# Brain networks interaction in migraine

Marina de Tommaso

# 1.1 Migraine without aura

- Previously used terms: Common migraine; hemicrania
- Simplex
- Description:Recurrent headache disorder manifesting in attacks lasting 4–72 hours Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

# 1.2 Migraine with aura

Previously used terms: Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagne´e; complicated migraine.

Description:Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central

nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

# 1.3 Chronic migraine

Headache occurring on 15 or more days/month for more than three months, which, on at least eight days/month, has the features of migraine headache.

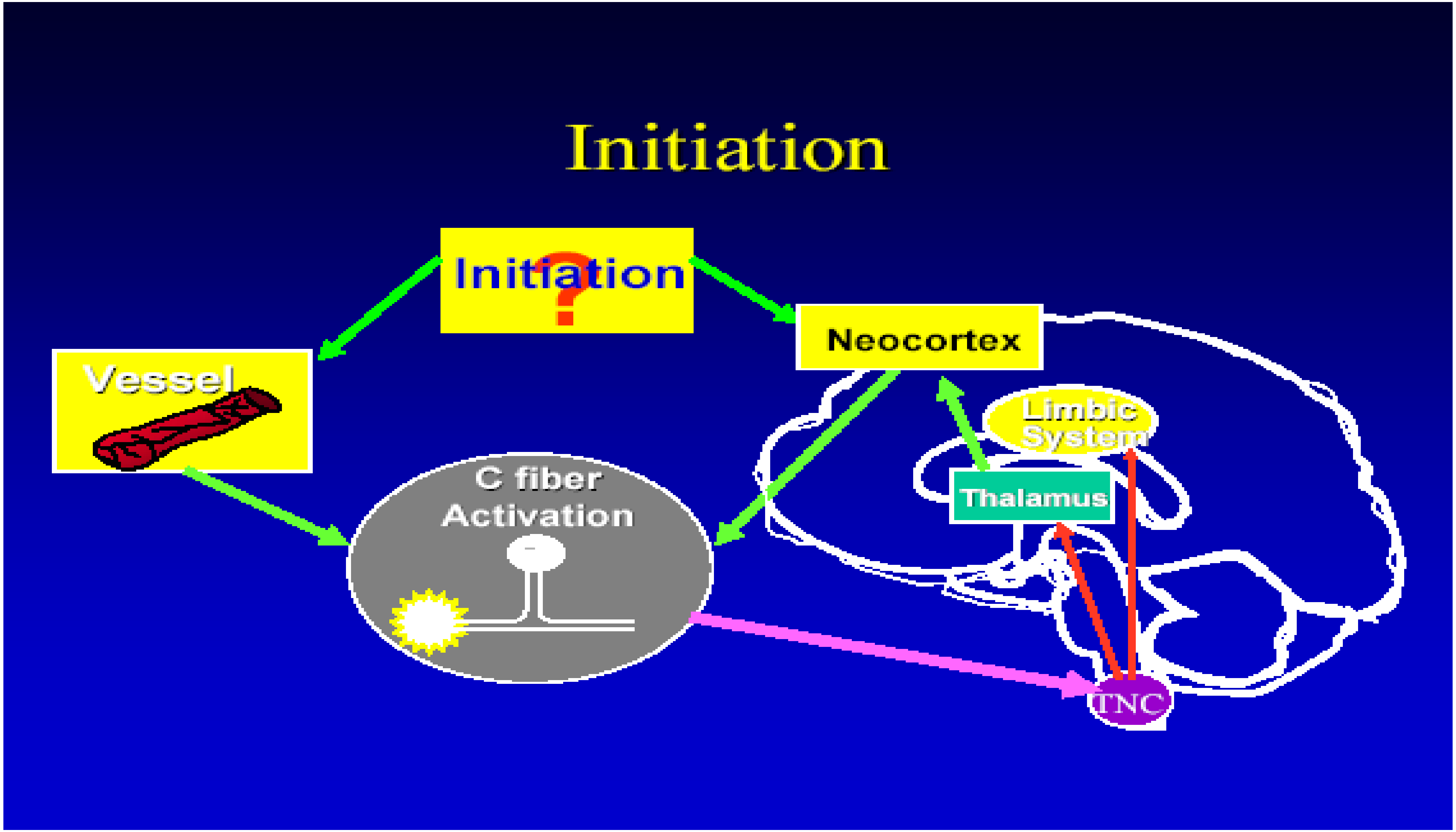
# Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

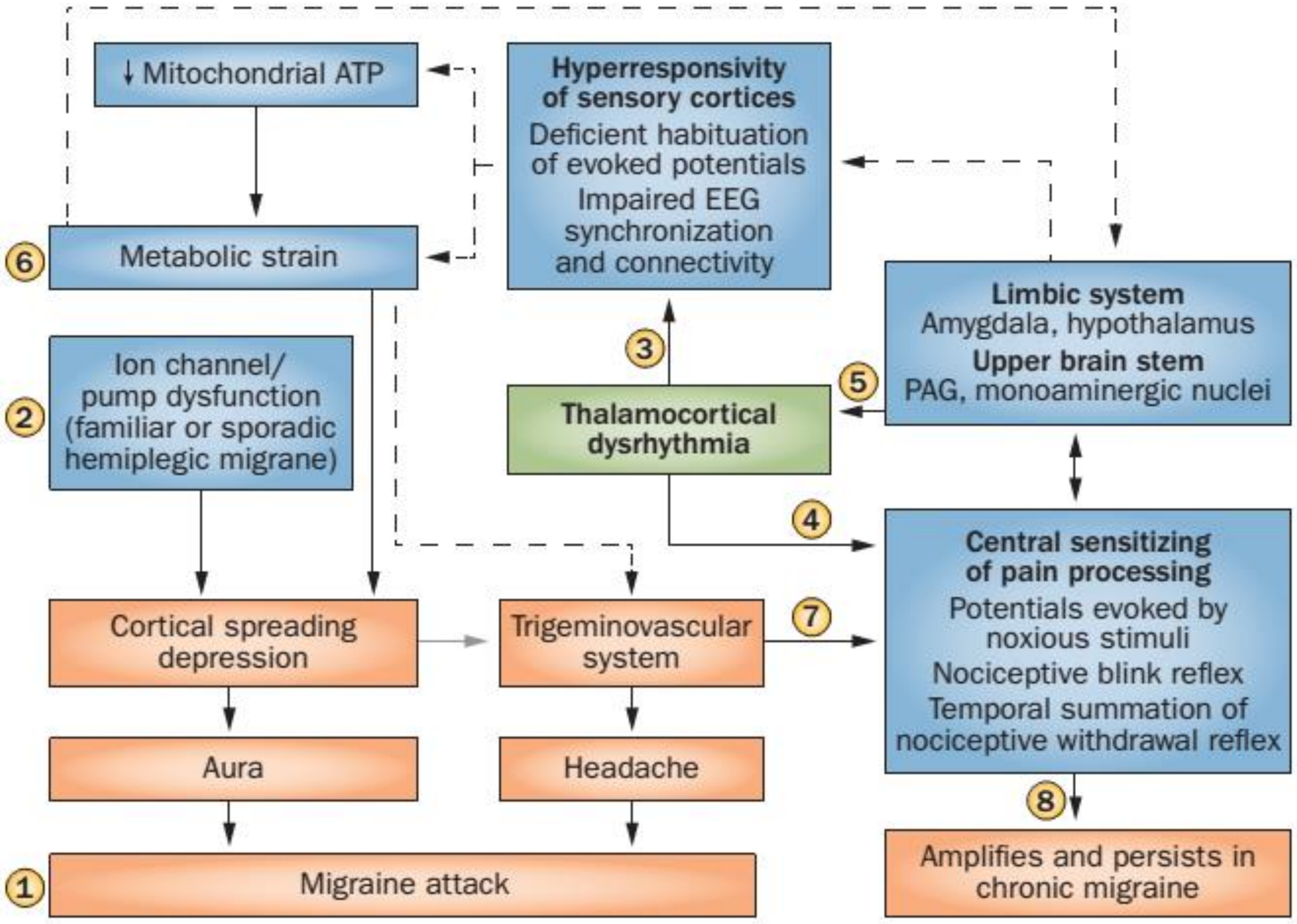
*GBD 2016 Neurology Collaborators**

Rank: 1 – 5 – 10 – 15

| | Global | East Asia | Southeast Asia | Oceania | Central Asia | Central Europe | Eastern Europe | High-income Asia Pacific | Australasia | Western Europe | Southern Latin America | High-income North America | Caribbean | Andean Latin America | Central Latin America | Tropical Latin America | North Africa and Middle East | South Asia | Central sub-Saharan Africa | Eastern sub-Saharan Africa | Southern sub-Saharan Africa | Western sub-Saharan Africa |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stroke | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Migraine | 2 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 4 | 3 | 3 | 3 |
| Alzheimer's disease and other dementias | 3 | 2 | 2 | 2 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 4 | 3 | 4 | 4 | 4 |
| Meningitis | 4 | 11 | 5 | 4 | 9 | 12 | 10 | 14 | 13 | 13 | 11 | 13 | 4 | 9 | 10 | 8 | 5 | 3 | 2 | 2 | 5 | 2 |
| Epilepsy | 5 | 5 | 4 | 5 | 3 | 7 | 8 | 6 | 7 | 6 | 5 | 6 | 5 | 4 | 4 | 4 | 4 | 6 | 5 | 5 | 2 | 5 |
| Spinal cord injury | 6 | 7 | 8 | 9 | 7 | 6 | 5 | 4 | 4 | 4 | 4 | 4 | 9 | 8 | 9 | 9 | 6 | 9 | 6 | 7 | 10 | 9 |
| Traumatic brain injury | 7 | 6 | 6 | 7 | 5 | 4 | 4 | 7 | 8 | 8 | 9 | 8 | 7 | 7 | 6 | 7 | 9 | 7 | 7 | 8 | 6 | 7 |
| Brain and other CNS cancer | 8 | 4 | 9 | 10 | 6 | 5 | 6 | 8 | 5 | 5 | 6 | 5 | 8 | 6 | 7 | 5 | 8 | 10 | 9 | 11 | 9 | 10 |
| Tension-type headache | 9 | 8 | 10 | 8 | 10 | 8 | 7 | 5 | 6 | 7 | 7 | 7 | 6 | 5 | 5 | 6 | 7 | 8 | 8 | 9 | 7 | 6 |
| Encephalitis | 10 | 9 | 7 | 6 | 8 | 13 | 11 | 11 | 14 | 14 | 12 | 14 | 11 | 10 | 11 | 12 | 10 | 5 | 10 | 10 | 11 | 8 |
| Parkinson's disease | 11 | 10 | 11 | 12 | 12 | 9 | 9 | 10 | 9 | 10 | 8 | 9 | 12 | 11 | 12 | 11 | 12 | 13 | 13 | 13 | 12 | 13 |
| Other neurological disorders | 12 | 12 | 12 | 11 | 11 | 10 | 12 | 9 | 10 | 9 | 10 | 10 | 10 | 12 | 8 | 10 | 11 | 12 | 12 | 12 | 8 | 12 |
| Tetanus | 13 | 15 | 13 | 14 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 13 | 15 | 15 | 15 | 14 | 11 | 11 | 6 | 15 | 11 |
| Multiple sclerosis | 14 | 14 | 15 | 15 | 13 | 11 | 13 | 13 | 12 | 11 | 13 | 11 | 15 | 14 | 14 | 14 | 13 | 14 | 14 | 14 | 13 | 15 |
| Motor neuron diseases | 15 | 13 | 14 | 13 | 14 | 14 | 14 | 12 | 11 | 12 | 14 | 12 | 14 | 13 | 13 | 13 | 15 | 15 | 15 | 15 | 14 | 14 |

**Figure 1: Ranking of age-standardised DALY rates for all neurological disorders by region, 2016**
DALY=disability-adjusted life-year.


