

Monoclonal antibodies against the CGRP receptor exert a differential effect at the level of the caudal trigeminal nucleus and at the level of the somatosensory cortex in migraine patients.

Francesco Casillo



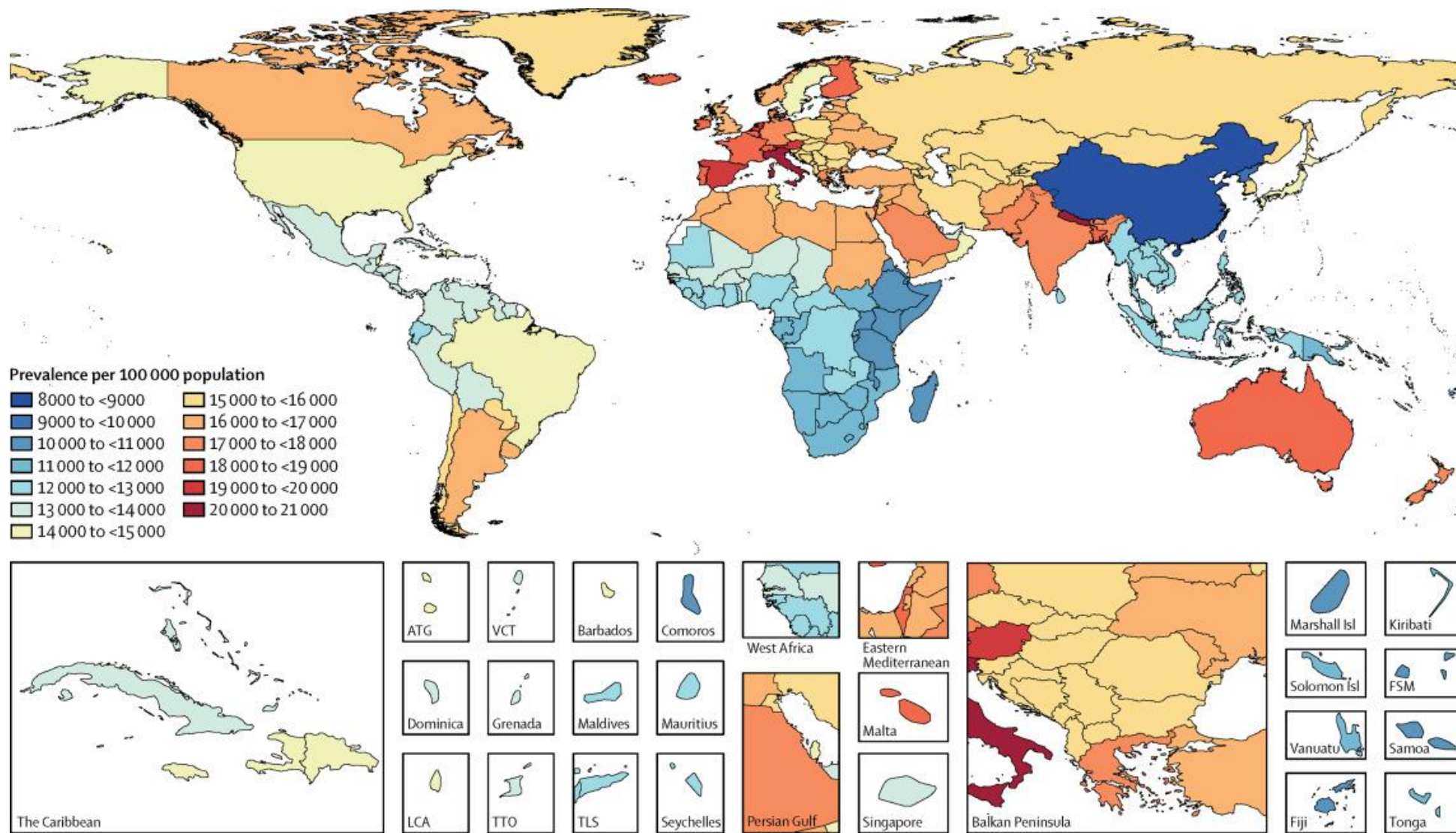
SAPIENZA
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Sapienza University of Rome Polo Pontino, Department of
Medico-Surgical Sciences and Biotechnologies, Latina, Italy

DISCLOSURES

No Disclosures

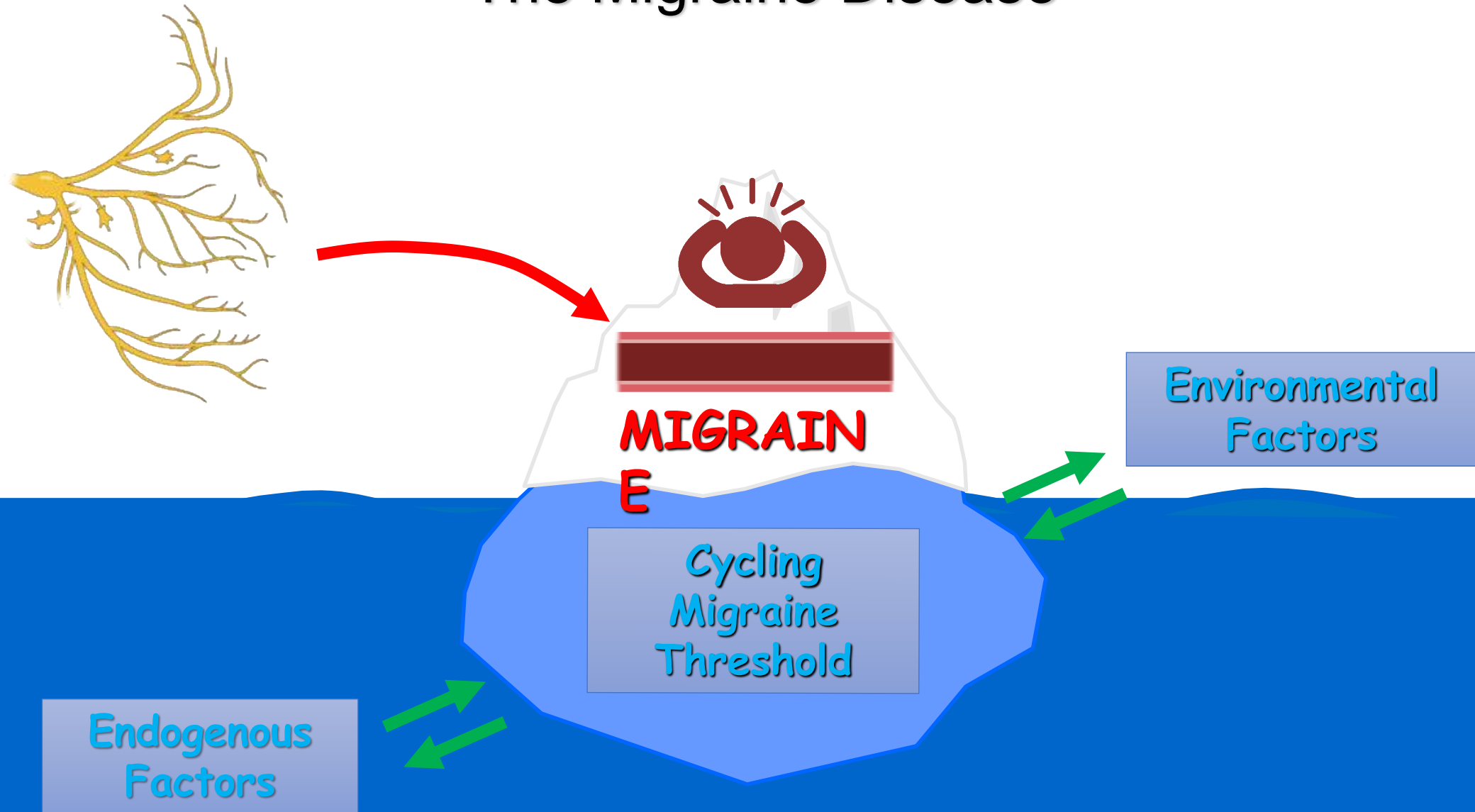
Migraine



THE LANCET: ARTICLES | VOLUME 17, ISSUE 11, P954-976, NOVEMBER 01, 2018

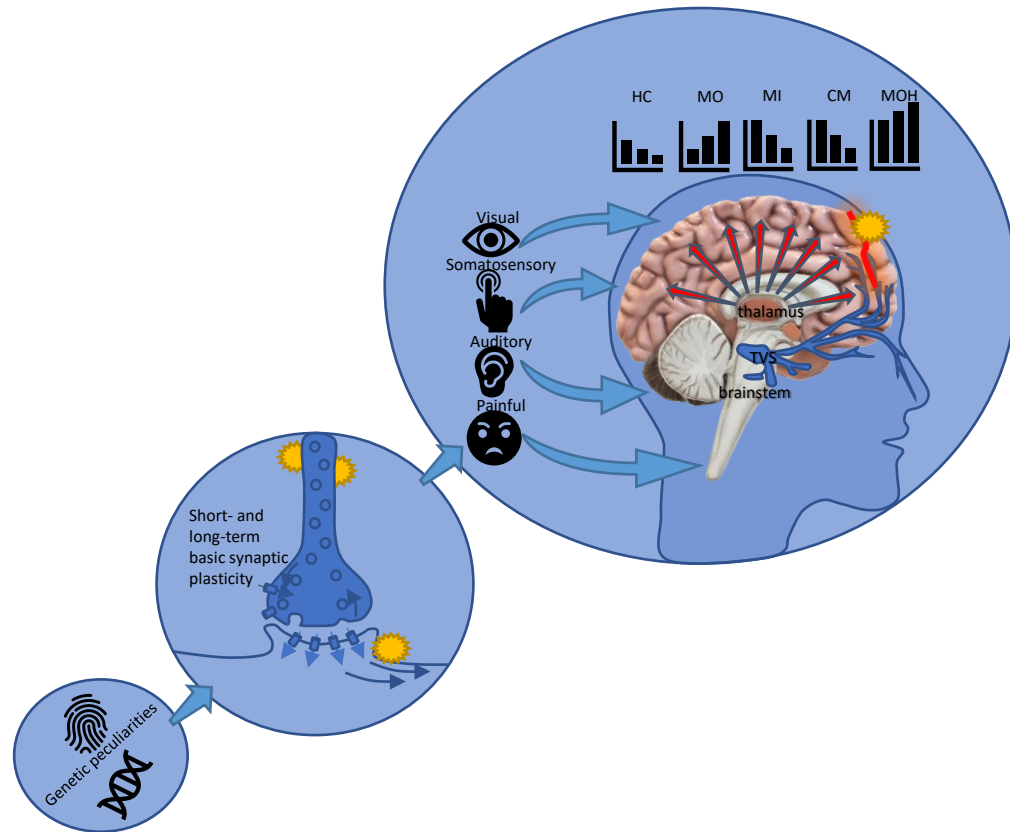
Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

The Migraine Disease



Combination of genomic peculiarities

Pathophysiological model of Migraine

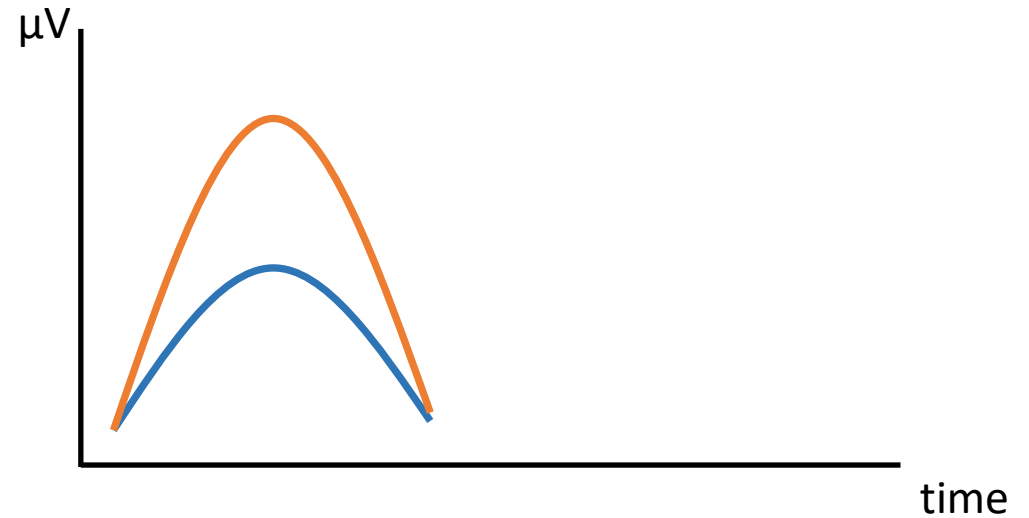
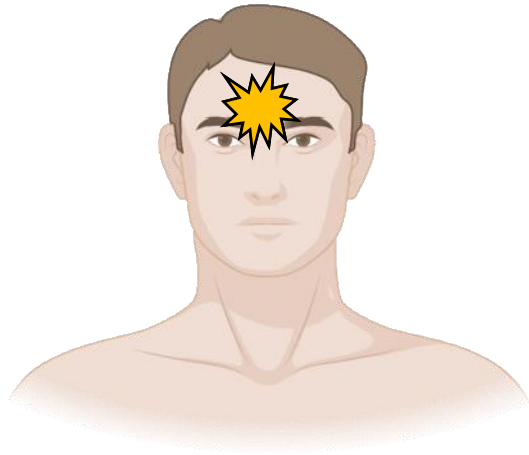


