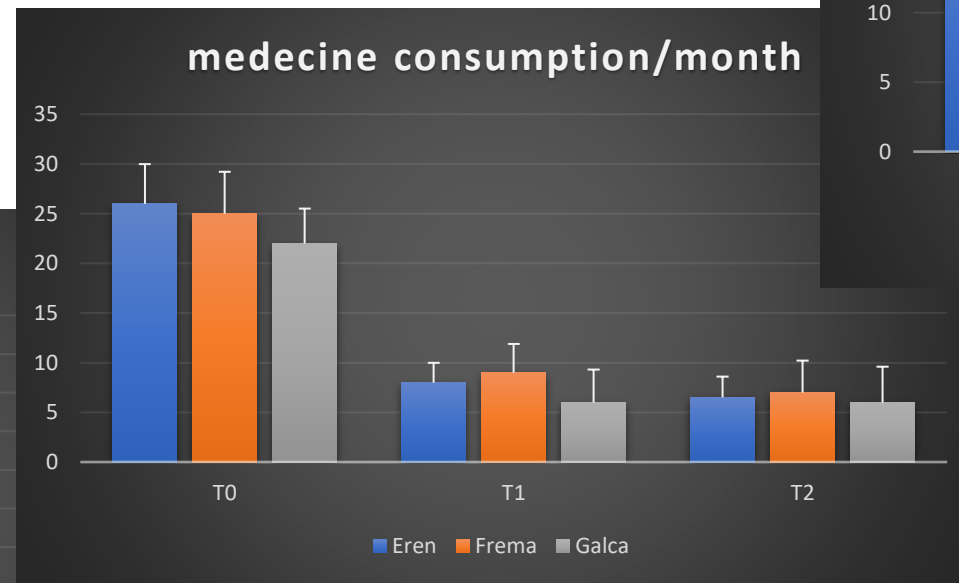
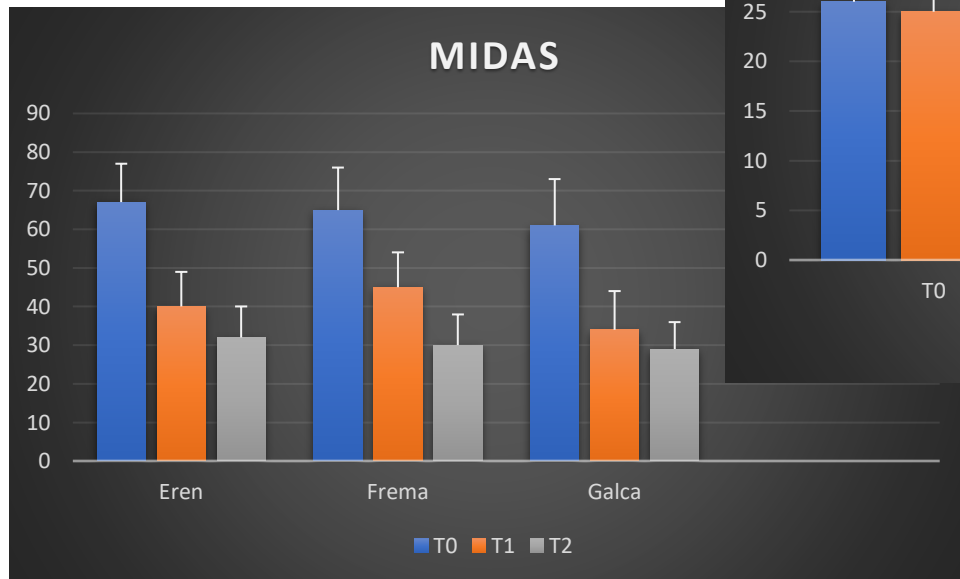
30 Healthy subjects (HS – mean age 50yrs \pm 8.6; 25F)