Initiation
Initiation
Neocortex
Vessel
Limbic System
Thalamus
C fiber Activation
TNC




de Tommaso et al, 2014

# TWO MAIN ASPECTS OF MIGRAINE:
# 1 MECHANISMS PREDISPOSING TO CORTICAL SPREADING DEPRESSION

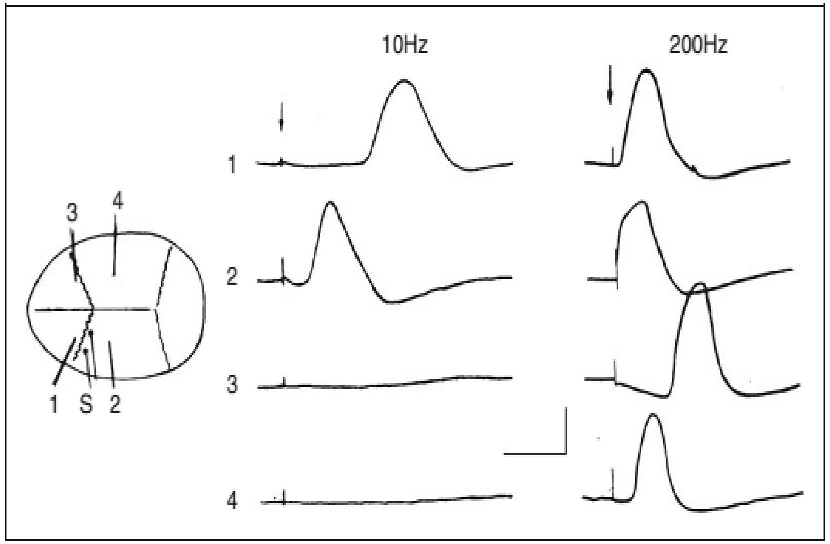
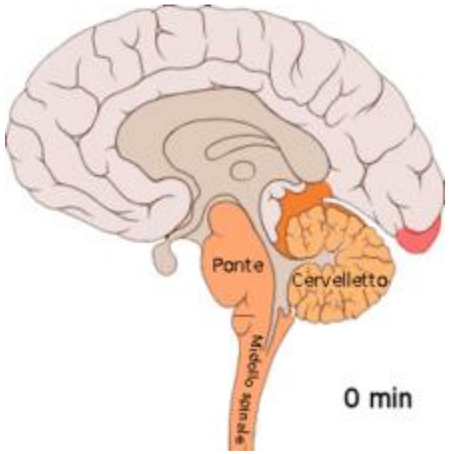



**Figure 1.** Cortical SD induced by low- and high-frequency electrical stimulation of the parietal cortex in rats. Left: Diagram indicating location of stimulating (S) and recording (1–4) cortical electrodes. Right: Representative examples of cortical SD induced by 10 Hz and 200 Hz stimulation of the cortex (marked by arrows) and recorded in the ipsilateral (sites 1–2) and contralateral (sites 3–4) hemispheres are shown. Calibration is 10 mV and 1 min. Note local unilateral initiation and slow non-synaptic propagation of SD induced by 10 Hz stimulation and multifocal initiation of cortical SD by 200 Hz stimulation revealing by remarkable reduction of SD latencies and triggering SD in the contralateral non-stimulated cortex (modified from (31)).

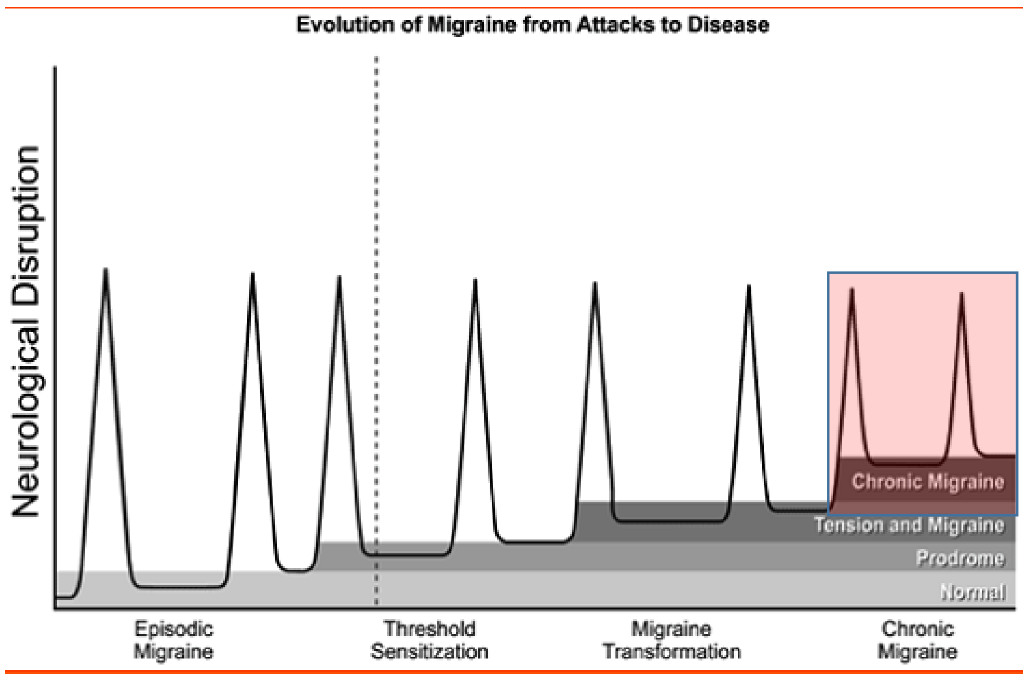


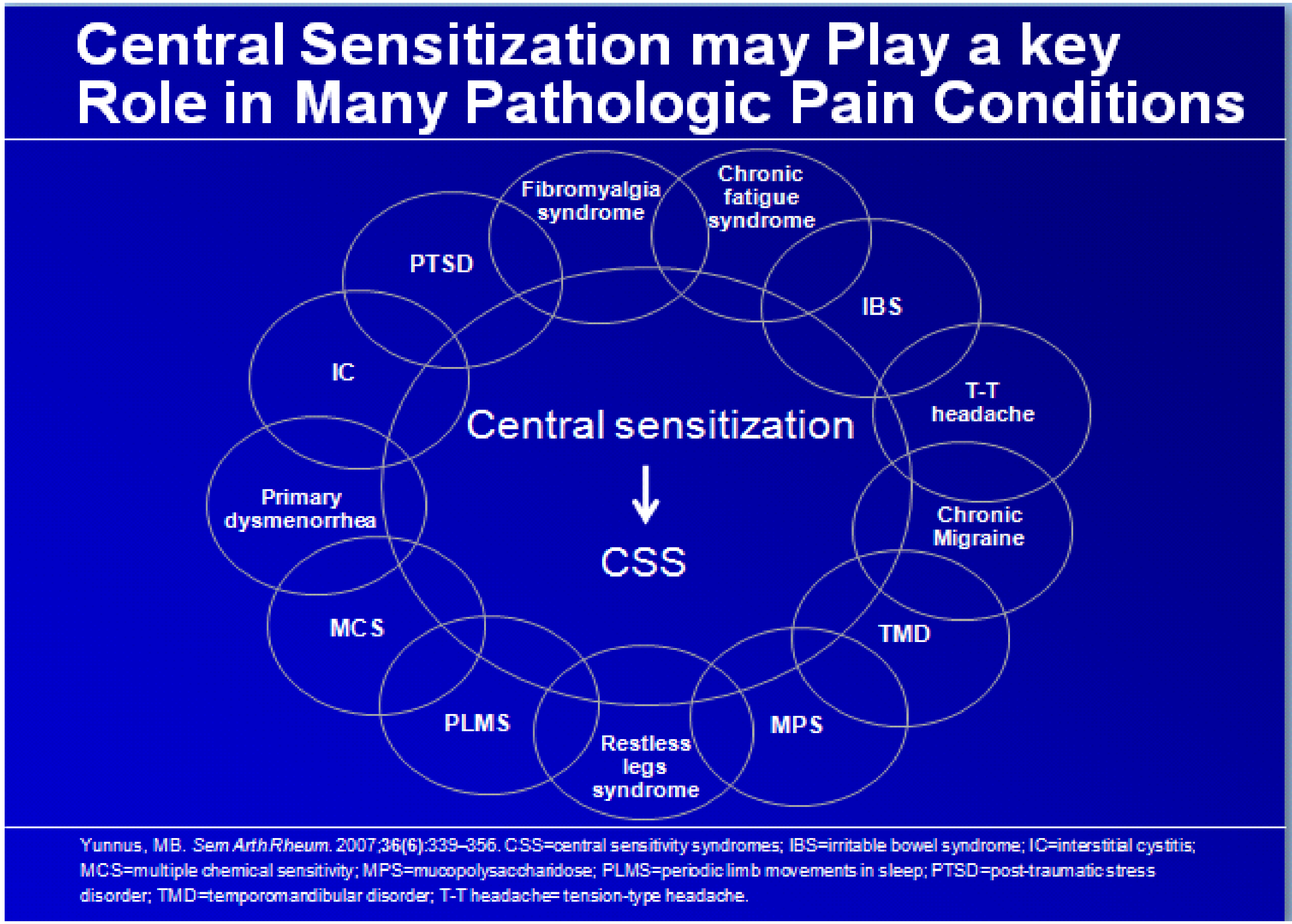

*Cephalalgia*
2018, Vol. 38(6) 1177–1187

**Initiation of spreading depression by synaptic and network hyperactivity: Insights into trigger mechanisms of migraine aura**

Lyudmila V Vinogradova

# TWO MAIN ASPECTS OF MIGRAINE:
# 2 MECHANISMS PREDISPOSING TO CHRONIC EVOLUTION



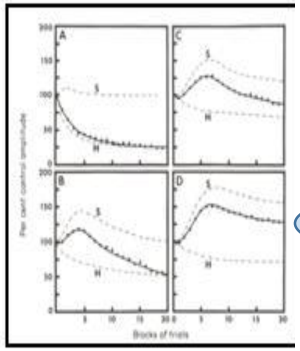

THE REAL PROBLEM IN CLINICAL SETTING IS TO PREVENT CHRONIC MIGRAINE

## Habituation

**Definition**: Habituation is defined as a response decrement that results from repeated stimulation and that is distinct from sensory adaptation/sensory fatigue and motor fatigue.

- Habituation probably is the simplest form of learning.

- Researchers who work on this form of learning believe that because habituation allows animals to filter out irrelevant stimuli and focus selectively on important stimuli, it is a prerequisite for other forms of learning and therefore to fully understand the mechanisms of more complex forms of learning and cognition it is important to understand the basic building blocks of habituation.



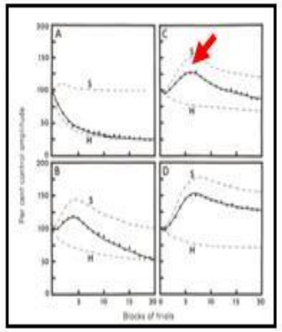

## Sensitization: behavioural point of view

- Learning is obviously not a unitary phenomenon.
- Broadly construed, it is reflected in changes in behaviour as a result of experience

- All too often sensitization is viewed as an unwanted stepchild or contaminating variable in studies of learning.

- Sensitization is an elementary form of behavioural plasticity, perhaps equal in importance to habituation and apparently generated by somewhat different neuronal mechanisms.

- Sensitization occurs at the beginning of the test session and is responsible for the transitory increase in response amplitude, and involves stimulus-induced changes in the level of arousal and is dependent on the aversiveness of the stimulus. However, sensitization gradually wanes because the salience of the stimulus decreases with repeated presentation, leaving the habituation process unopposed.



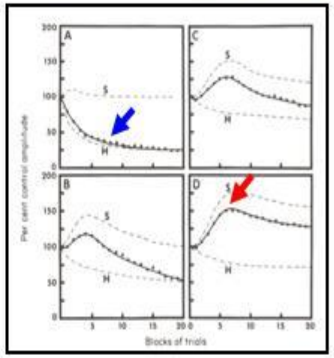

# *REDUCED HABITUATION TO REPETITIVE STIMULI AS STRESSFUL PHENOMENON FOR MIGRAINE TRIGGERING*

## The "dual process" theory

- Two distinct and independent processes govern the behavioural response to repetitive sensory stimulation:

(1) an incremental process called sensitization, and

(2) a decremental process called habituation.