Sensitization

Habituation

Sensitization

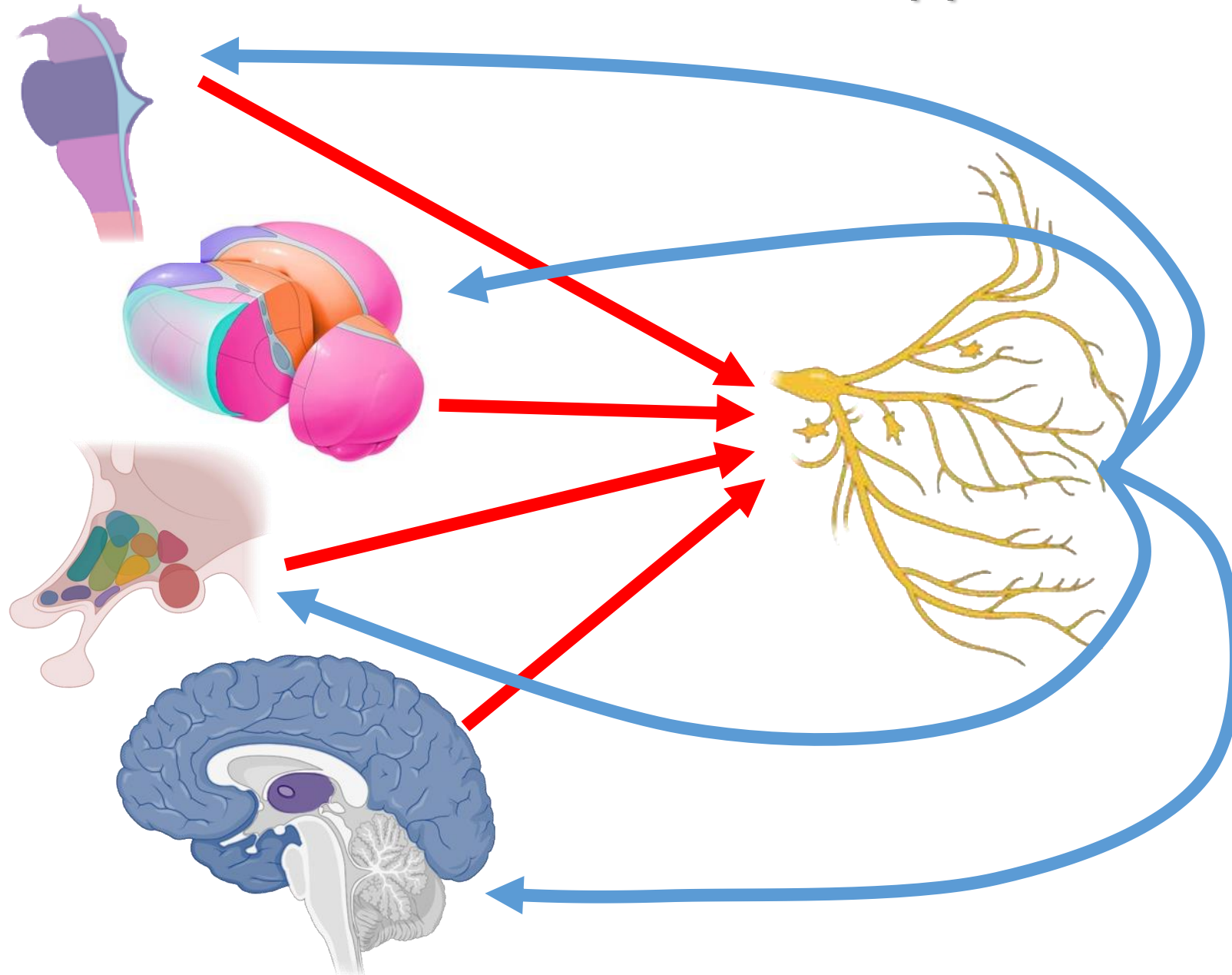
Sensitization is defined as an increase in response as a result of stimulation.



■ Non migraineurs

■ Migraineurs

How it happens

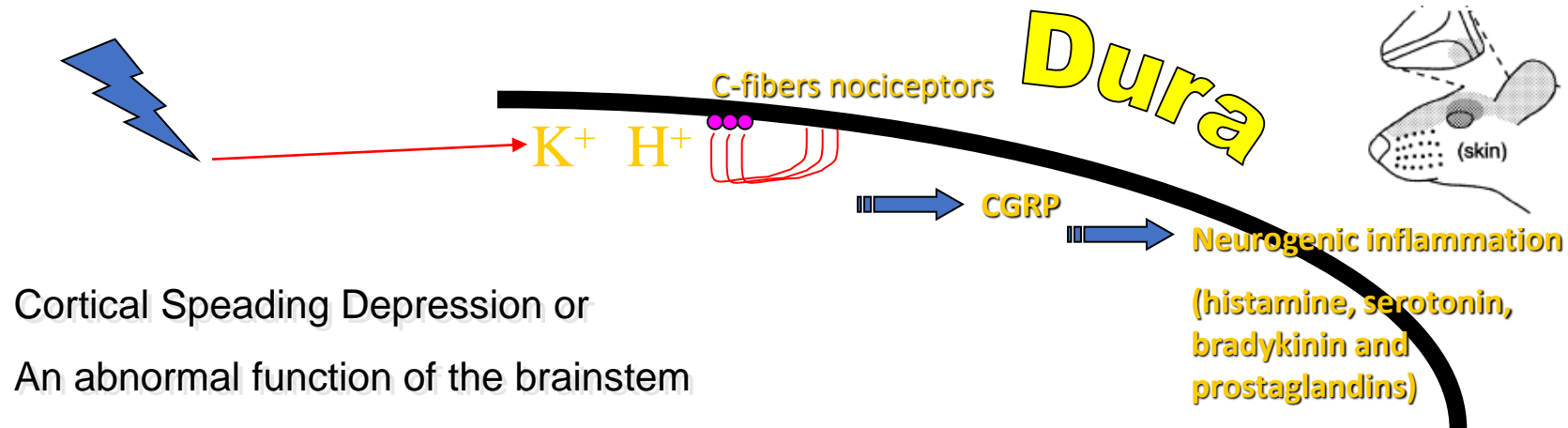


- Some experimental evidences point towards sequential sensitization of **first-order**
- or, more probable, **via an indirect activation of pain modulatory structures in the brainstem and the forebrain** (Lambert et al., 2011; Goadsby and Akerman, 2012).

Role in migraine cycle

Sensitization of trigeminovascular neurons conveys the pulsating quality of pain

The induction of headache after electrical stimulation of the dura in awake patients gave the first demonstration that activating peripheral sensory fibers that innervate the dura could play a critical role in migraine.



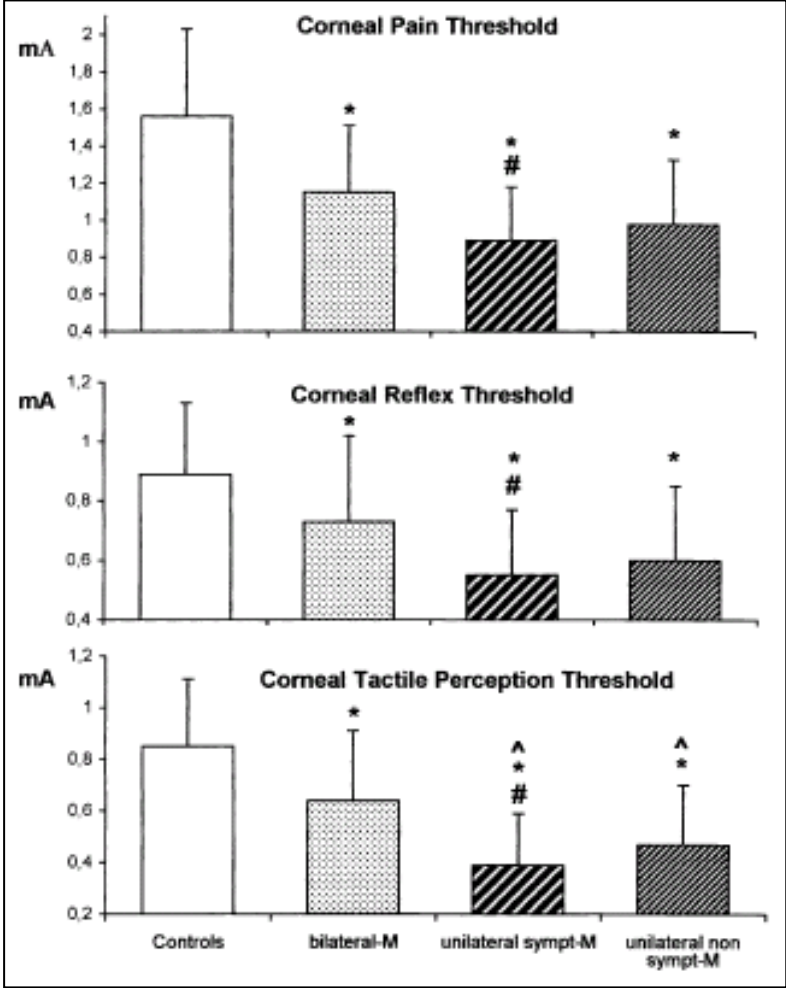
Cortical Spreading Depression or
An abnormal function of the brainstem

- When meningeal nociceptive receptors are sensitised they become responsive to imperceptible rhythmic fluctuations in intracranial pressure (pulsation) produced by normal arterial pulsation.

- This mechanical hypersensitivity may mediate the pulsating quality of the headache and its worsening during coughing, bending over, or other physical activities that increase intracranial pressure.

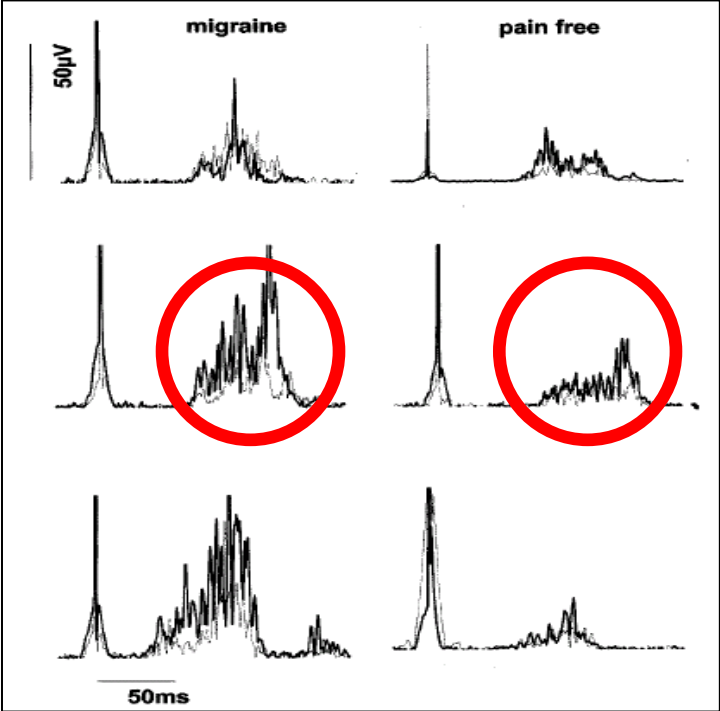
How to study Sensitization

Corneal reflex



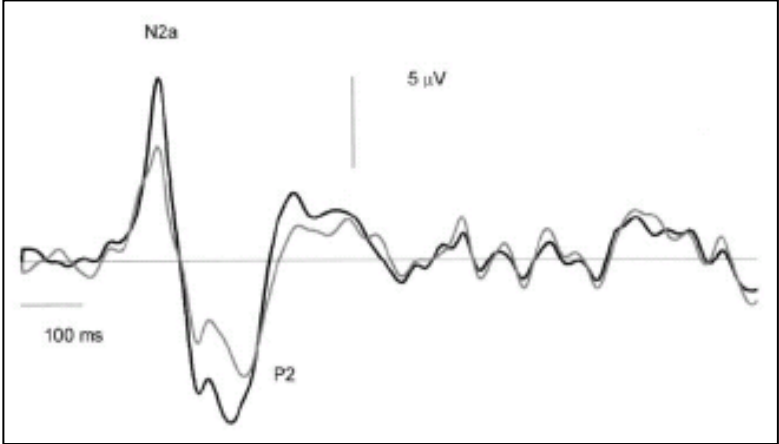
(Sandrini et al., Neurosci Lett 2002)

Blink reflex



(Kaube et al., Neurology 2002)