Methods

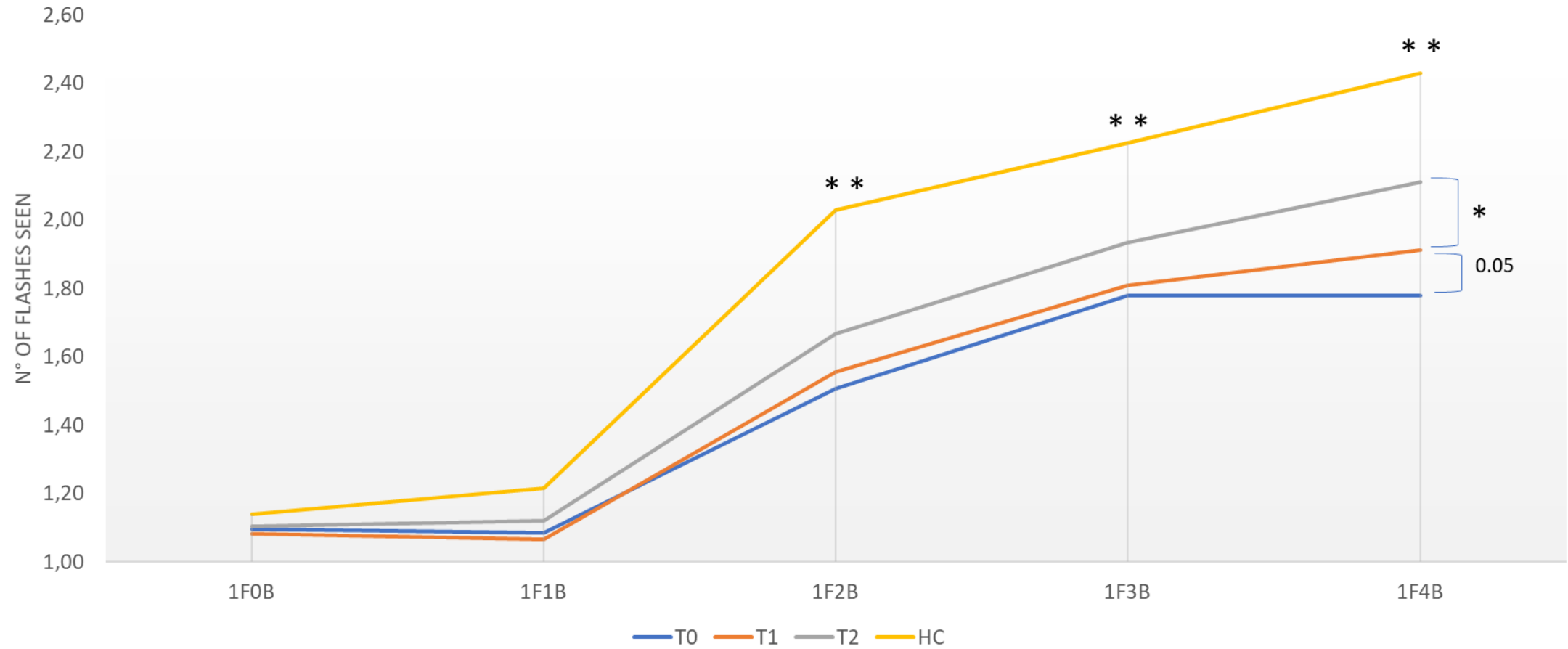
- dimly illuminated room
- participants sat ~60 cm in front of a LCD computer monitor (resolution 1024×768, refresh rate 75 Hz)
- Single **flash** and concurrent **beeps** trials.
- **Task:** to count aloud flashes seen each time (total duration ~5 minutes)
- 5 trials randomly presented 9 times:
 - 1FxB, where x goes from 0 to 4; F=flash, B=beep).
- Comparisons were performed by rm ANOVA with Duncan's test for post-hoc;
- Clinical measures: migraine days/month; medicine consumption/month, MIDAS
- Recording of SIFI and clinical parameters was planned at the timeline below:



Effects of anti-GRP on SIFI



Effects of anti-GRP on SIFI



Discussion and Conclusion

- SIFI confirmed cheap, well tolerated and effective tool to explore cortical excitability and its changes in chronic migraine (CM) under anti-CGRP MAB treatment
- CM patients show an increased visual cortical excitability compared to healthy controls in agreement with previous evidence
- Anti-CGRP treatment induced also appreciable and significant but late changes also in visual cortical excitability, at T2 (after six months treatment)
- So this change occurred long after the starting of clinical effect that are relevant and consistent already a T1 time, and are known to occur as early as the first treatment months. This could follow to longer times to induce plastic indirect effects.
- If these changes will show to be lasting after stopping treatment together with persistent clinical effects, its potential role as marker of disease modifying effect would be worth to explore.



Neuropsychology lab

Prof. Giuseppe Vallar

Prof. Nadia Bolognini



Dipartimento di Psicologia

University of Milan Bicocca, Italy

Neurophysiopathology Unit

Dipartimento di Biomedicina Neuroscienze e
Diagnostica avanzata (BIND)

University of Palermo, Italy



Thanks for your attention