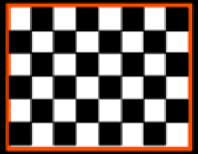

- Sensitization occurs at the beginning of the test session and is responsible for the transitory increase in response amplitude,

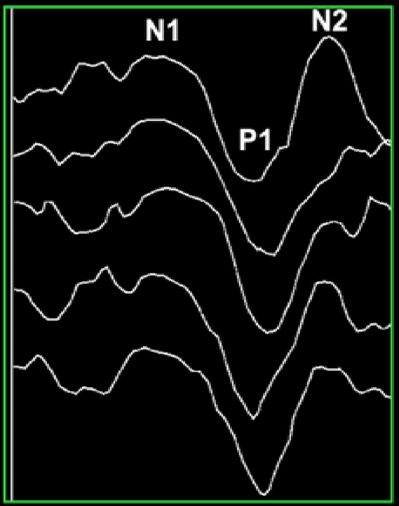
- Habituation occurs throughout the test session and is responsible for the delayed response decrement

(Groves and Thompson, 1970)

(Schoenen et al, 1998; Siniachtin et al, 2001;  Di Clemente et al, 2007;  Valeriani et al, 2003

Nei periodi intericali i **pazienti emicranici** sono caratterizzati da un **deficit della *habituation*** o persino da un **potenziamento** dell'ampiezza delle risposte corticali evocate da **stimoli visivi ripetuti** a tipo ***pattern-reversal***






Schoenen et al., Eur J Neurol, 1995; Afra et al., Brain, 1998)

## Visual evoked responses

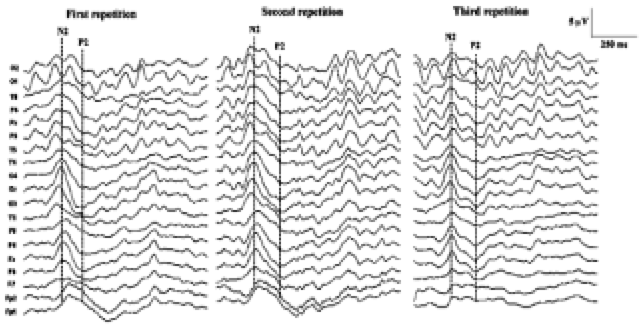
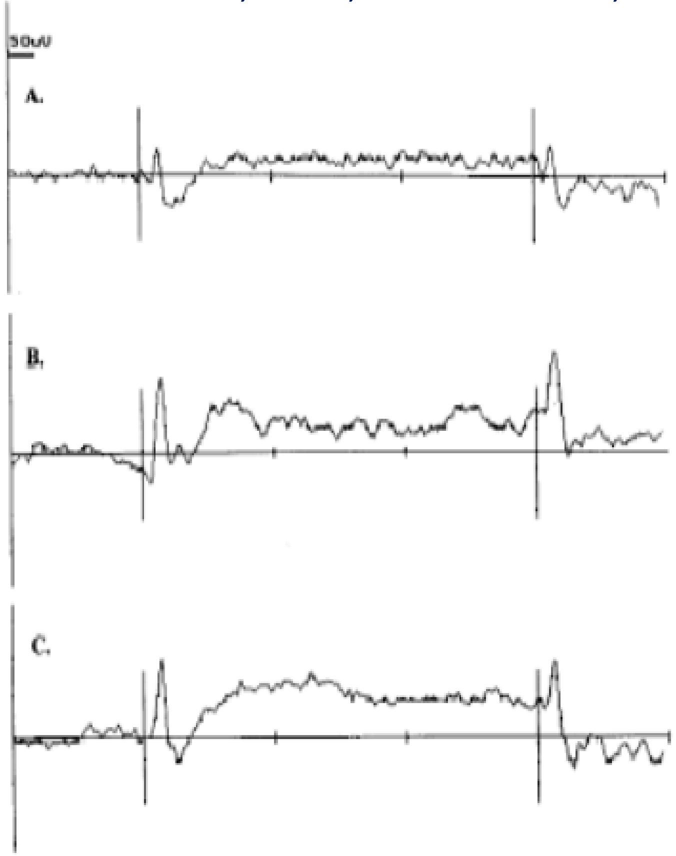



Fig. 2. LEPs recorded from 19 scalp electrodes in a representative migraine patient after right hand stimulation. The amplitude of the N2 and P2 potentials is only slightly reduced in the second and third repetition.

## Laser evoked  evoked responses




## Contingent Negative Variation

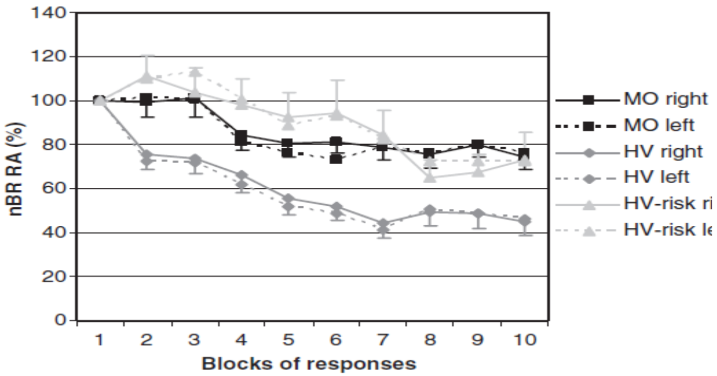



**Fig. 4** Habituation of the R2 response area of ipsi- and contralateral nBR in 10 blocks of five averagings (interstimulus interval: 15–17 ms; interblock interval: 2 min) expressed as percentage of the 1st block.

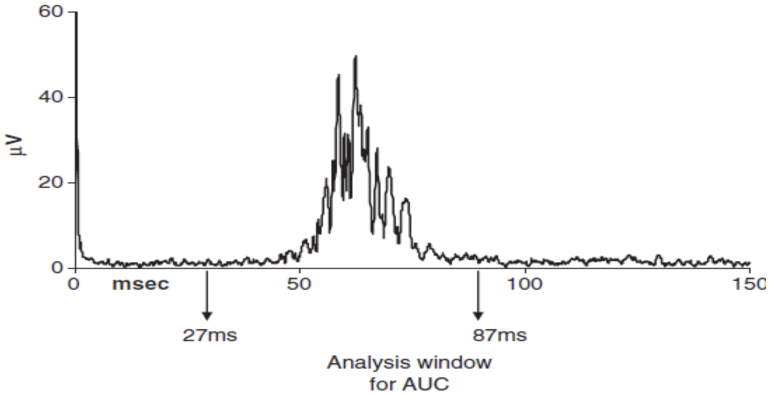



**Fig. 1** Nociception blink reflex recording: one block of five rectified and averaged responses with an ISI of 15–17 s.

## Nociceptive Blink Reflex

***In migraine reduced habituation to repetitive multimodal stimuli cause***

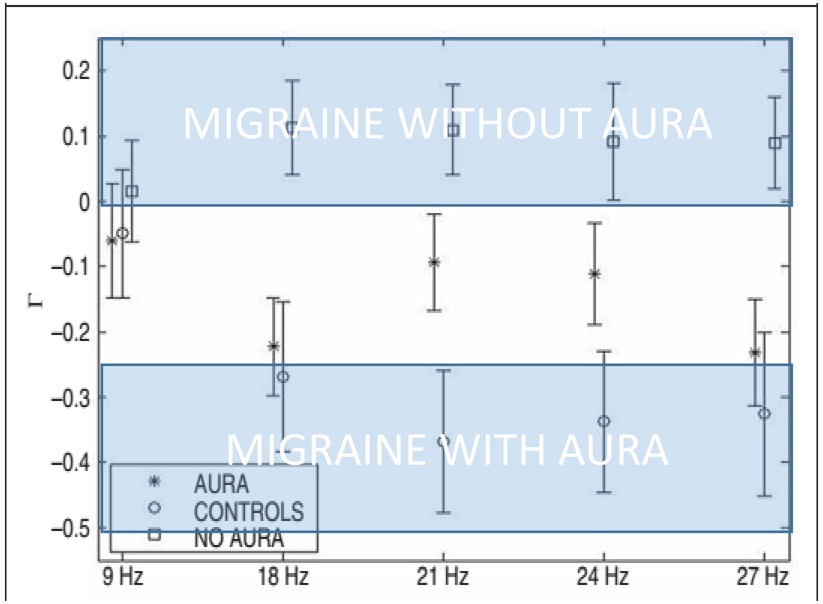
***1)a sensory overload which could  result in CSD generation***

***2) a disturbance in pain processing with facilitation of central sensitization phenomena***

# MIGRAINE IS AN “OSCILLOPATHY”


Abnormal synchronization of alpha rhythm during intermittent light stimulation.

ALPHA SYNCHRONIZATION PATTERN

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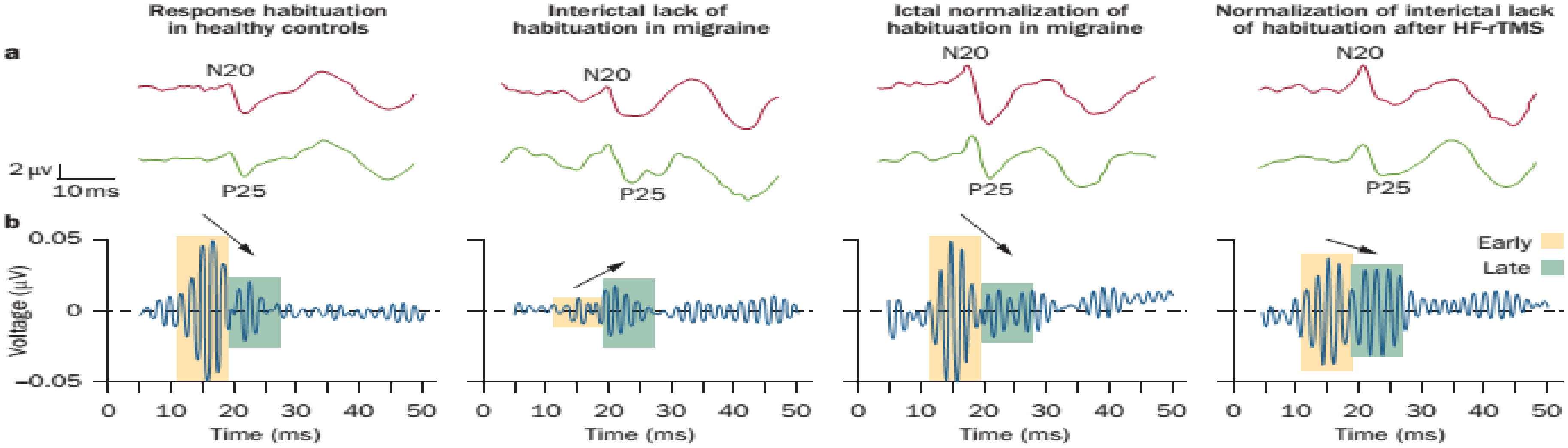
**Functional and effective connectivity in EEG alpha and beta bands during intermittent flash stimulation in migraine with and without aura**

Marina de Tommaso[1], Sebastiano Stramaglia[2], Daniele Marinazzo[3], Gabriele Trotta[2] and Mario Pellicoro[2]

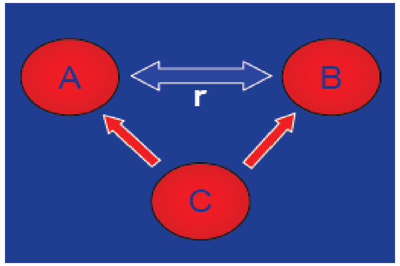
# MIGRAINE IS AN "OSCILLOPATHY"



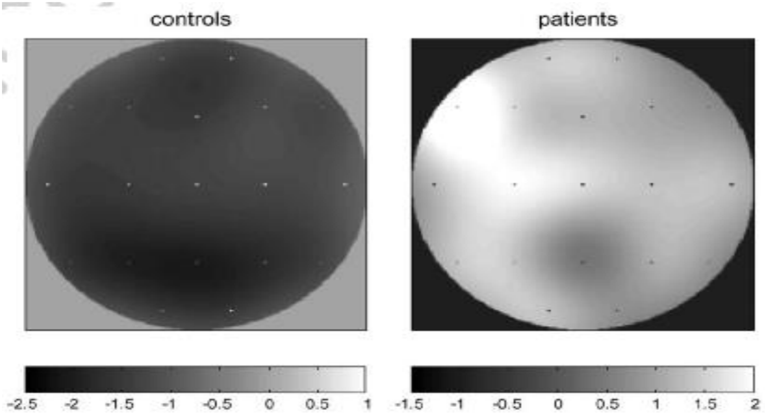

| | | | | |
|---|---|---|---|---|
| Thalamo-cortical drive | Intact | Decreased | Increased | Increased |
| Cortical activation | Intact | Not affected | Not affected | Increased |

**Figure 2** | Cortical response patterns during the migraine cycle. This schematic overview shows amplitude changes in the N20–P25 component of averaged EEG recordings in patients with migraine and healthy controls. **a** | HFOs and **b** | somatosensory evoked potentials. In healthy controls (panel 1), the N20–P25 component habituates, and early HFOs (reflecting thalamocortical drive) are greater than late HFOs (generated by intrinsic cortical activation). In patients with migraine between attacks (panel 2), habituation is absent and early HFOs are reduced, although late HFOs are normal. During a migraine attack (panel 3), habituation and early HFOs normalize. After 10 Hz HF-rTMS is applied over the somatosensory cortex in patients with episodic migraine (panel 4), the interictal lack of habituation reverses, and both early and late HFOs increase. Abbreviations: HFO, high-frequency oscillation; HF-rTMS, high-frequency repetitive transcranial magnetic stimulation.