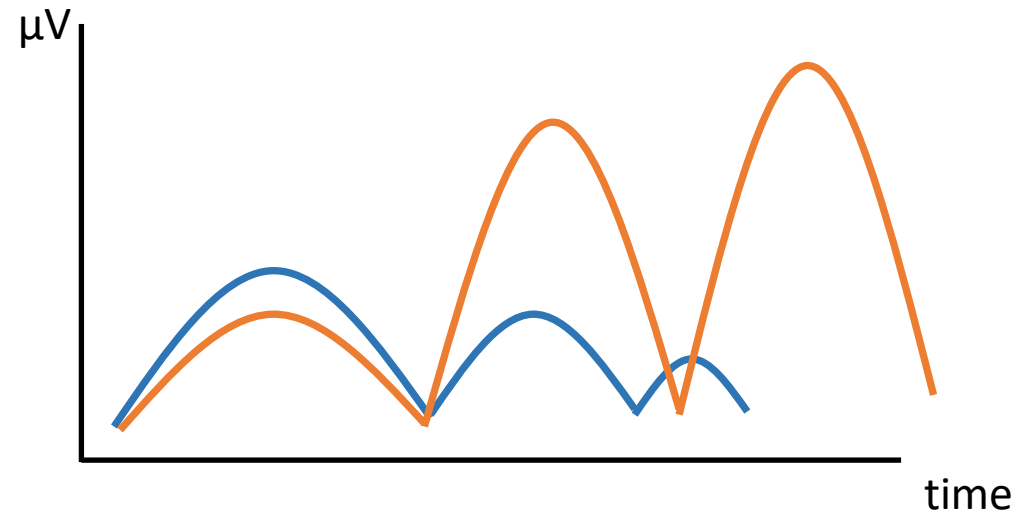
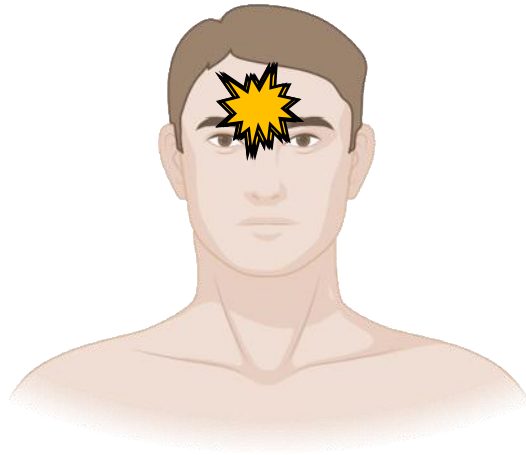
Laser evoked potentials



(de Tommaso et al., Neurosci Lett 2002
Valeriani et al., Pain 2005)

Habituation

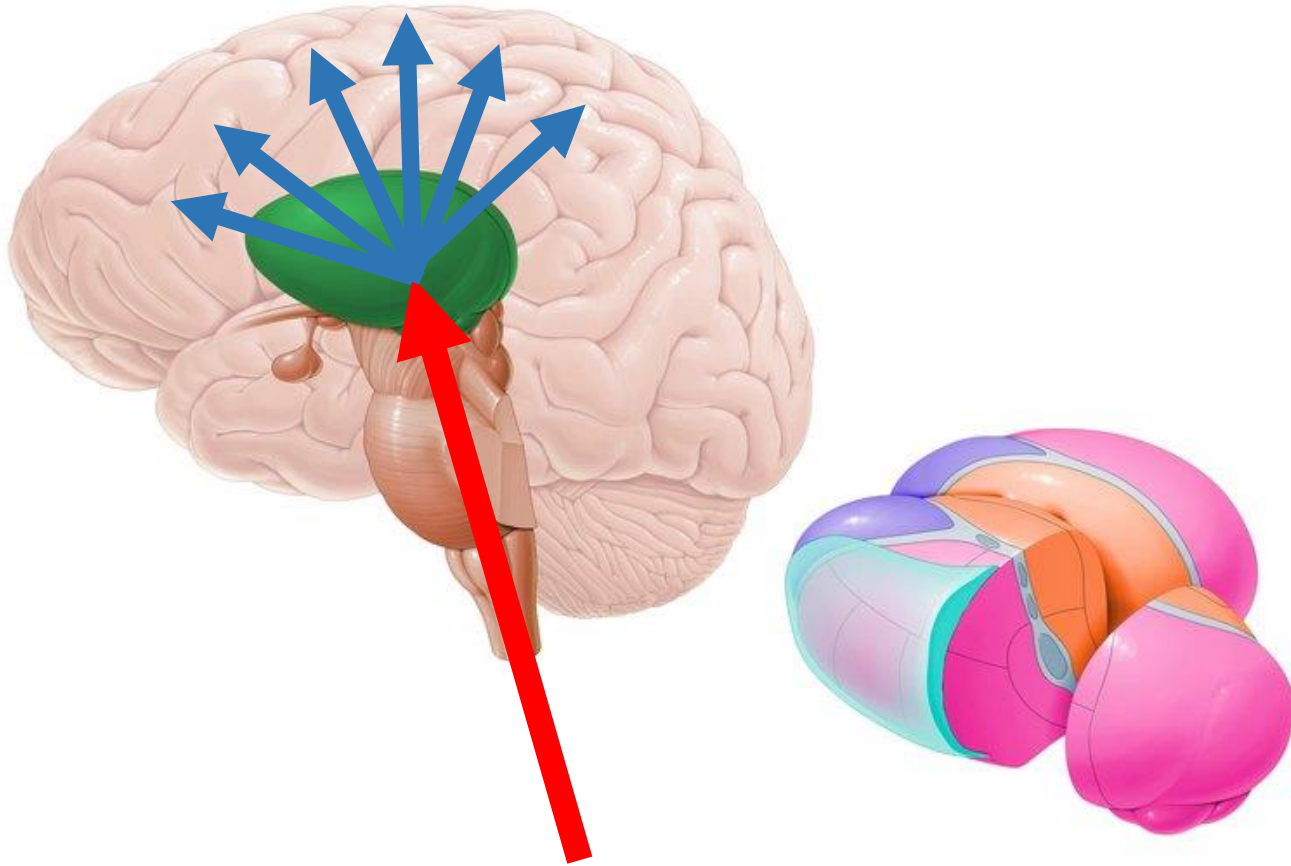
Habituation is defined as “a response decrement as a result of repeated stimulation”



■ Non migraineurs

■ Migraineurs

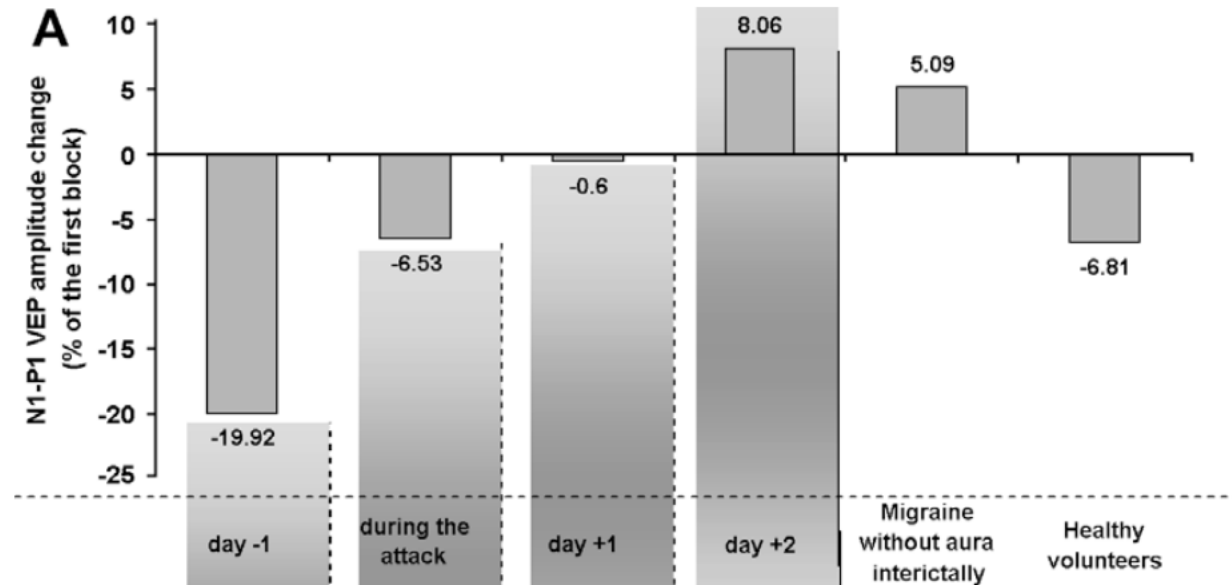
How it happens



➤ An **abnormal rhythmic activity between thalamus and cortex**, namely thalamocortical dysrhythmia, may be the pathophysiological mechanism subtending abnormal information processing in migraine.

➤ Probably a **genetically determined** property of the brain in migraineurs between attacks.

Role in migraine cycle

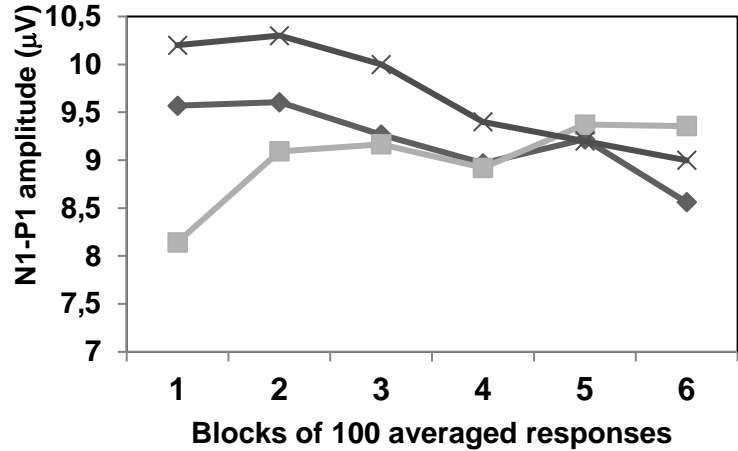


• Sequential recordings have shown that during the days preceding the attack there is an habituation deficit.

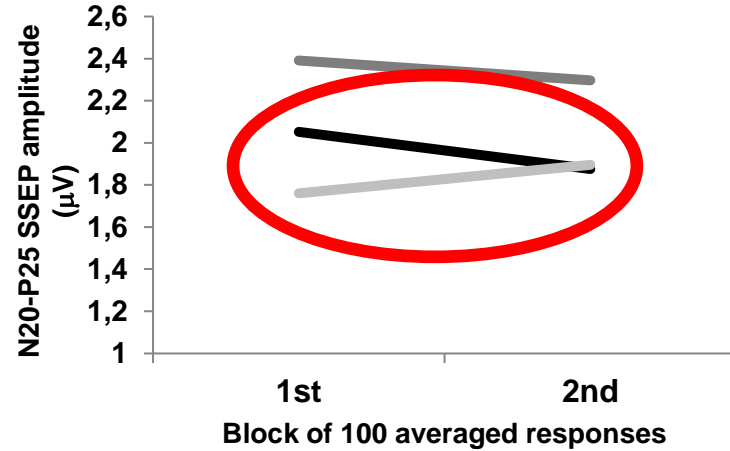
• Within the 12–24 h that immediately precede the attack, i.e. at a time point when premonitory symptoms may occur, the pattern of evoked potentials normalizes.

How to study Habituation

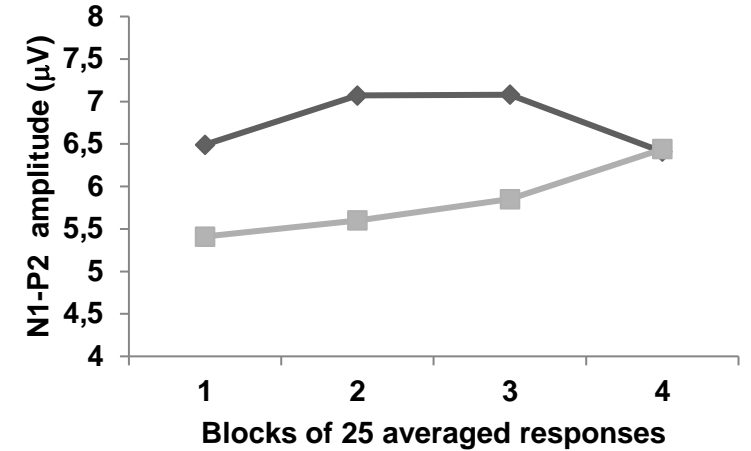
Visual EP



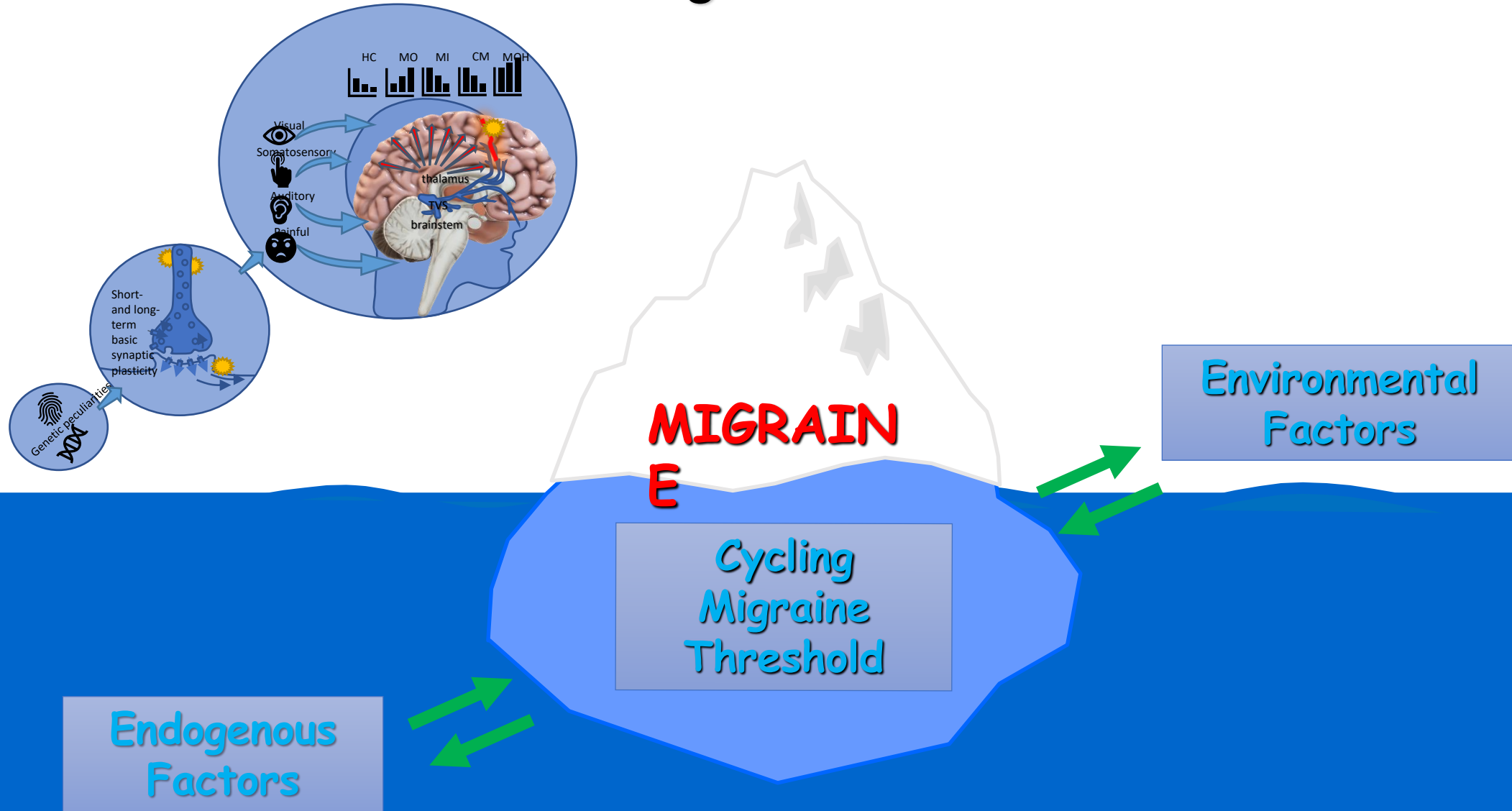
Somatosensory EP



Auditory EP

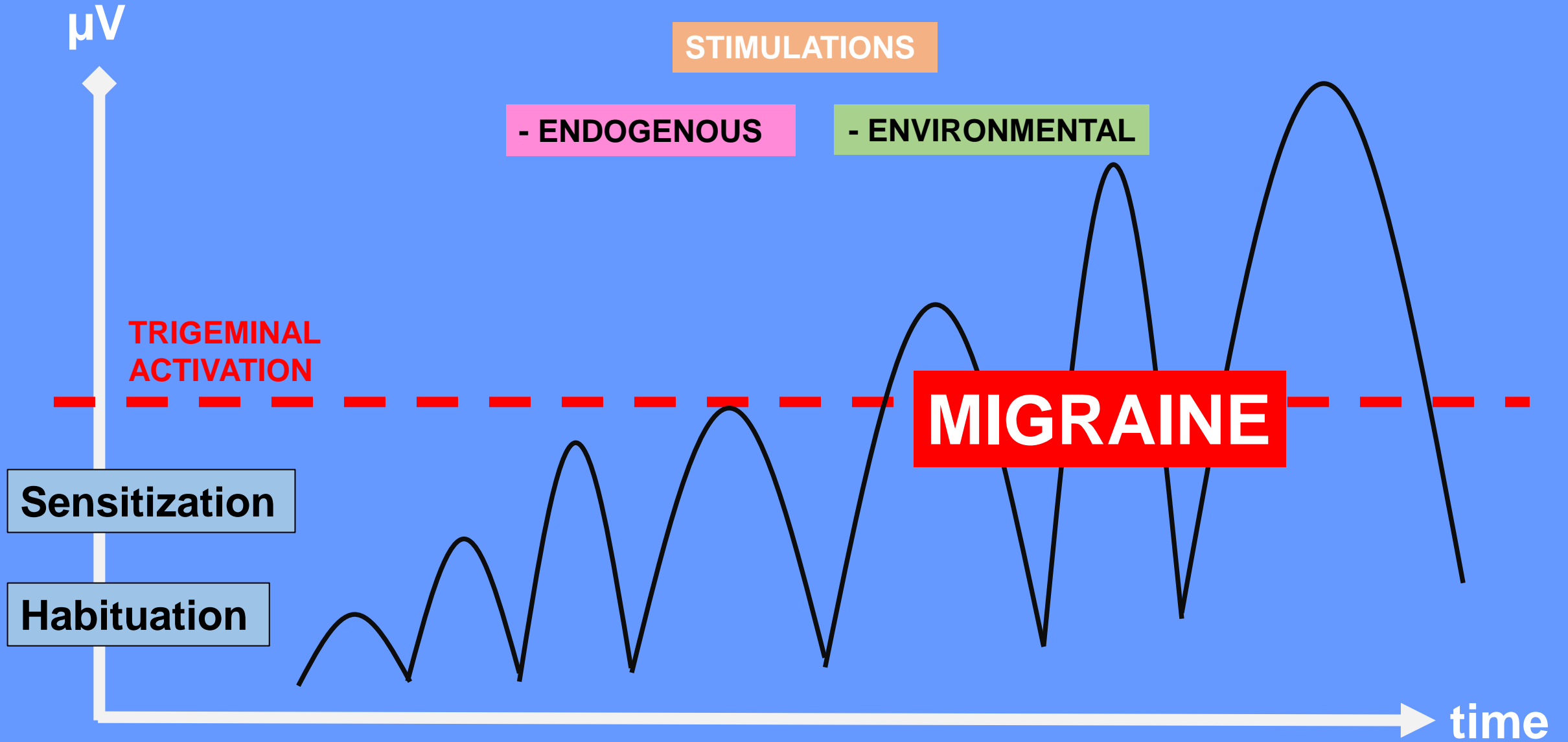


The Migraine Disease



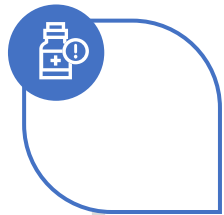
Combination of genomic peculiarities

Cycling Migraine Threshold



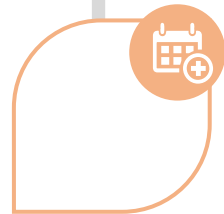
Do we need new migraine treatments?

Unmet needs exist with:



Acute therapies

- Ineffective in 1 out of 4 patients¹
- Possible **side-effects**, **CI**s and MOH²



Preventive therapies

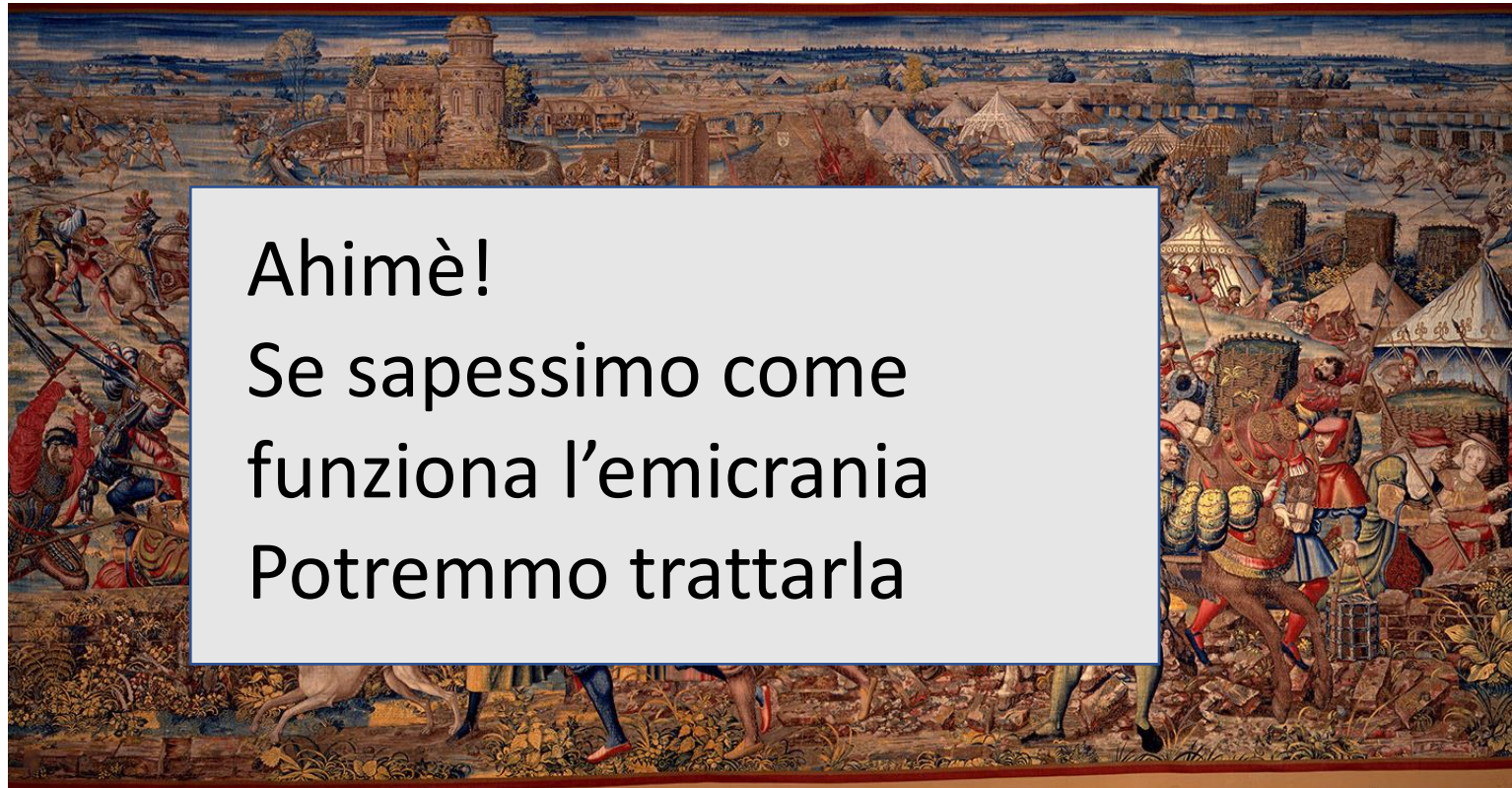
- Ineffective in 1 out of 2 patients (9 out of 10 in CM)³
- Frequent, intolerable **side-effects** and **CI**s^{3,4}
- Poor compliance (50% discontinue after 2 months)³



We urgently need effective new therapeutic options with favourable safety profiles to improve patient adherence

Anti-CGRP mAbs are a mechanism-specific migraine-targeted therapy⁵

Neurophysiology may be useful to study brain changes related to a specific treatment



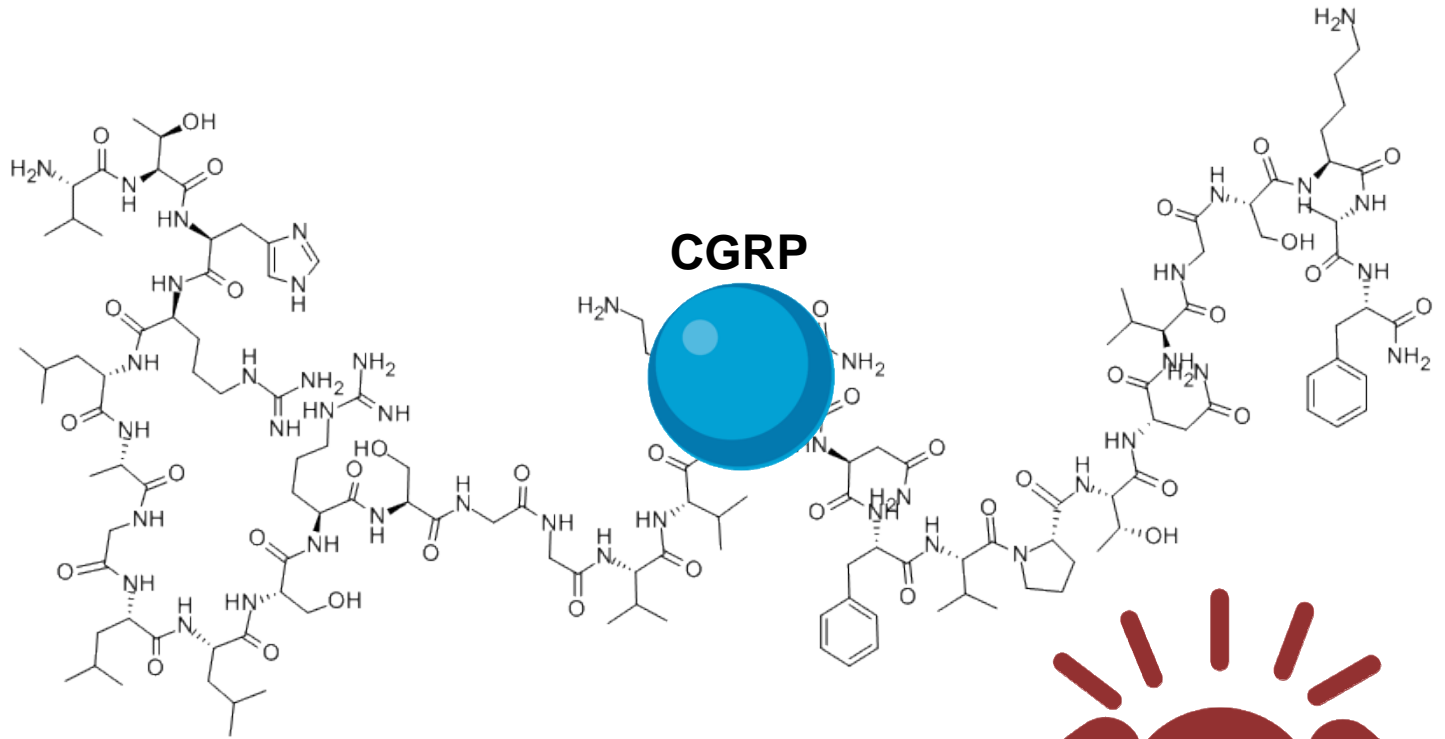
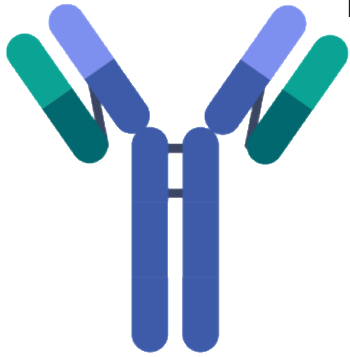
Ahimè!
Se sapessimo come
funziona l'emicrania
Potremmo trattarla

(FR) «Hélas !
La Palice est
mort,
il est mort
devant Pavie ;
Hélas ! s'il
n'estoit pas
mort,
il seroit
encore en
vie.»