Interictal synchronization pattern is not simply modulated by cortical inhibition induced by LF rTMS . It is modulated in a complex modality by AED (only levetiracetam reverts alpha hypersynchronization )

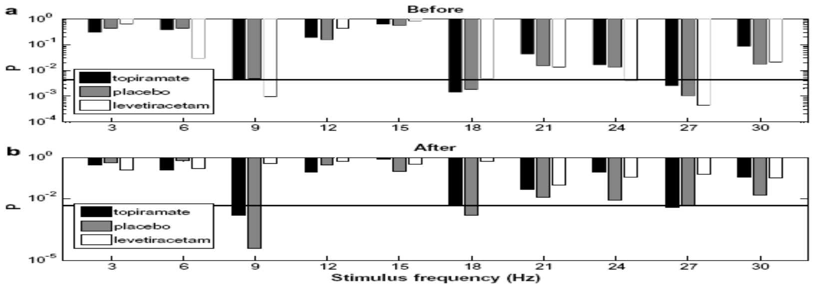



Alpha hypersynchronization under visual stimuli)




(Angelini et al, 2004

Complex modulation by AEDs




(de tommaso et al, 2007)

No effect by LF rTMS cortical inhibition

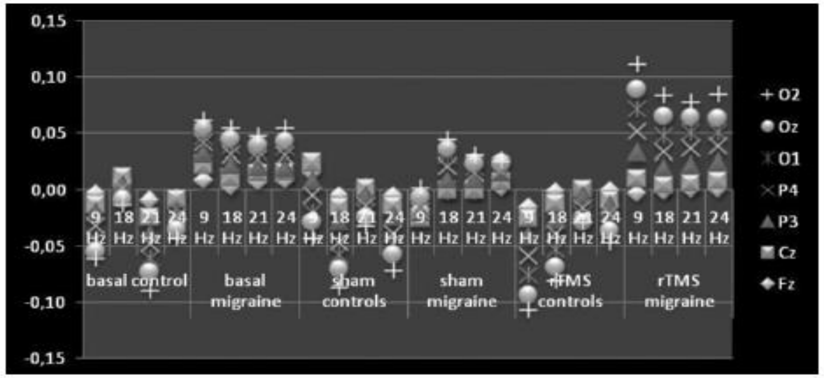



**Fig. 1.** Mean values of synchronization index $\Gamma$ computed across migraine patients (no. 15) and controls (no. 10). The standard deviations are detailed in the supplementary table.

(de tommaso et al, 2011)

EXPERT REVIEW OF NEUROTHERAPEUTICS
https://doi.org/10.1080/14737175.2019.1586534

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REVIEW

Check for updates

# An update on EEG in migraine

Marina de Tommaso

Table 3. Relevant studies on functional connectivity applied to EEG and MEG signals in migraine patients.

| Authors | Year | Type of signal | Method | Cases | Condition | Migraine phase | Results |
|---|---|---|---|---|---|---|---|
| Cao et al [52] | 2016 | EEG | Coherence | Migraine without aura | Resting state | Pre-ictal<br>Ictal<br>Post-ictal | variability across migraine phases, in the fronto-occipital networks |
| Wu et al [53] | 2016 | MEG | Graph Theory | Migraine with aura, migraine without aura | Resting state | Inter-ictal | increased functional connectivity in the theta band in occipital areas in migraine with aura. Increased connectivity in frontal areas in migraine with and without aura vs controls |
| Angelini et al [56] | 2004 | EEG | Phase Synchronization | Migraine without aura | Visual stimulation (repetitive flash 15–30 Hz) | Inter-ictal | Alpha rhythm synchronization in migraine without aura, desynchronization in controls |
| de Tommaso et al [60] | 2013 | EEG | Phase synchronization<br>Granger causality | Migraine without aura<br>Migraine with aura | Visual stimulation (repetitive flash 15–30 Hz) | Inter-ictal | Alpha rhythm synchronization in migraine without aura, increased Granger causality in beta band in migraine with aura |
| de Tommaso et al [41] | 2017 | EEG<br>FMRI | Graph Theory | Migraine without aura<br>Migraine with aura | Visual stimulation (pattern reversal) | Inter-ictal | increased activation of occipital cortex in migraine with aura (bold signal) with segregated cluster of connections in occipital areas (EEG), as compared to normal subjects and migraine without aura group. |
| Porcaro et al [61] | 2017 | EEG | Functional source separation algorithm | Migraine without aura | Electrical stimulation of median nerve | Inter-ictal | significantly lower brainstem (BS) and thalamic (Th) High Frequency Oscillations |
| de Tommaso et al [62] | 2015 | EEG | Phase synchronization<br>Granger Causality | Migraine without aura | Laser stimulation right hand | Inter-ictal | Increased laser-induced Granger Causality in migraine compared to controls, correlated with reduced laser evoked potentials habituation |

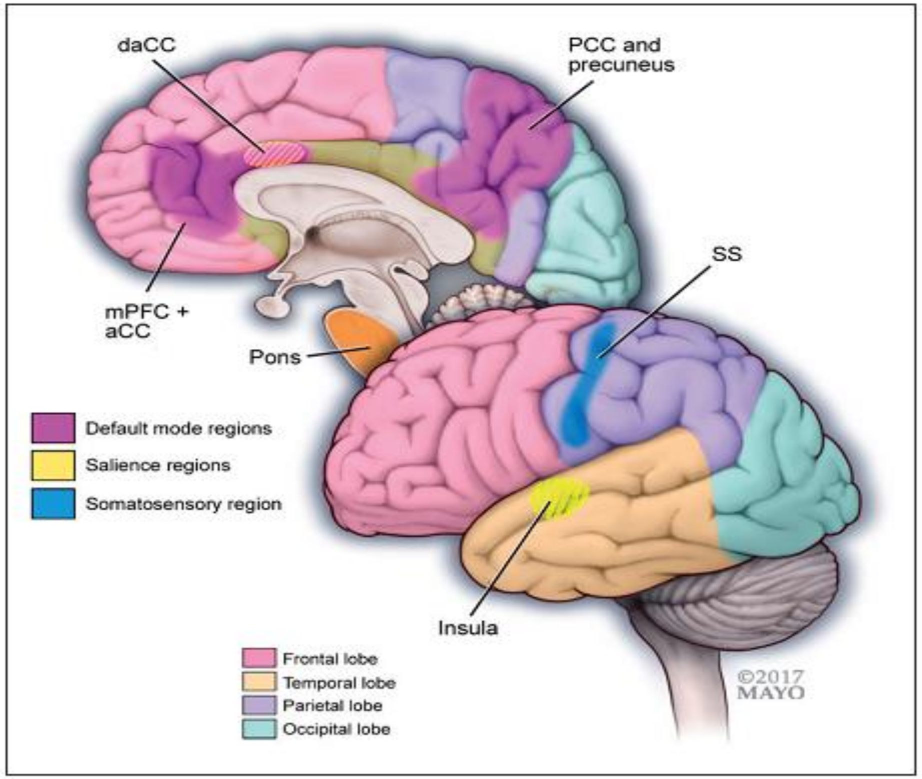



**Figure 2.** A schematic illustration of regions and functional networks (default mode, salience, sensory) where studies have shown altered functional connectivity in migraine patients during attacks compared to between attacks. Important regions of functional networks that are altered in migraineurs during the attack compared to between attacks include the following:
Default mode network regions: medial prefrontal cortex (mPFC) and anterior cingulate cortex (aCC), precuneus and posterior cingulate cortex (pCC).
Salience network regions: insula and (dorsal) anterior cingulate.
Sensory network region: somatosensory cortex (SS).
Migraineurs during the attack have stronger functional connectivity between the pons and the somatosensory cortex (SS).

# Brain functional connectivity in headache disorders: A narrative review of MRI investigations

Catherine D Chong[1], Todd J Schwedt[1] and Anders Hougaard[2]

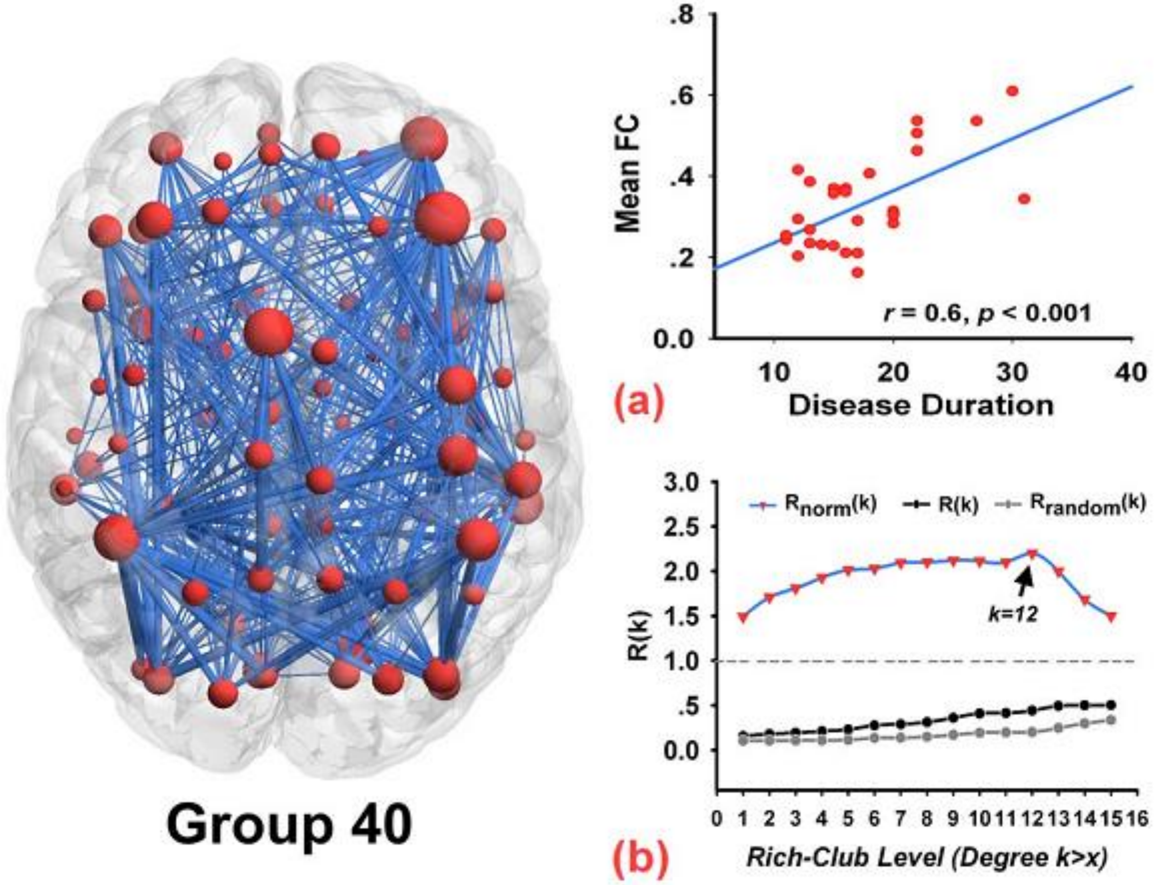
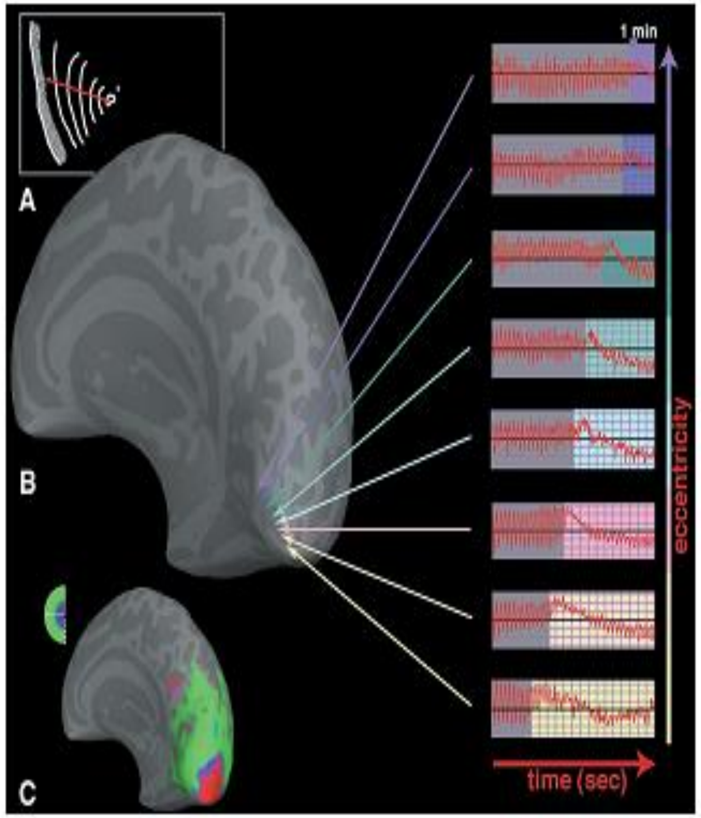
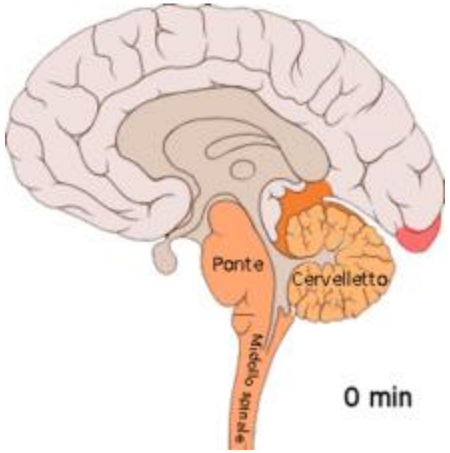