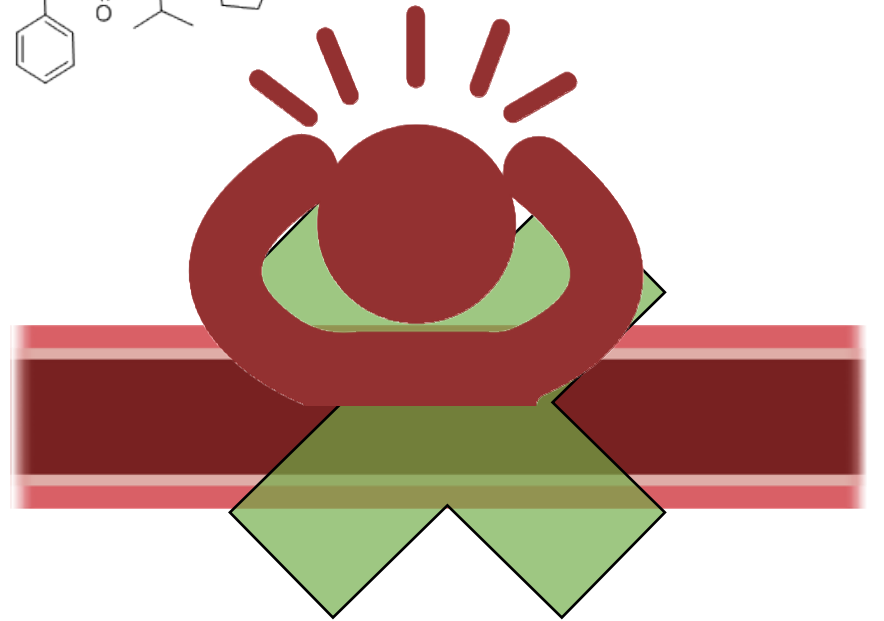
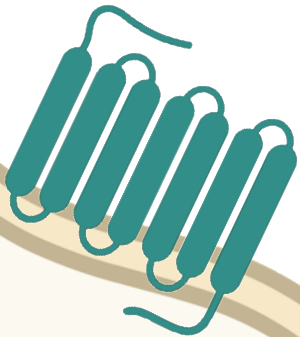
(IT) «Ahimè!
La Palice è
morto,
è morto
davanti a
Pavia;
Ahimè! se non
fosse morto,
sarebbe
ancora in
vita.»

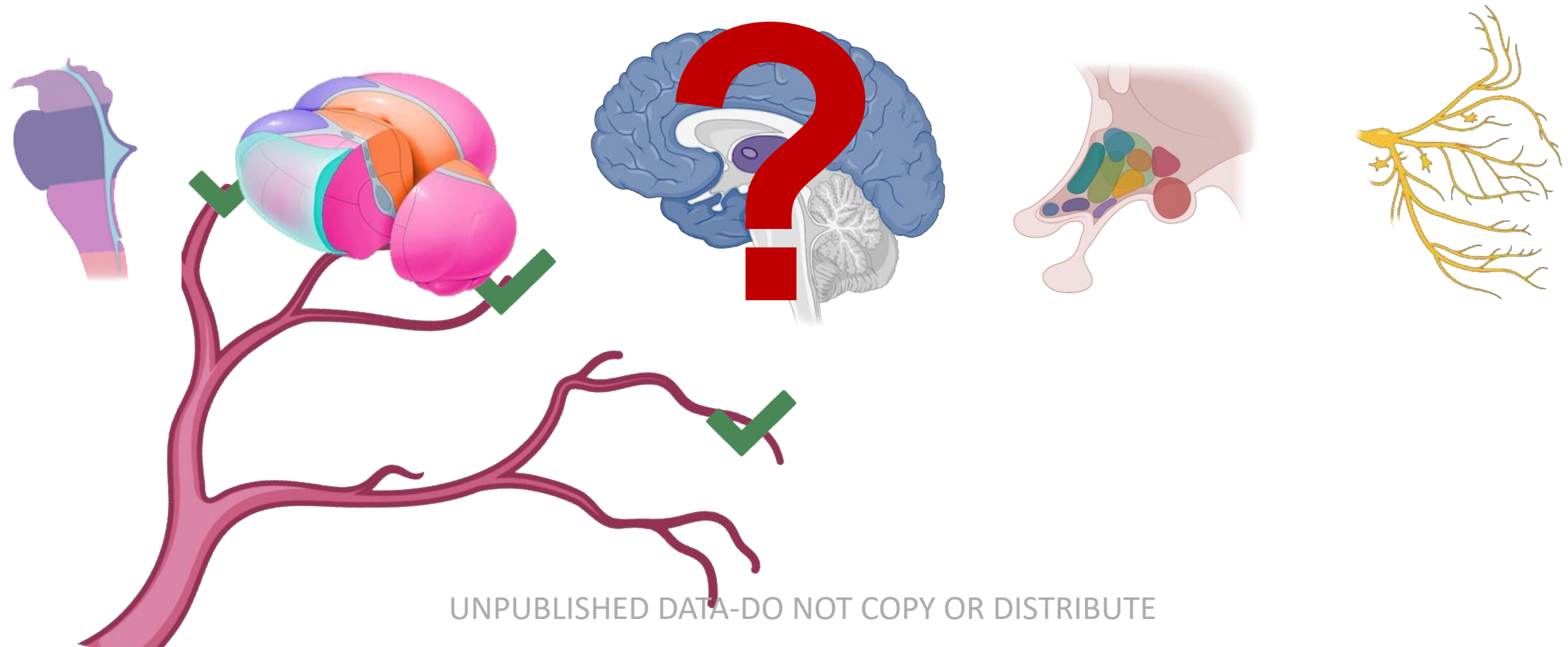
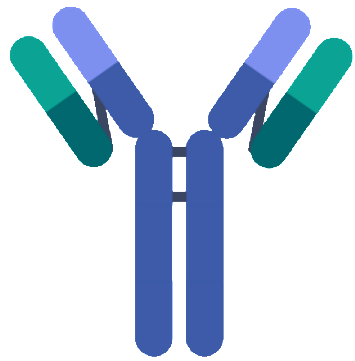
Pavia 1525

Erenumab

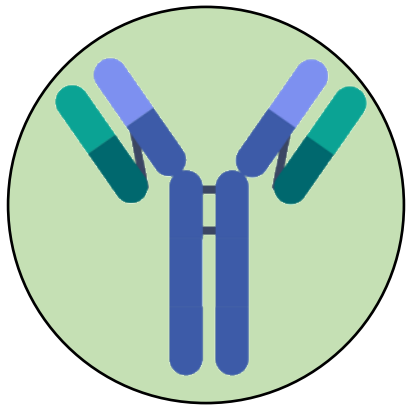
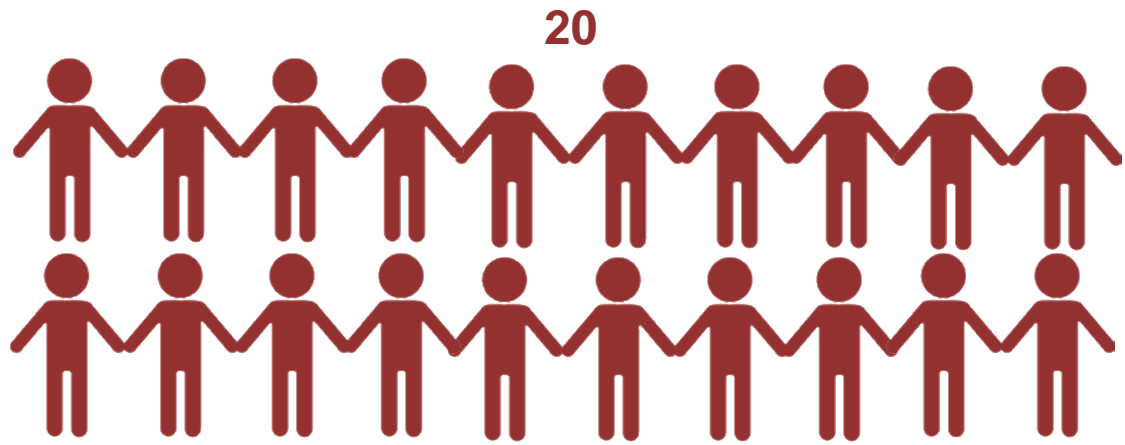


CGRP-R





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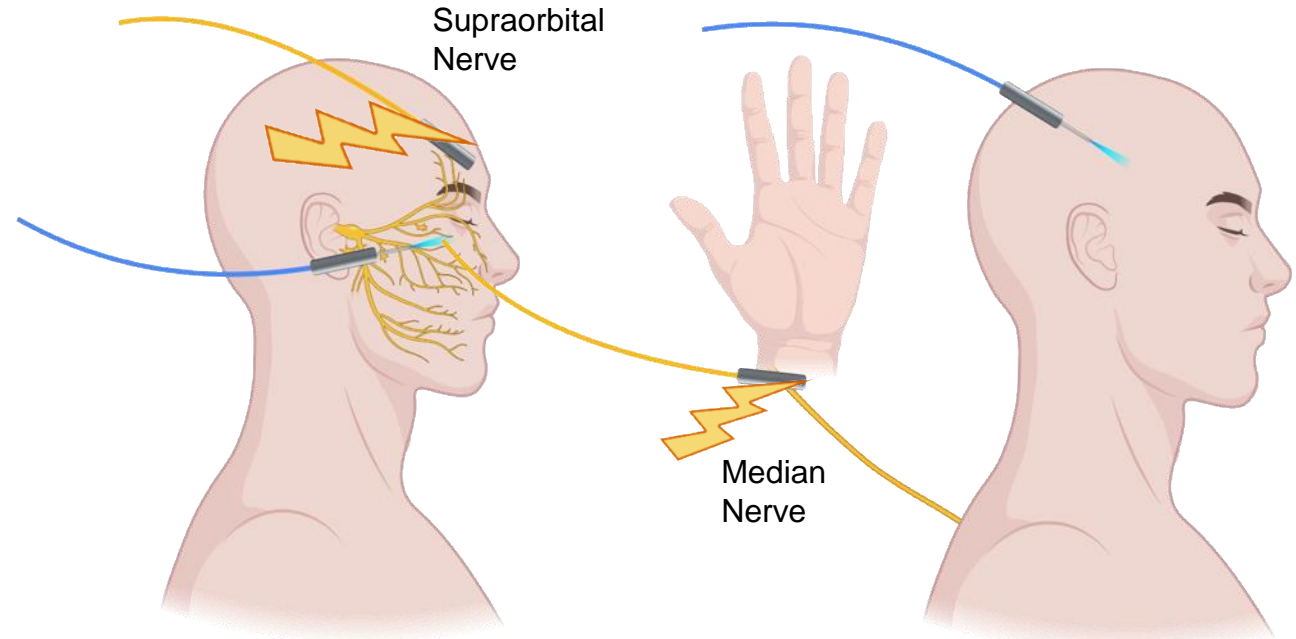
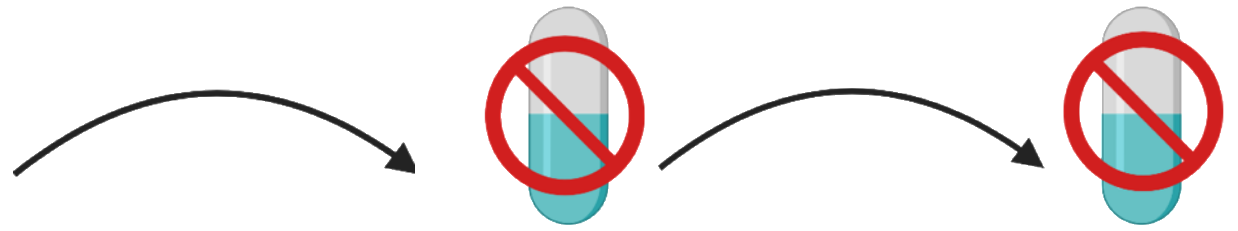
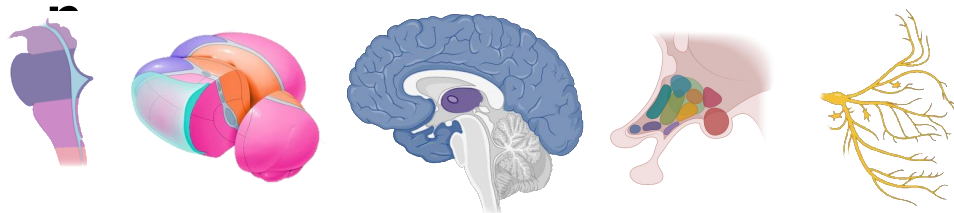
3 MONTHS

BUT FIRST!



Sensitizatio

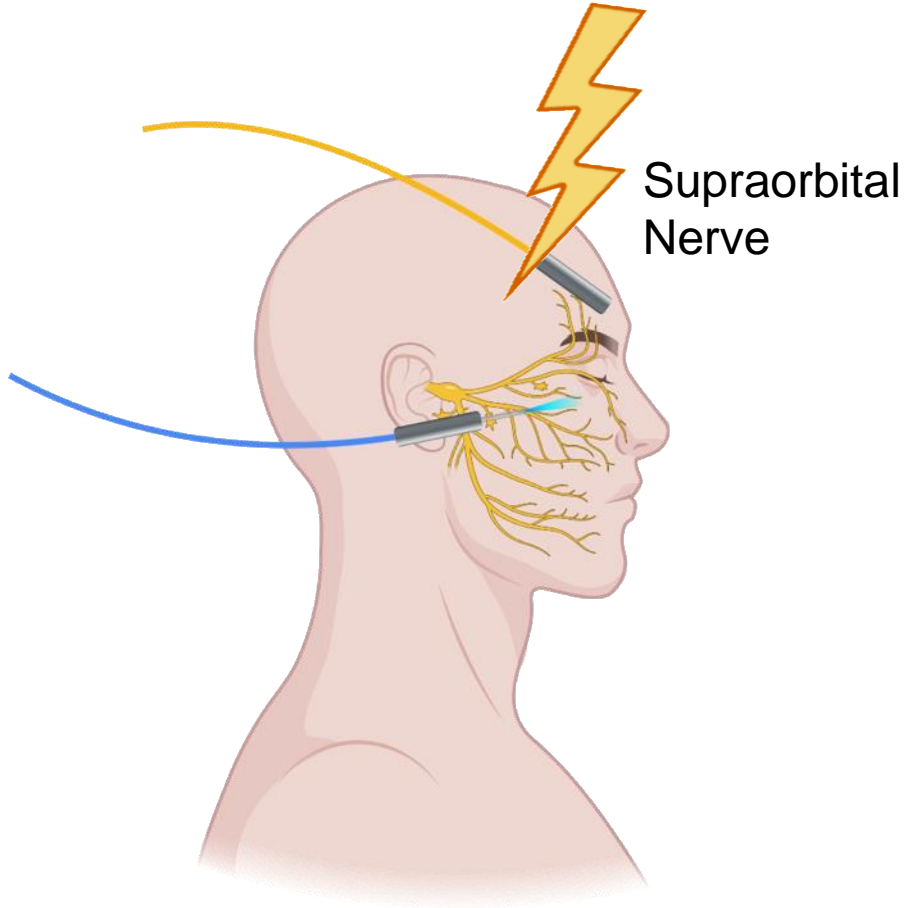
Habituation



nBR

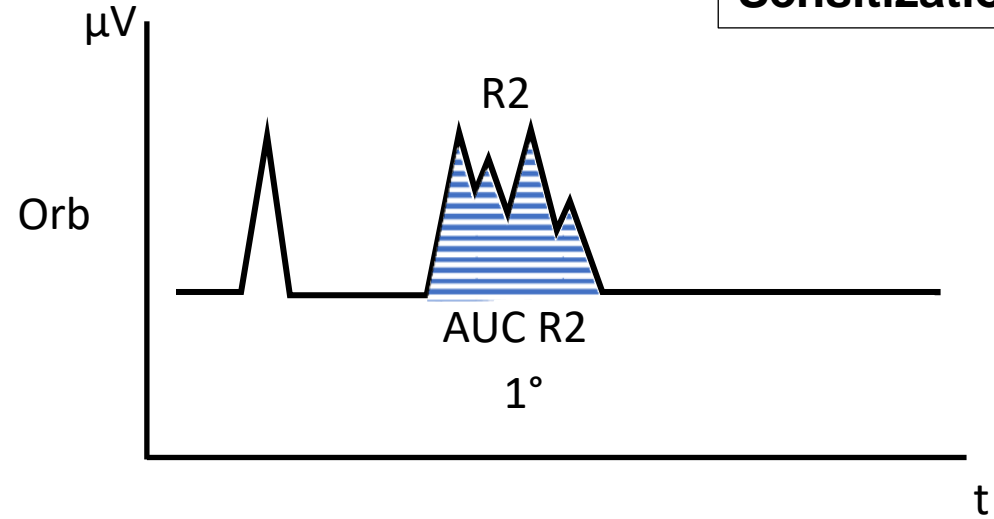
SSEP

10 Stimuli divided in 2 blocks of 5

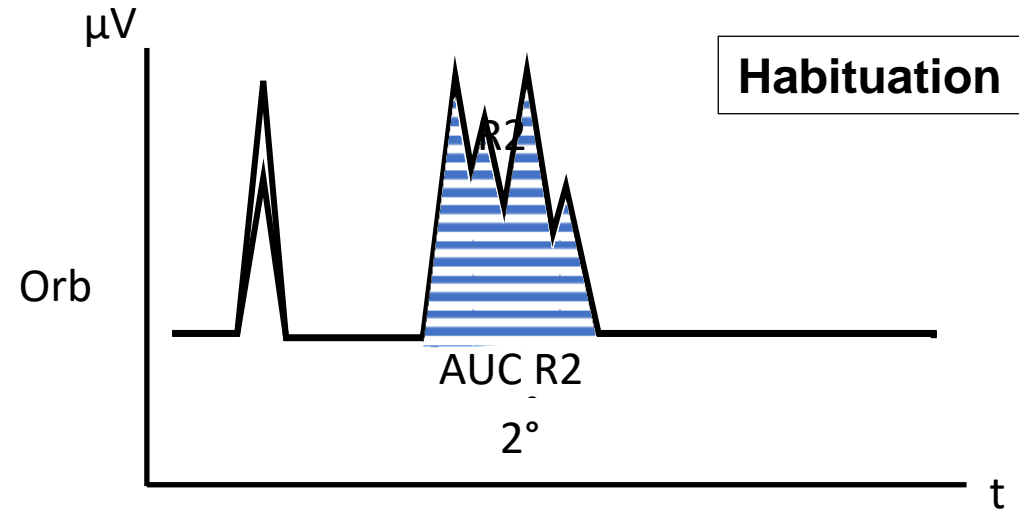


Blink Reflex

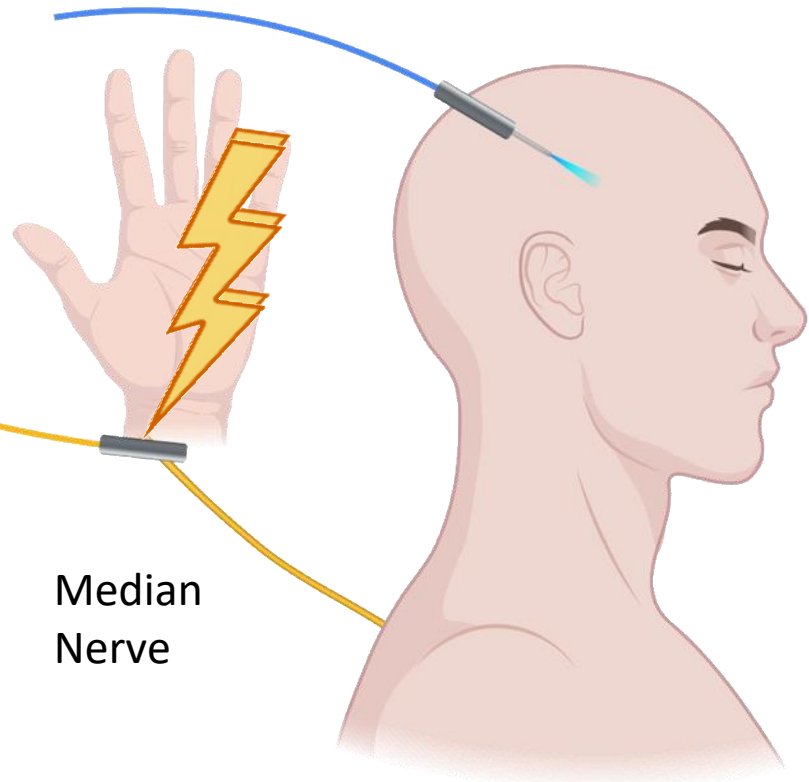
Sensitization



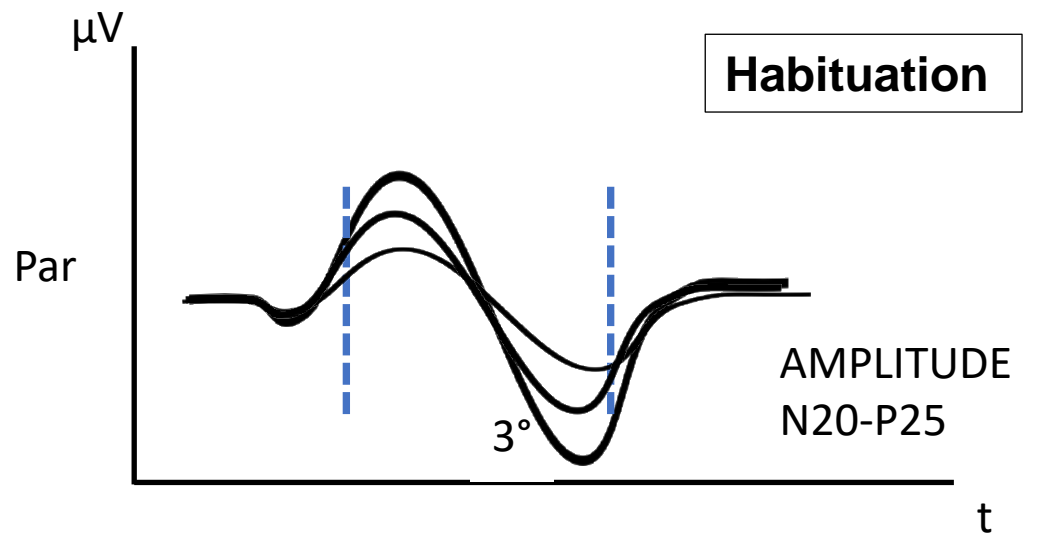
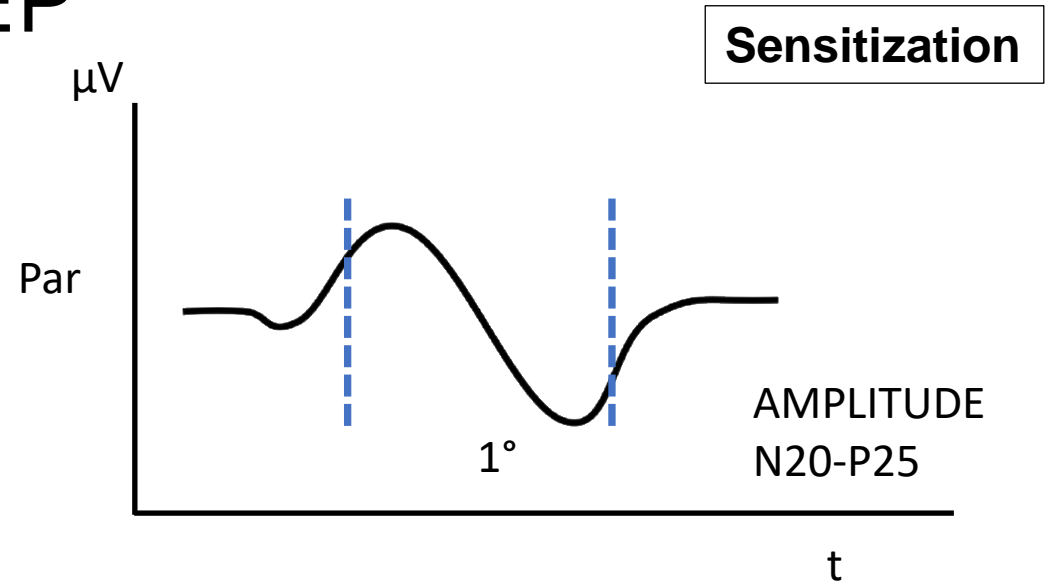
Habituation