**Figure 4.**

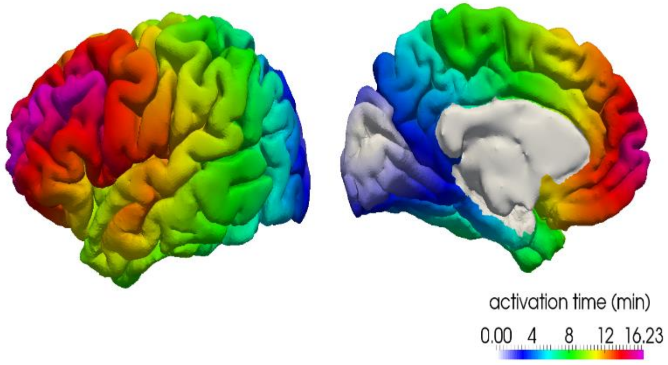
Using the interconnected component of the difference network between the last patient group (Group 40) and HC as a reference, the mean dysfunctional connectivity strength was positively associated with the disease duration across patients in this group (**a**). (**b**) shows the rich-club coefficient curves in the between-group difference network. Rich-club coefficients $\boldsymbol{R}(\boldsymbol{k})$ are indicated with a black line, and corresponding parameters for a random graph $\boldsymbol{R}_{random}(\boldsymbol{k})$ with the same number of nodes and edges are shown in dark gray. The normalized rich-club coefficient $\boldsymbol{R}_{norm}(\boldsymbol{k})$ is shown by the blue line. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

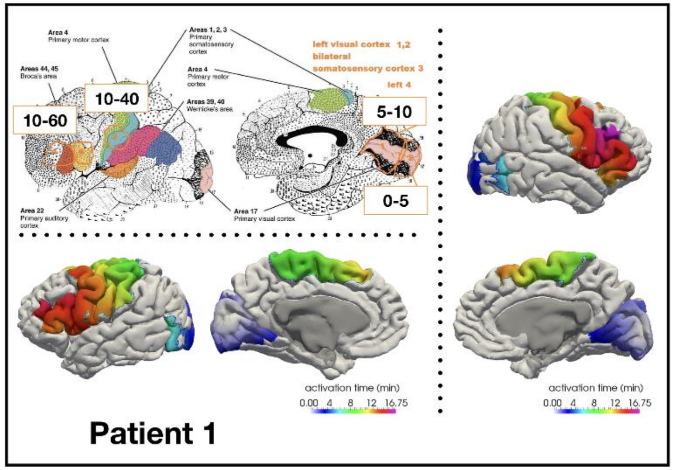
# PROGRESSION OF CSD PHENOMENON

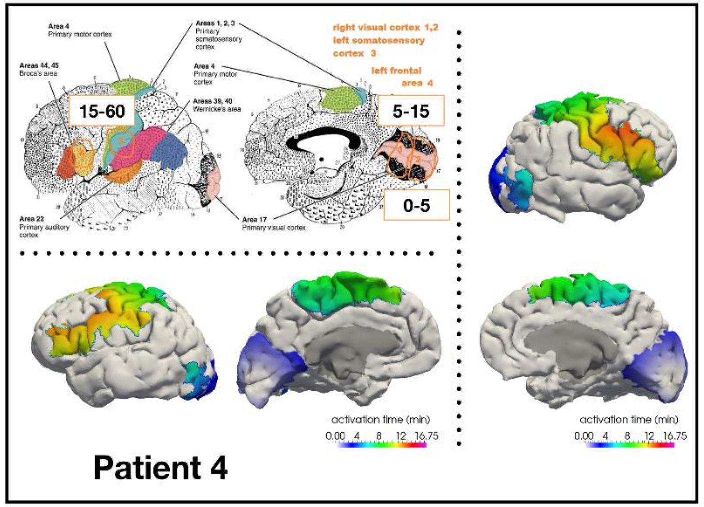


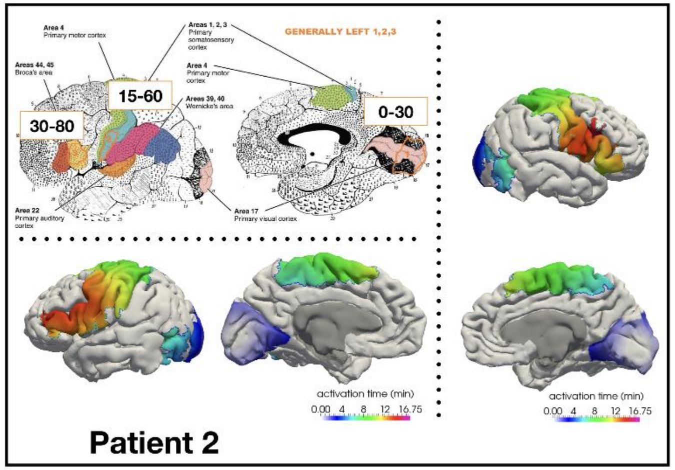
# PROGRESSION OF CSD PHENOMENON

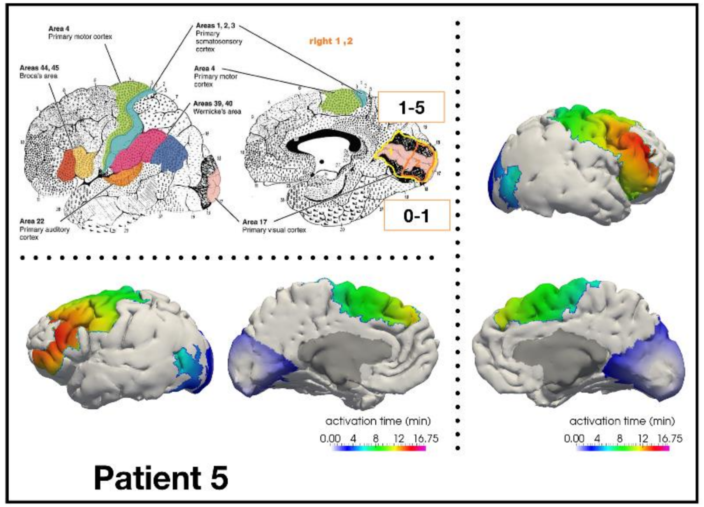


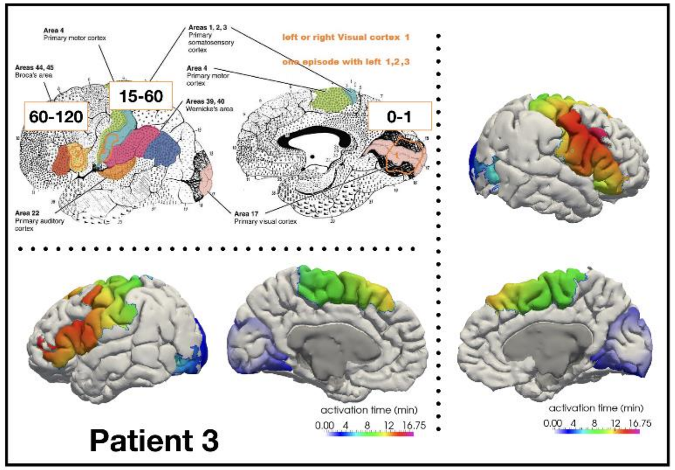




Kroos et al,
under revision




| eloquent areas | right hem. |
|---|---|
| left hemisphere | |




| eloquent areas | right hem. |
|---|---|
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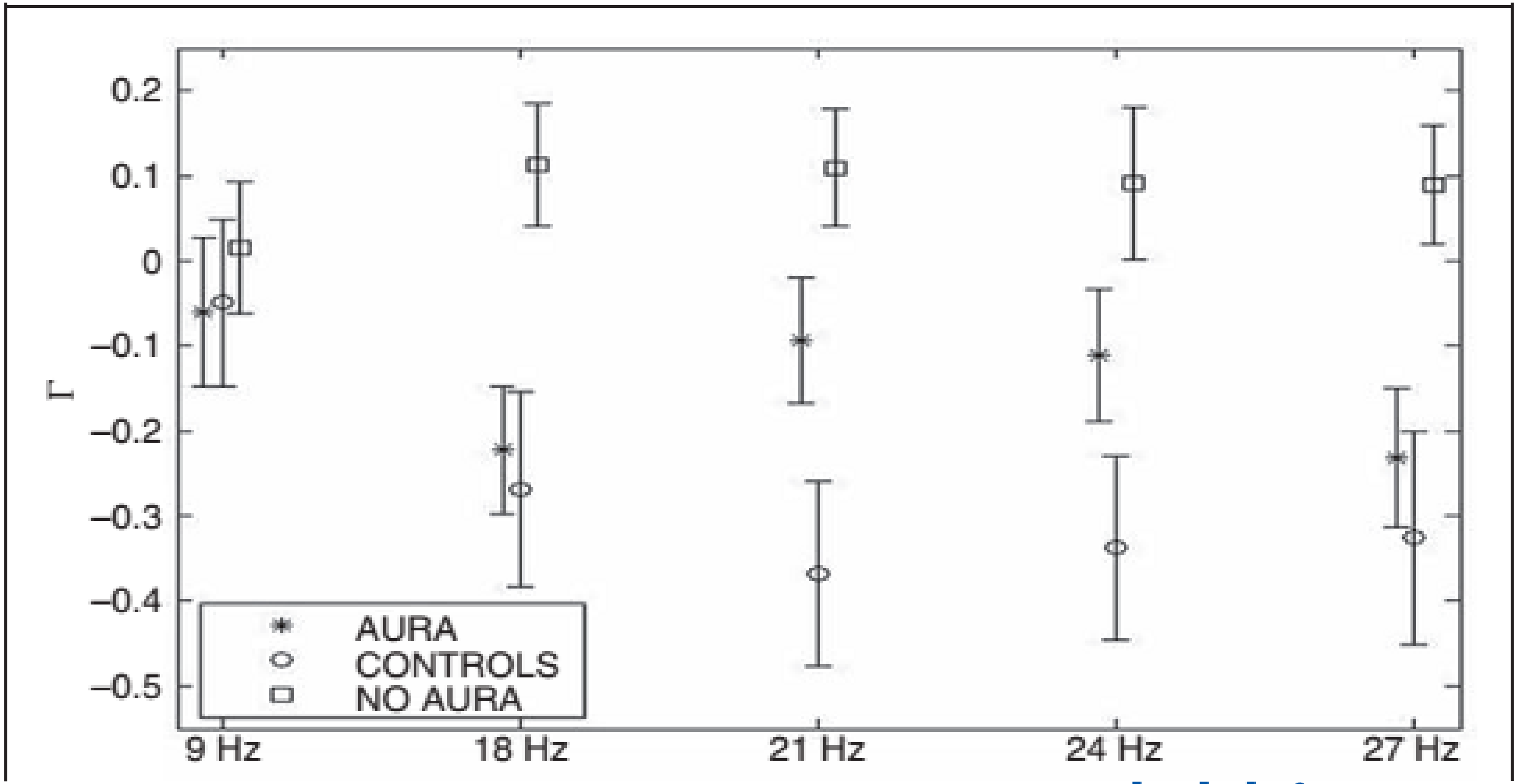


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# Functional and effective connectivity in EEG alpha and beta bands during intermittent flash stimulation in migraine with and without aura

Marina de Tommaso[1], Sebastiano Stramaglia[2], Daniele Marinazzo[3], Gabriele Trotta[2] and Mario Pellicoro[2]

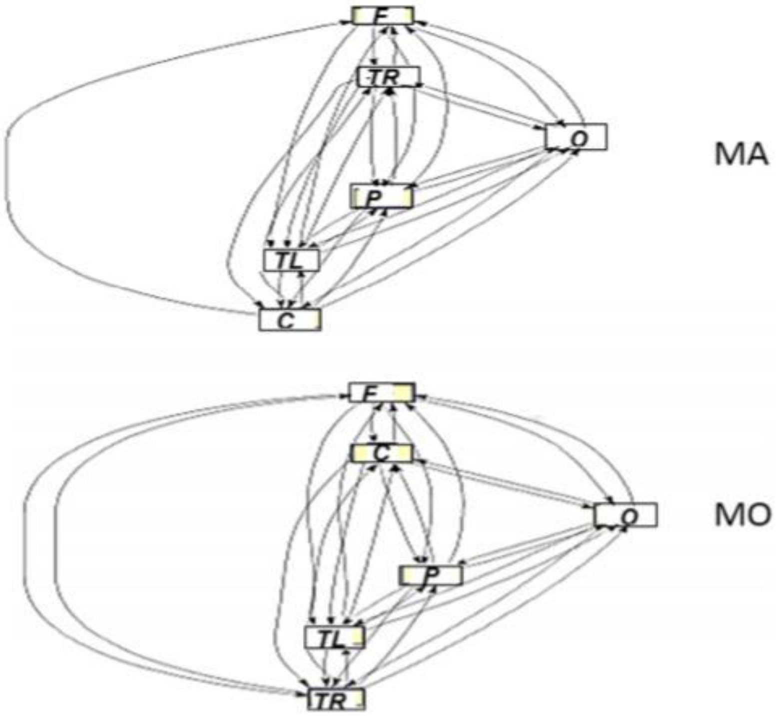



**Fig. 8** Network diagrams for Migraine with aura (MA) and without aura (MO) for alpha band at 2 cpd stimulation. The by-pass role of the occipital area (O) in the MA in the anterior / posterior connection emerges. (further data on analysis are available in the Supplementary section, chapter 5.6.2) F: Frontal; C: Central; P: Parietal; RT: Right Temporal; LT: Left Temporal

Increased activity of occipital cortex in migraine with aura could be explained in terms of segregated pattern of connections induced by visual stimuli

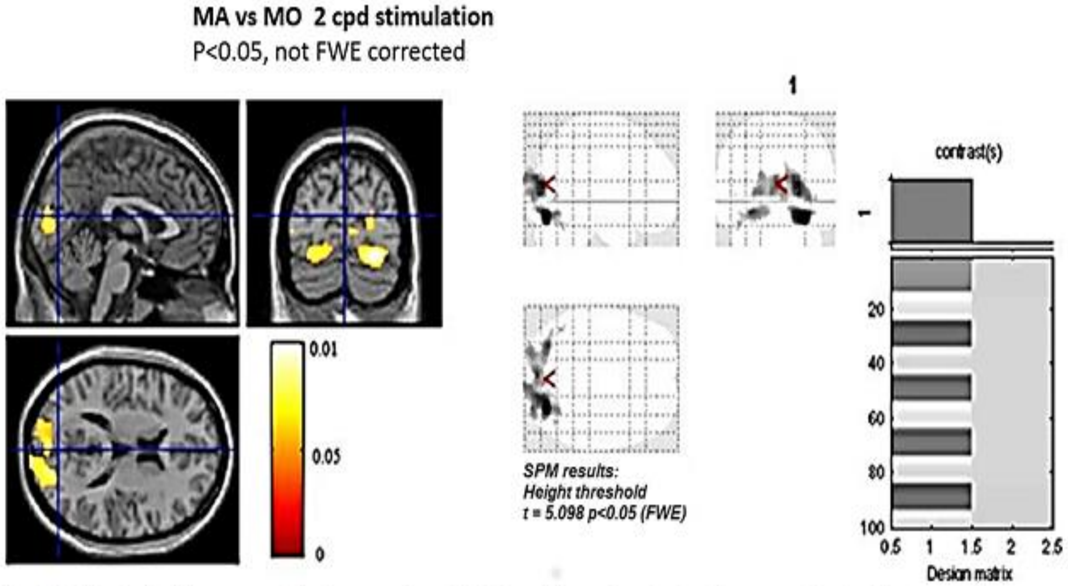
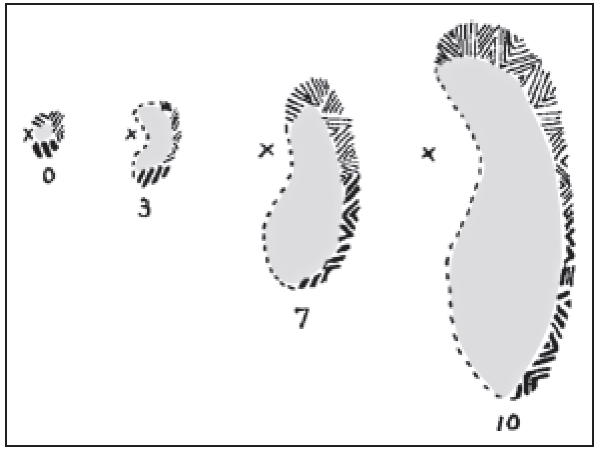



**Fig. 9** Statistical probability maps reporting the comparison of bold signal changes in migraine with aura vs migraine without aura sub groups during 2 cps spatial frequency visual stimulation




de Tommaso *et al. The Journal*
DOI 10.1186/s10194-017-0803-5

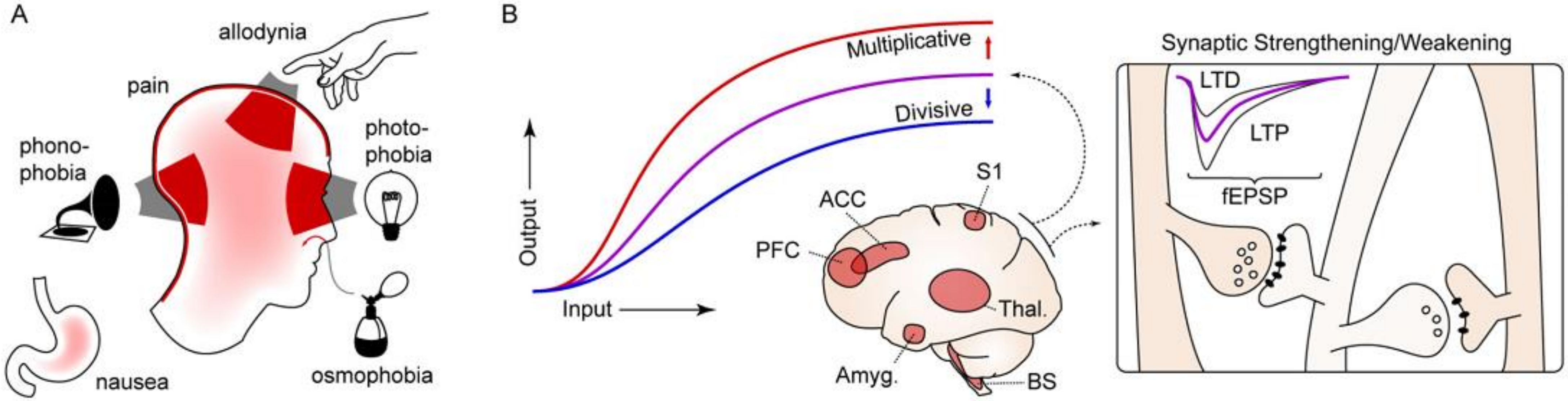



**Figure 1. Characteristics of migraine**

**A. The migraine attack involves changes in multiple sensory percepts.** Head and neck

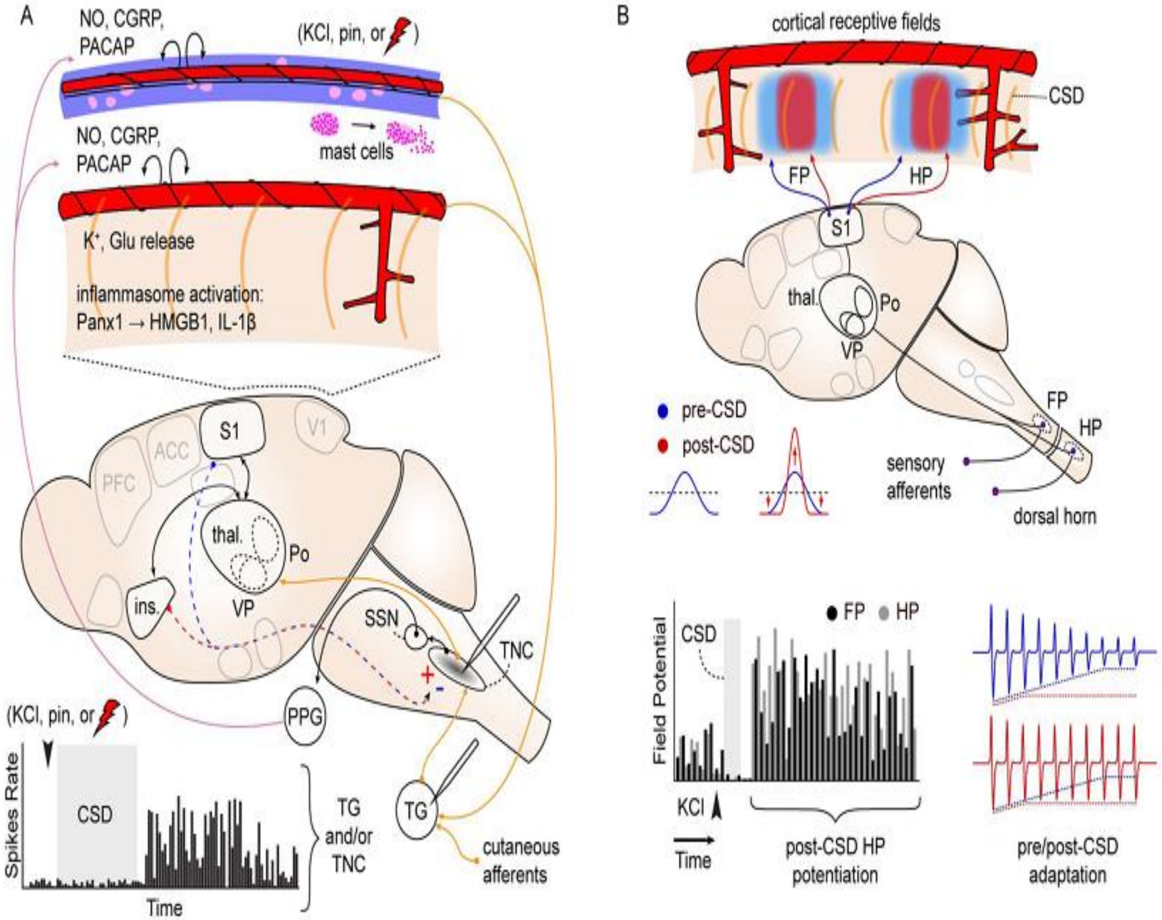
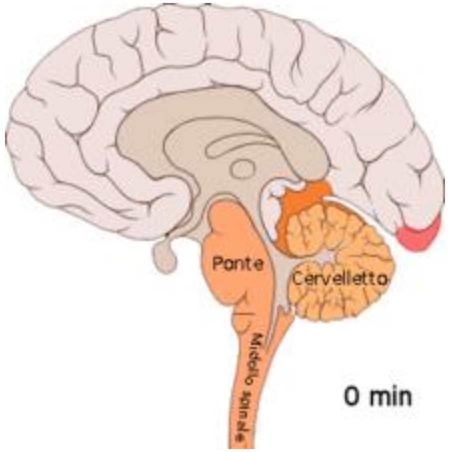



**Figure 3. Effects of CSD on network activity**

**A. Spontaneous firing rate of TG and TNC neurons increases after experimentally-induced CSD** (graph at bottom). Recording sites indicated on schematic. c-fos immediate



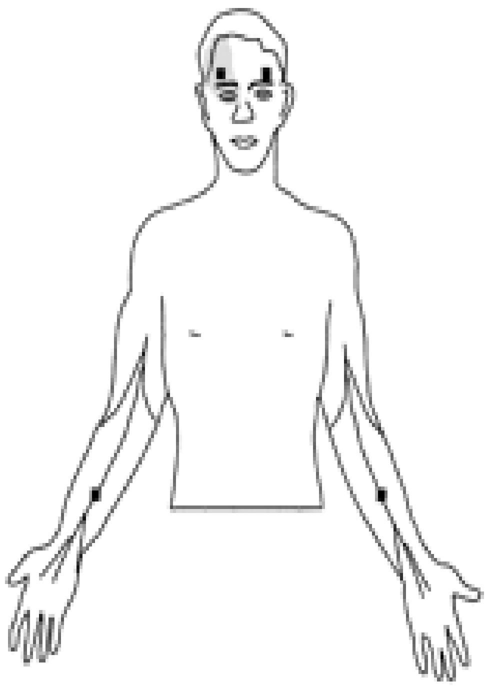

**Initiation of spreading depression by synaptic and network hyperactivity: Insights into trigger mechanisms of migraine aura**

Lyudmila V Vinogradova

Temporal and spatial development of cutaneous allodynia during migraine

| | Before migraine | During migraine | | |
|---|---|---|---|---|
| | Baseline | 1 h | 2 h | 4 h |
| Pain (0–10) | 0 | 5.5 | 7.0 | 7.5 |
| Mechanical (g) | 281 | 28 | 3.6 | 2.0 |
| Cold (°C) | 15.3 | 21.9 | 24.7 | 26.6 |
| Heat (°C) | 43.7 | 45.3 | 41.9 | 40.5 |
| Brush | No pain | No pain | Pain | Pain |

| | Before migraine | During migraine | | |
|---|---|---|---|---|
| | Baseline | 1 h | 2 h | 4 h |
| Pain (0–10) | – | – | – | – |
| Mechanical (g) | 281 | 125 | 11.7 | 3.6 |
| Cold (°C) | 15.2 | 15.2 | 25.7 | 24.5 |
| Heat (°C) | 44.6 | 46.3 | 44.0 | 39.4 |
| Brush | No pain | No pain | No pain | No pain |



| | Before migraine | During migraine | | |
|---|---|---|---|---|
| | Baseline | 1 h | 2 h | 4 h |
| Mechanical (g) | 281 | 125 | 125 | 125 |
| Cold (°C) | 17.2 | 14.8 | 25.0 | 26.5 |
| Heat (°C) | 48.4 | 46.7 | 47.0 | 44.7 |
| Brush | No pain | No pain | No pain | No pain |

| | Before migraine | During migraine | | |
|---|---|---|---|---|
| | Baseline | 1 h | 2 h | 4 h |
| Mechanical (g) | 281 | 125 | 125 | 125 |
| Cold (°C) | 21.1 | 16.5 | 13.4 | 21.1 |
| Heat (°C) | 46.4 | 47.8 | 46.0 | 47.5 |
| Brush | No pain | No pain | No pain | No pain |