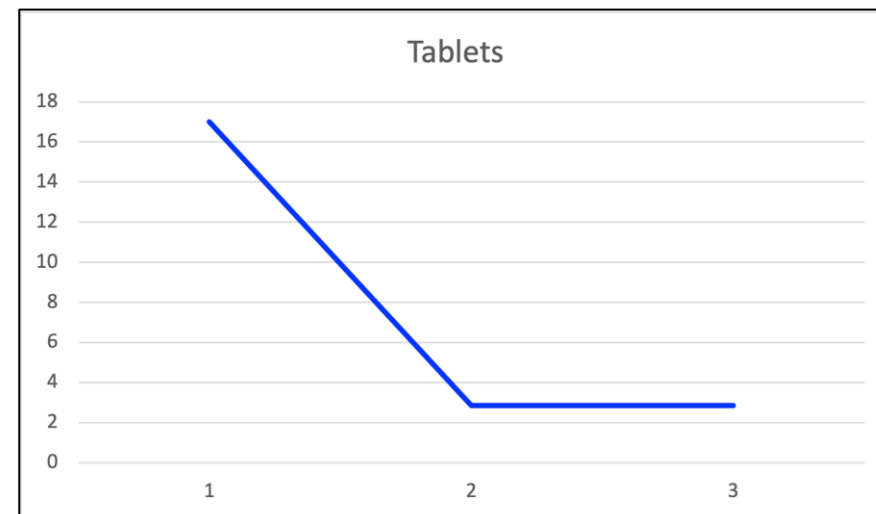
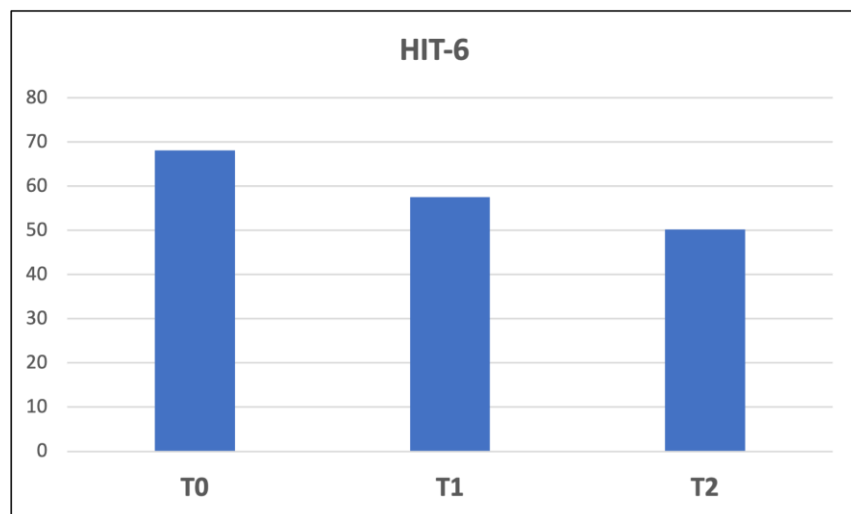
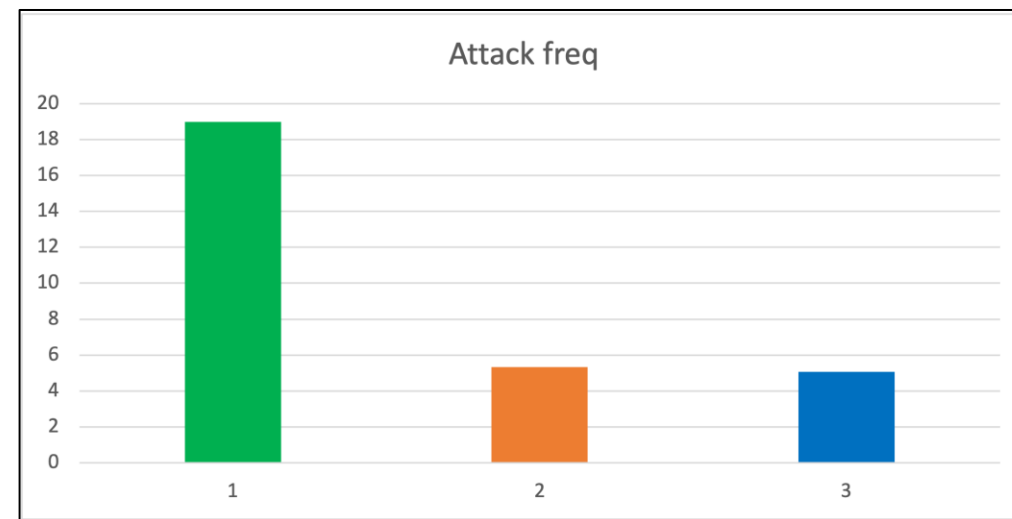
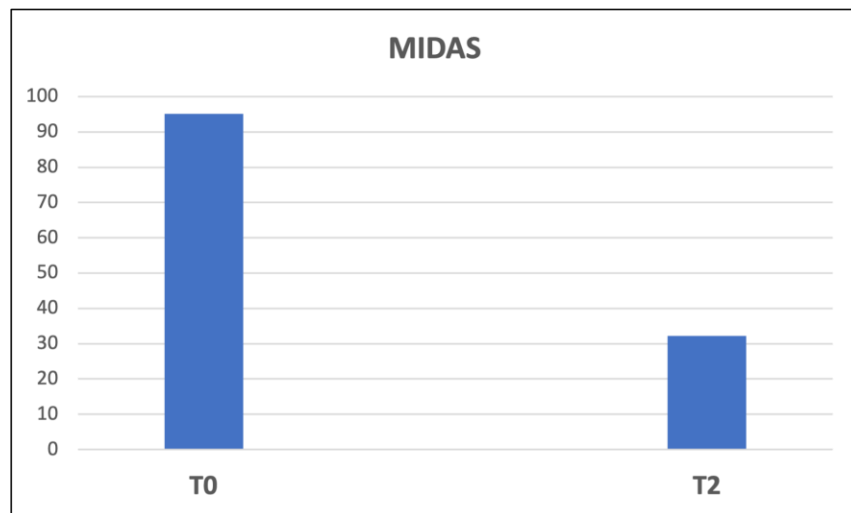
300 Stimuli divided
in 3 blocks of 100



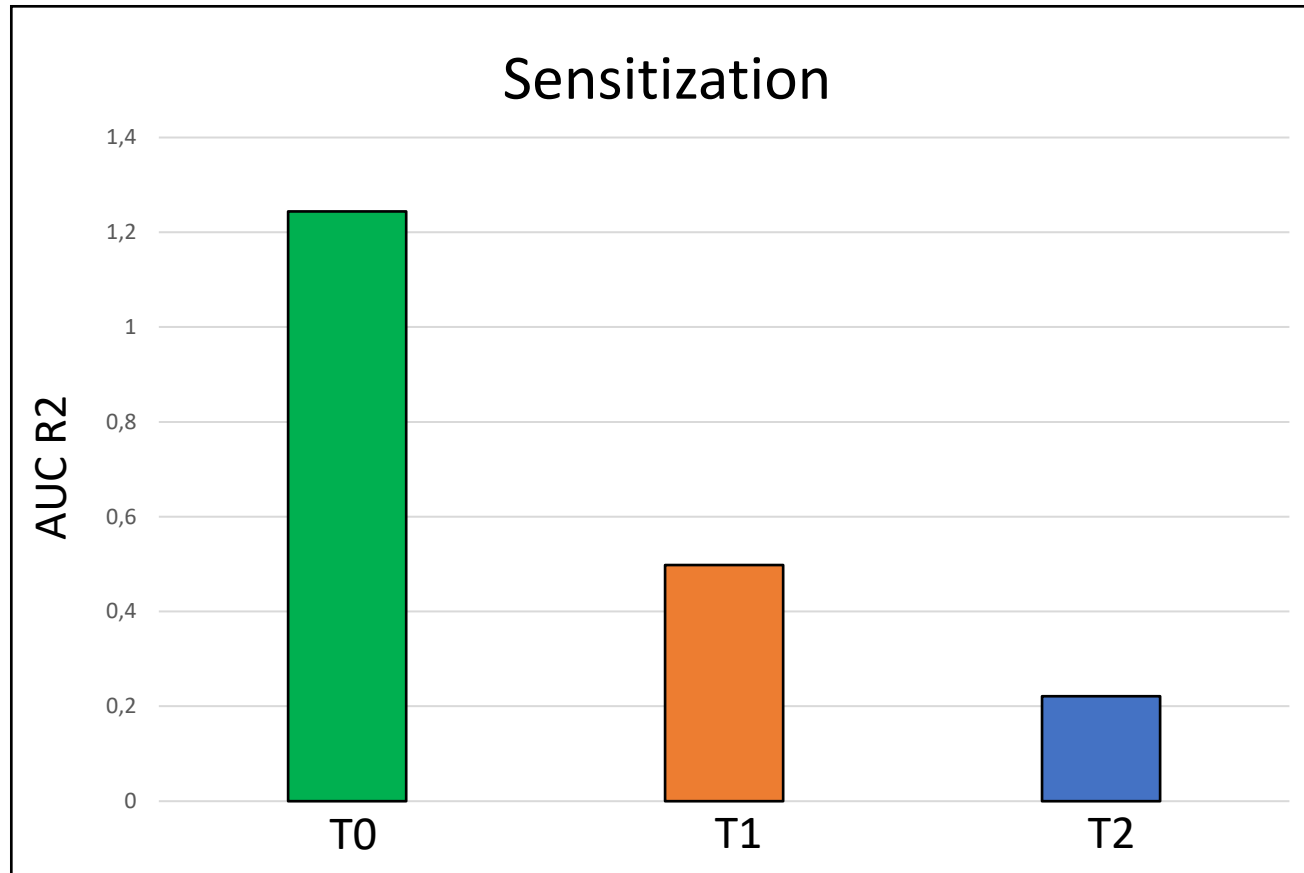
SSEP



Effects of Erenumab on migraine severity

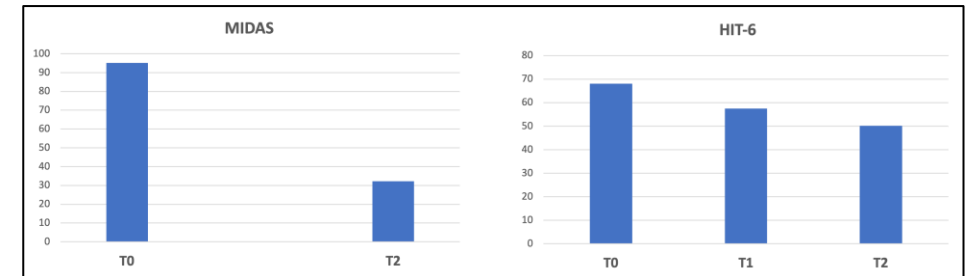


Blink reflex

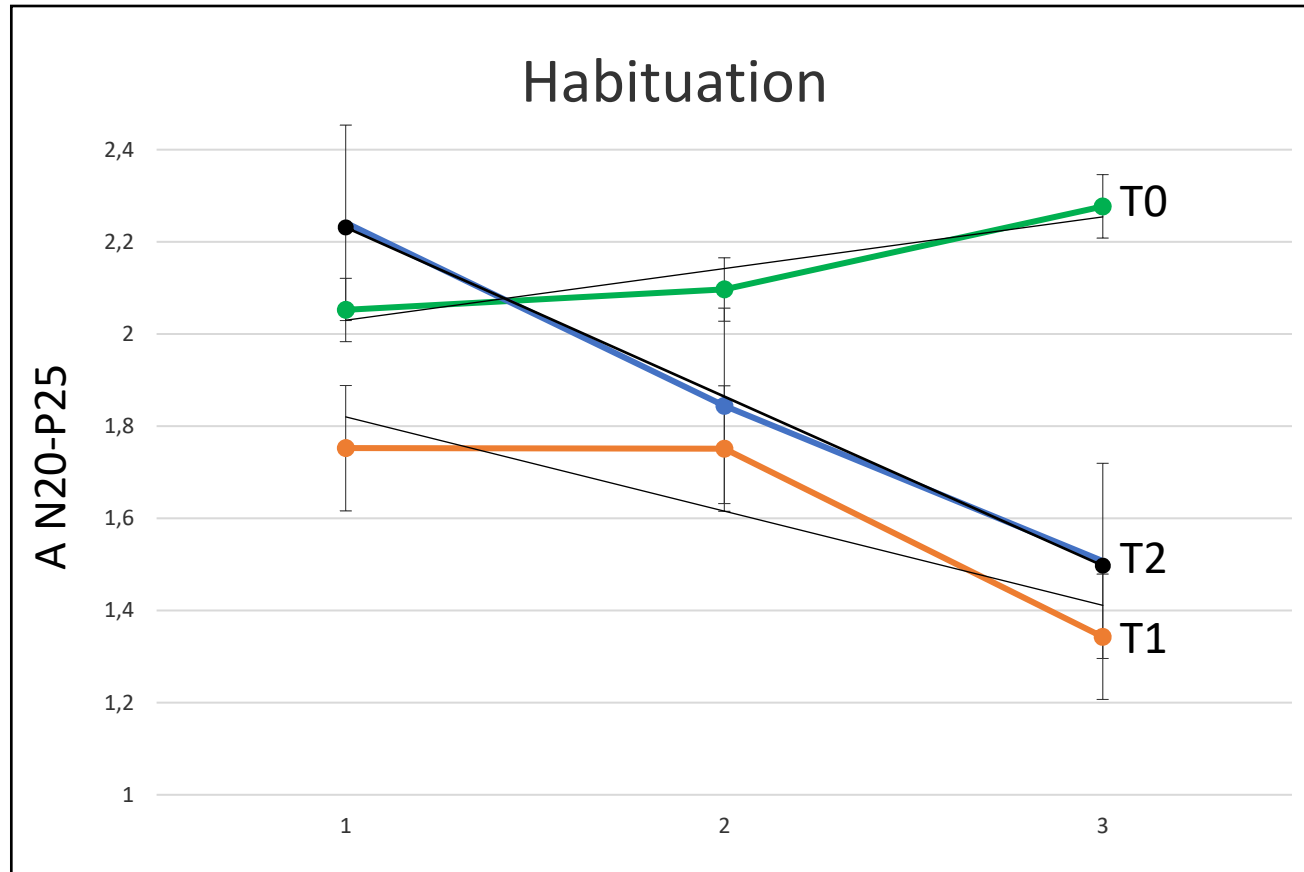


Reduction of sensitization: nBR AUC was significantly reduced at T1, but not at T2 ($p = 0.04$).