ALLODYNIA IS A SIGN OF CENTRAL SENSITIZATION

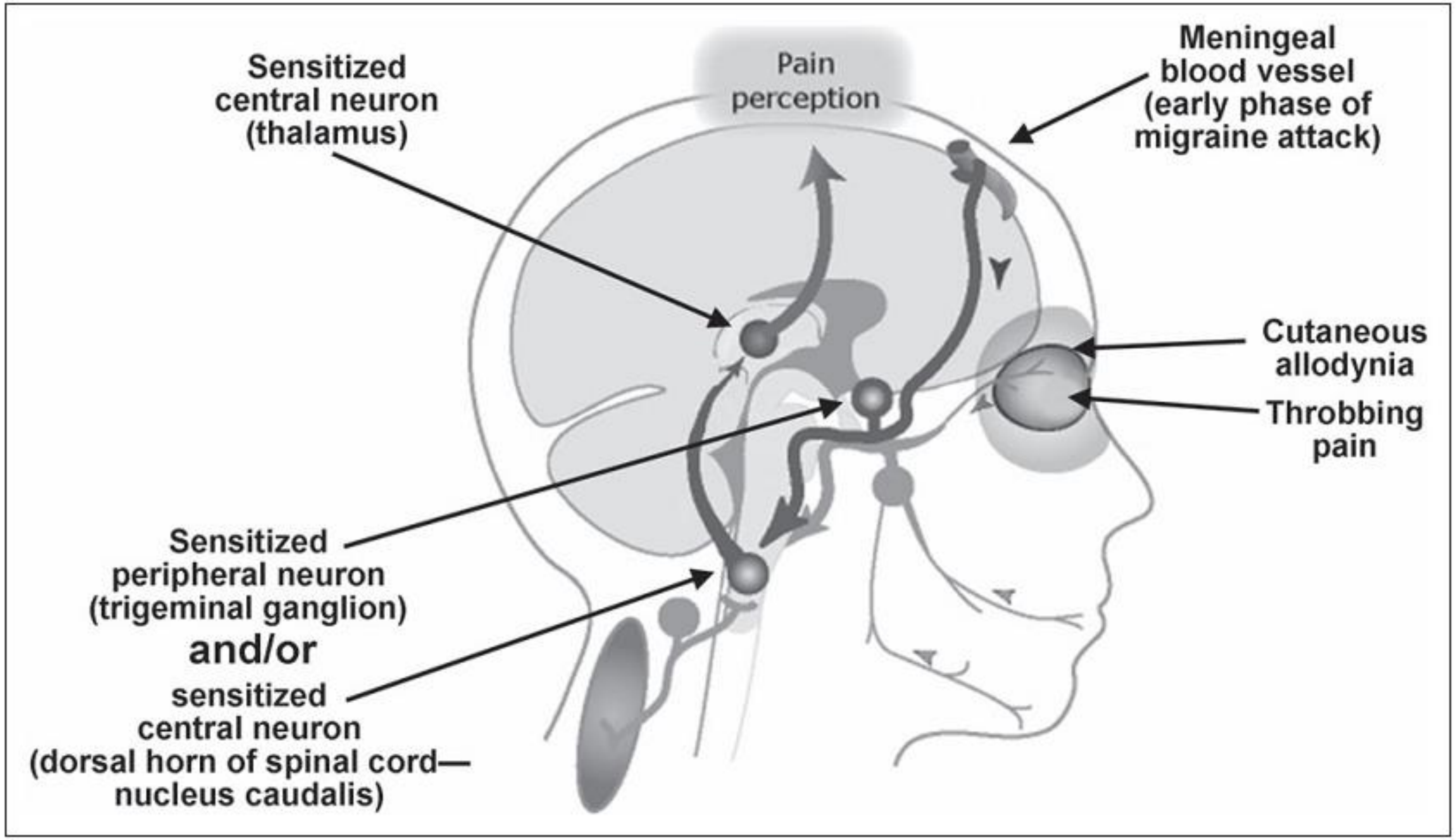
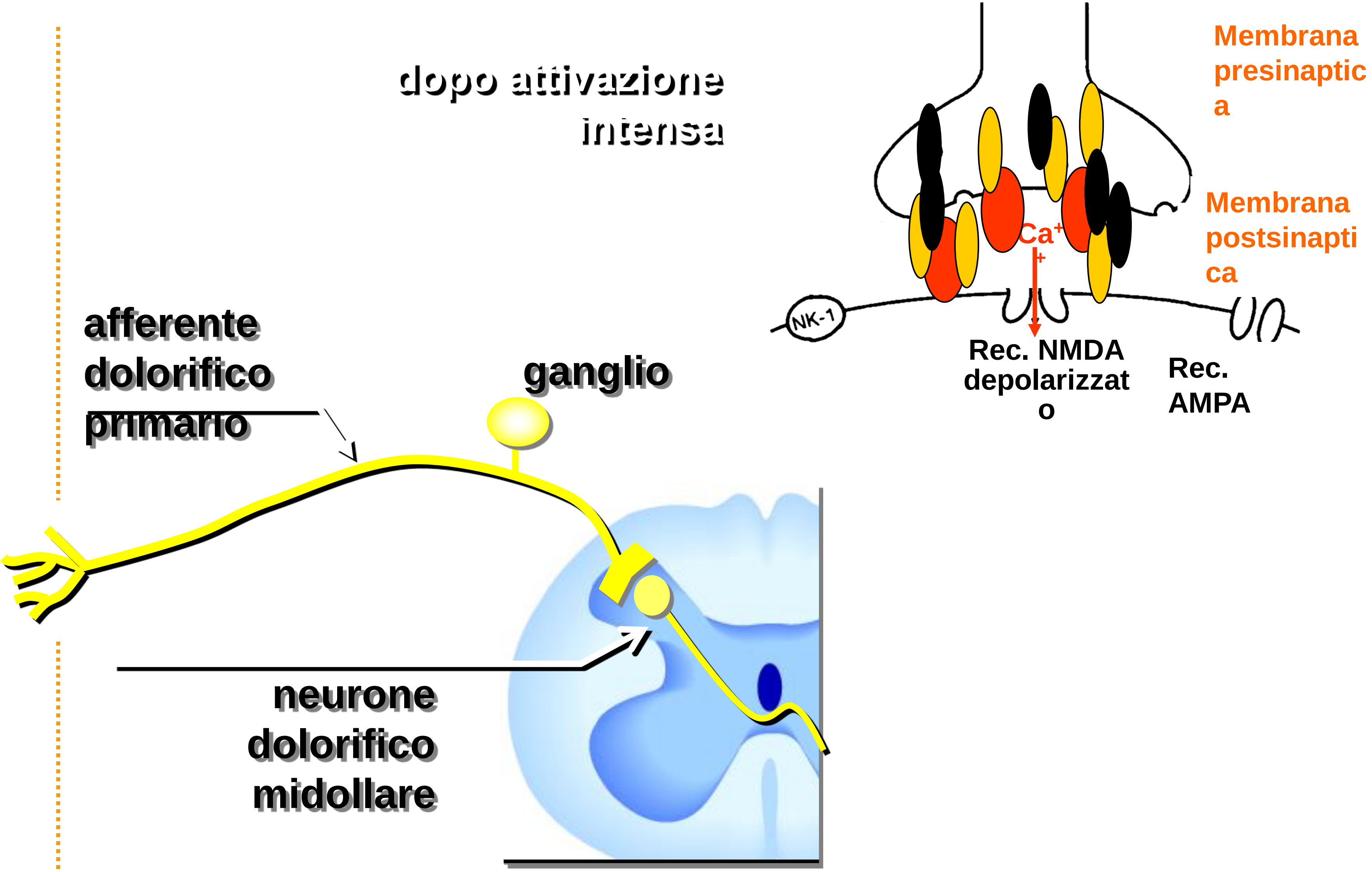



**Fig 2.—Sensitization of central trigeminovascular neurons in nucleus caudalis mediates cutaneous allodynia. Adapted with permission.[19]**

# Sensibilizzazione centrale



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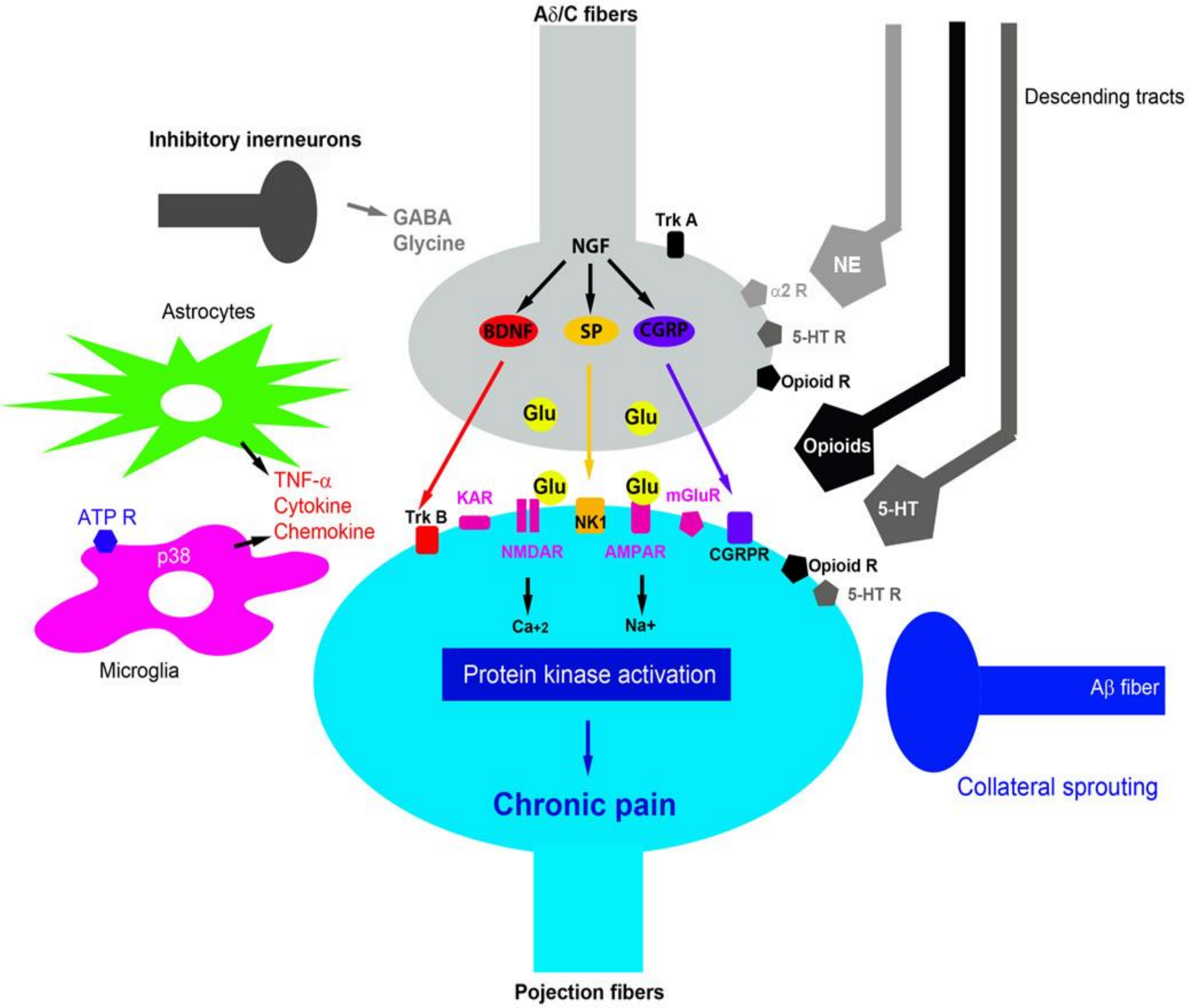


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lateral hemisphere (orange).

Laser evoked potentials are a suitable method for the psychophyisiological study of pain.
They are generated in cortical areas devoted to the elaboration of the discriminative , attentive and affective compounds of pain.