Reduction of the mean monthly headache days, severity of headache (0-10), and the mean monthly tablet intake (all $p < 0.001$).

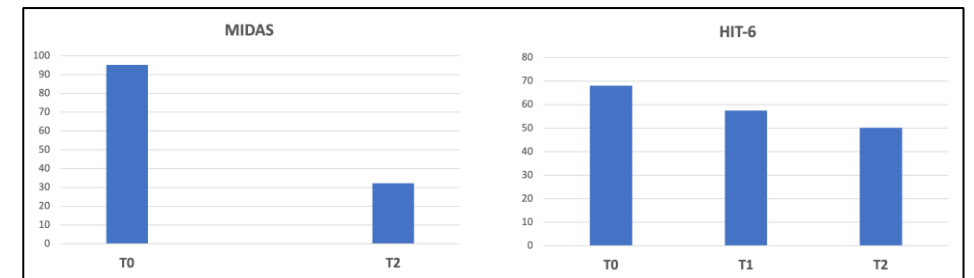


SSEP

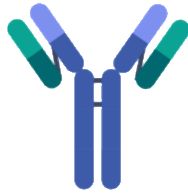


Normalization of habituation: significant increase in delayed SSEP amplitude decrement (habituation) (slope baseline = +0.103, T1 = -0.167, T2 = -0.229, $p < 0.05$).

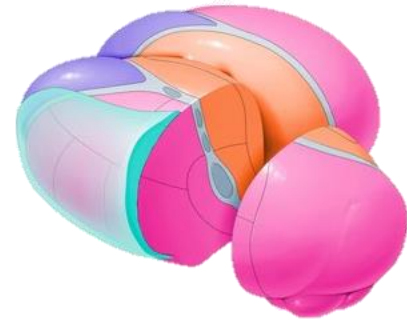
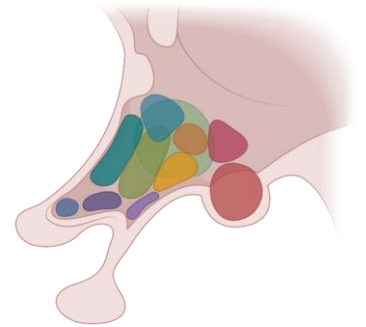
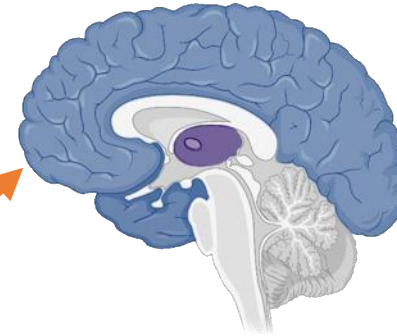
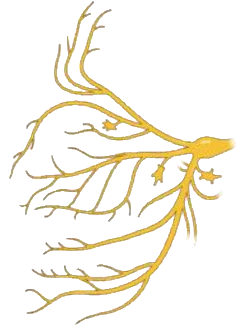
Reduction of the mean monthly headache days, severity of headache (0-10), and the mean monthly tablet intake (all $p < 0.001$).



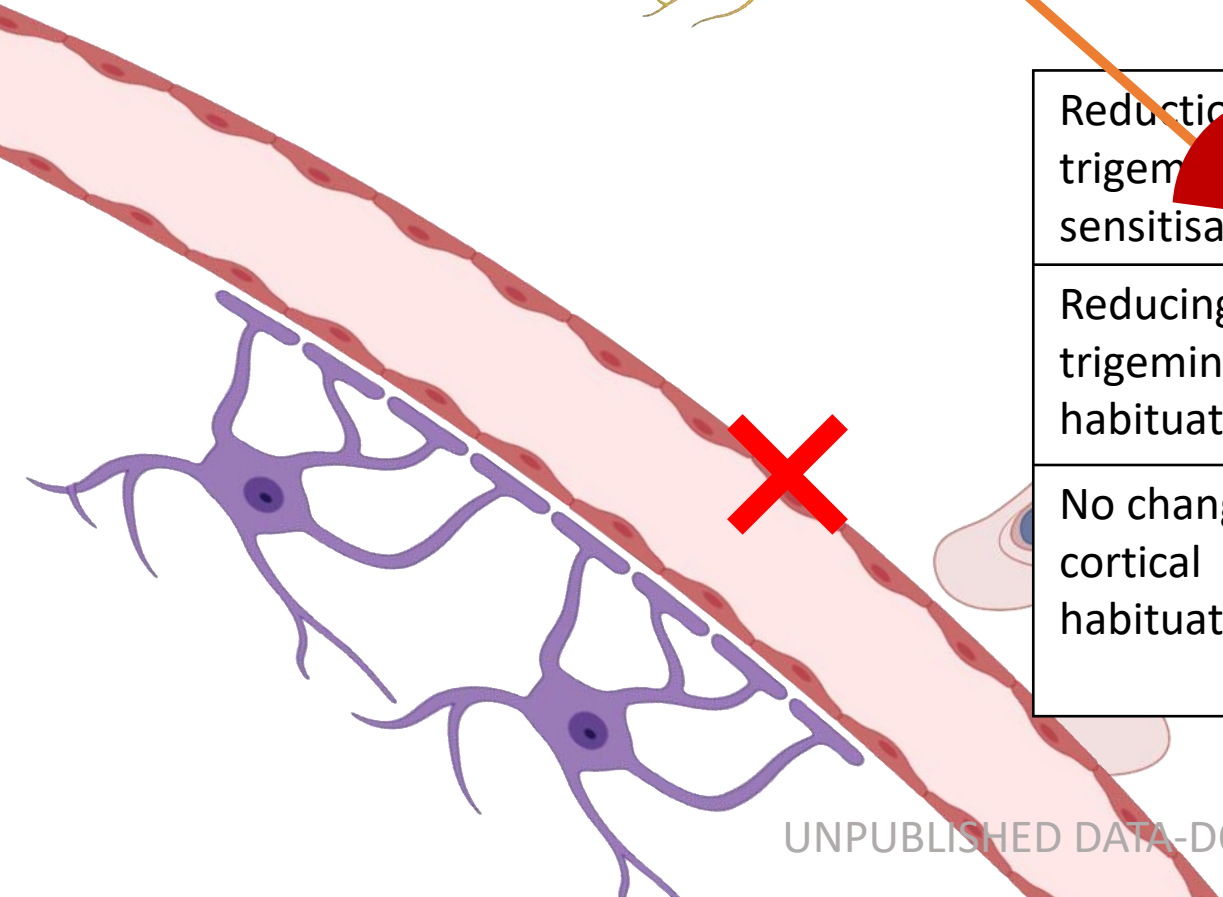
Reducing sensitization

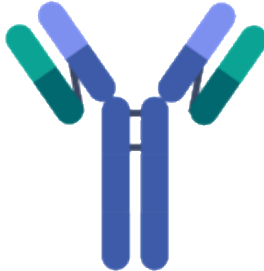


Normalizing habituation

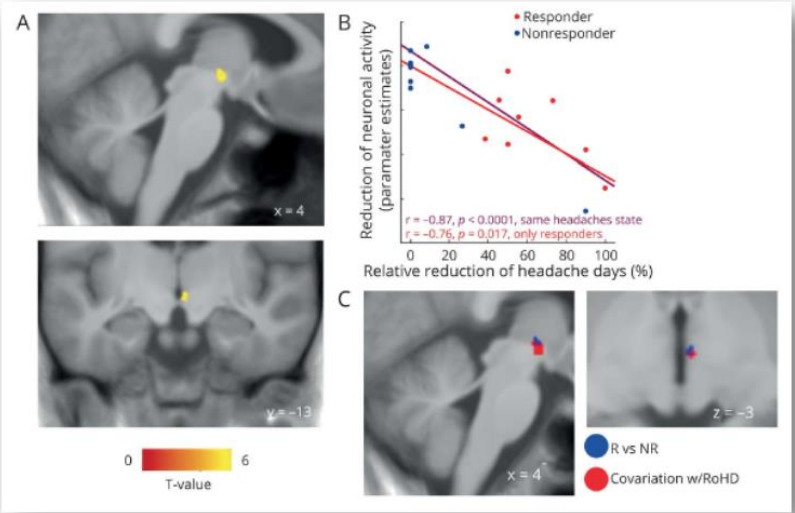
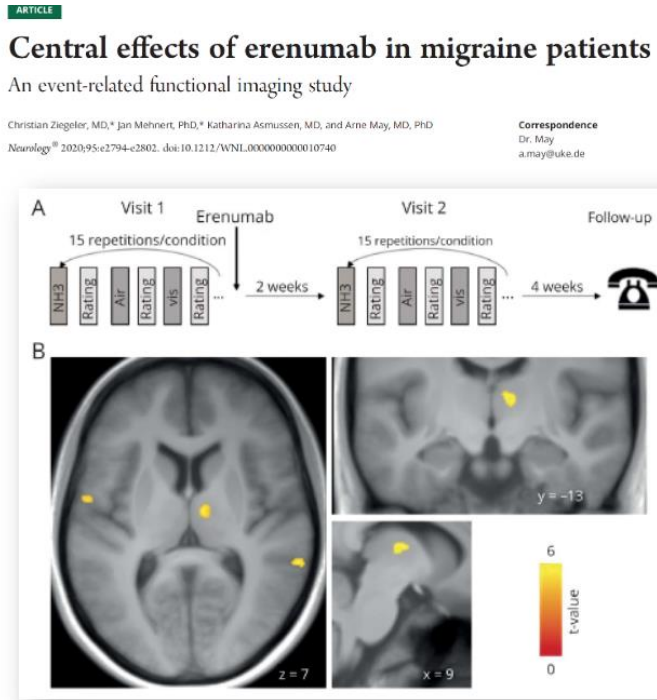
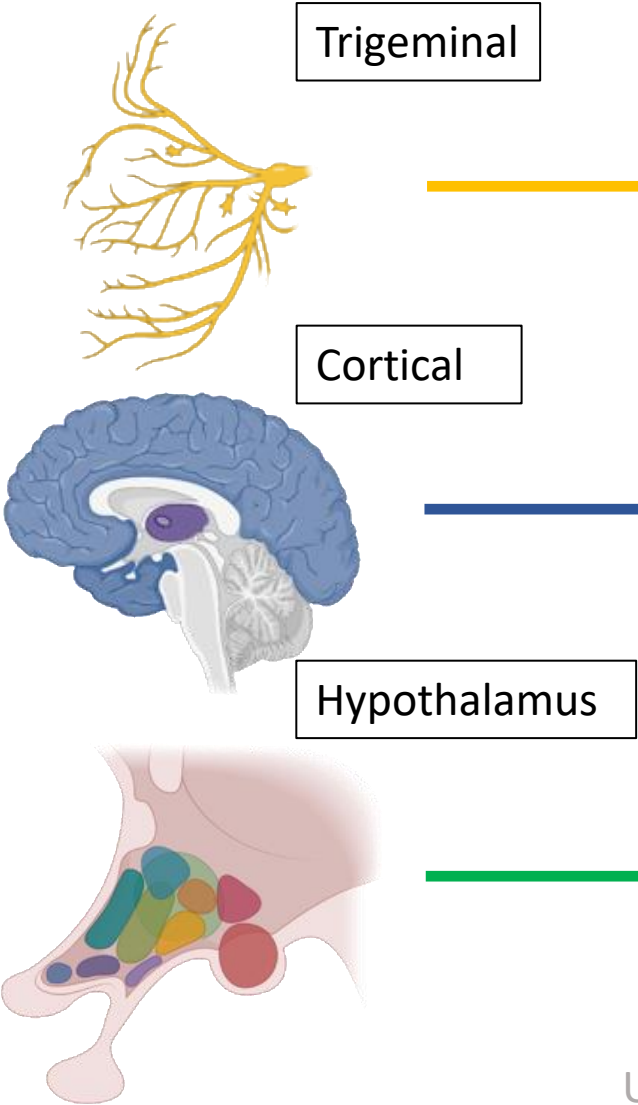


Reduction trigeminal sensitisation	✓
Reducing trigeminal habituation	✗
No change in cortical habituation	✗





- We showed for the first time the cortical and trigeminal effects of erenumab.



(C) Overlap of the activation in the **hypothalamus** for the covariation with decrease of monthly headache days (red) and the comparison of responders and nonresponders.