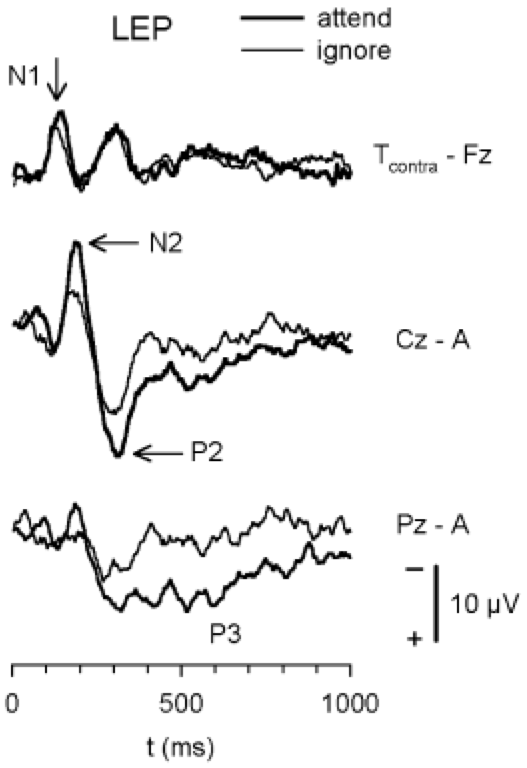
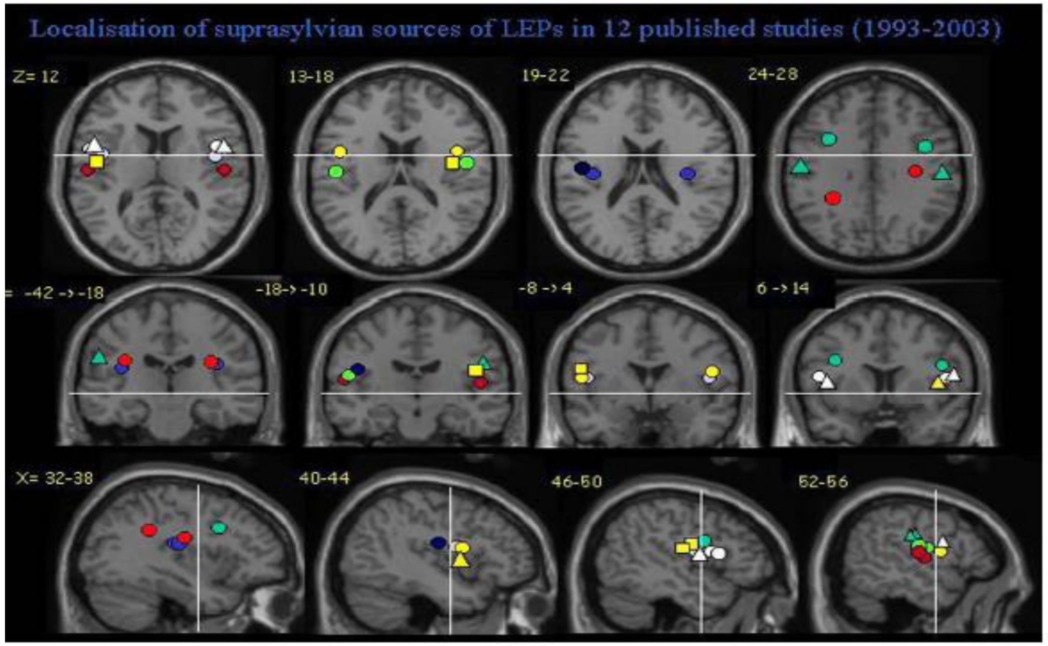



Fig. 2. LEP components and attention effects. Early component N1, late

L. Garcia-Larrea et al. / Neurophysiologie clinique 33 (2003) 279–292 2

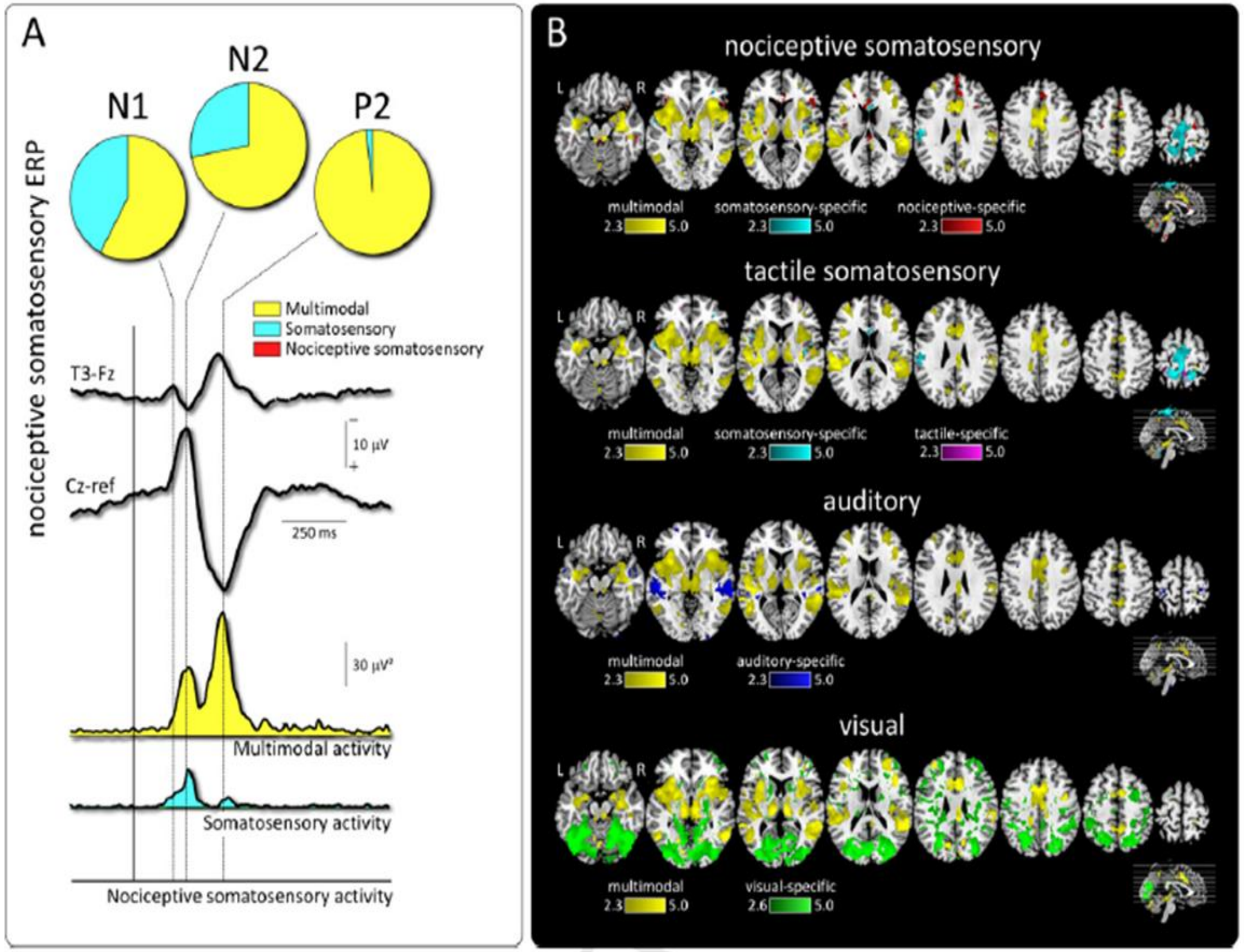


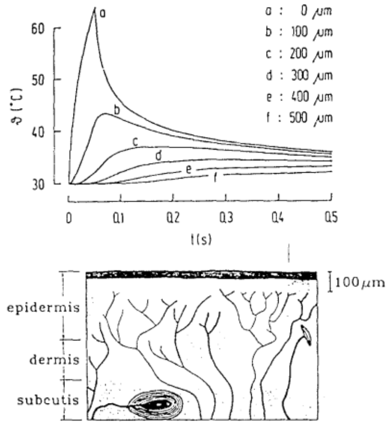
A PIVOTAL QUESTION: LEPs ARE NOT SPECIFIC FOR PAIN, BUT FOR RELEVANT STIMULI, WORTHY OF A MOTOR REACTION:

SALIENCE MATRIX INSTEAD OF PAIN MATRIX

NEVERTHELESS, THE ACTIVATED CORTEX RESPONDS TO SPECIFIC NOCICEPTIVE PATHWAYS ACTIVATION

V. Legrain et al. / Progress in Neurobiology xxx (2010) xxx–xxx 7



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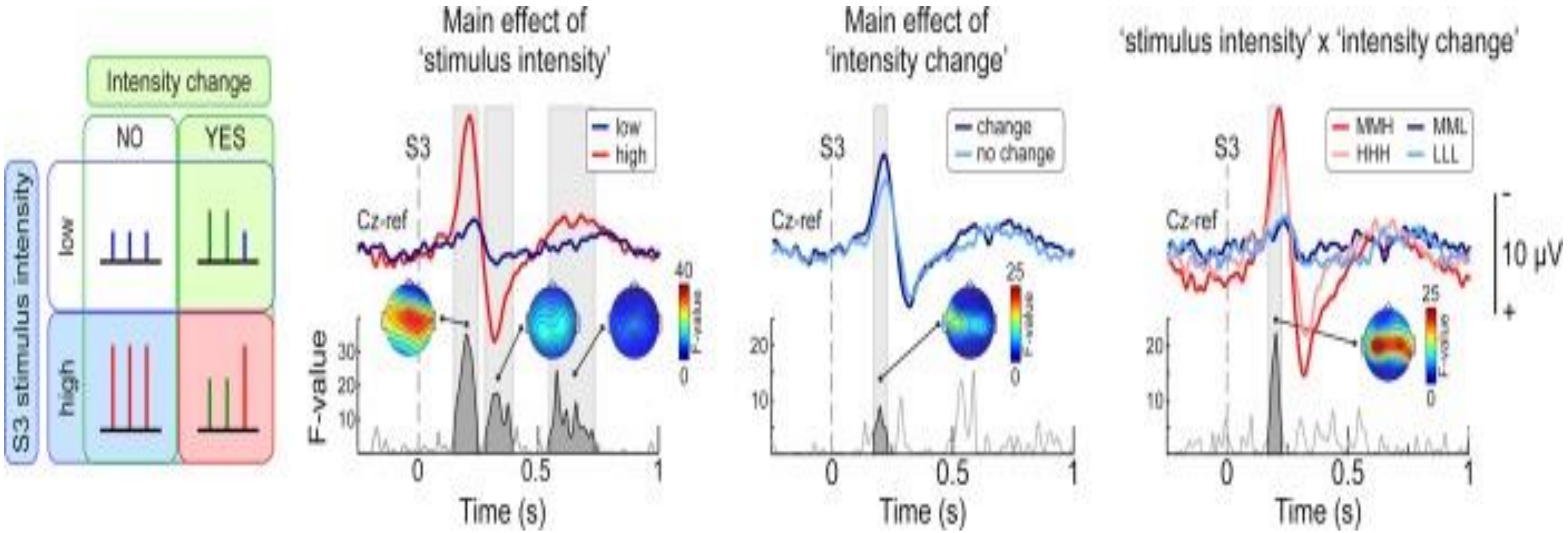
J Neurophysiol. 2013 Feb 1; 109(3): 692–701.
Published online 2012 Nov 7. doi: 10.1152/jn.00464.2012

PMCID: PMC3567386
PMID: 23136349

Novelty is not enough: laser-evoked potentials are determined by stimulus saliency, not absolute novelty

I. Ronga,[1,2] E. Valentini,[1,3] A. Mouraux,[4] and G. D. Iannetti

# LEP's reflect stimulus novelty, not stimulus intensity
# How they can describe nociceptive system in migraine patients?



# What said LEPs in migraine? Physiopathology.
# Abnormal pain processing-critical increase of nociceptive (?) cortex activation-

## Increase of laser – related cortical activation during migraine attack

ELSEVIER
Neuroscience Letters 333 (2002) 29–32
Neuroscience Letters
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**Abnormal brain processing of cutaneous pain in migraine patients during the attack**

Marina de Tommaso*, Marco Guido, Giuseppe Libro, Luciana Losito, Vittorio Sciruicchio, Carlo Monetti, Francomichele Puca

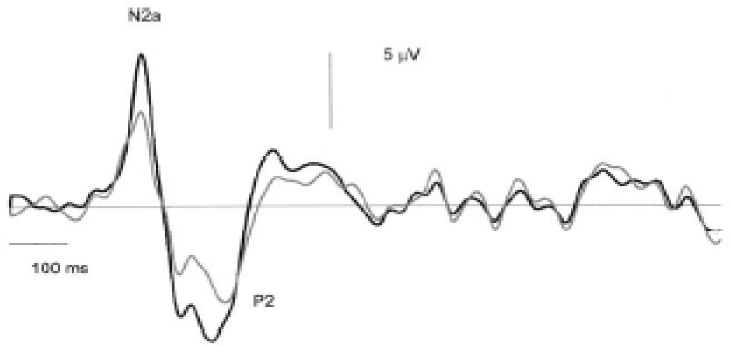
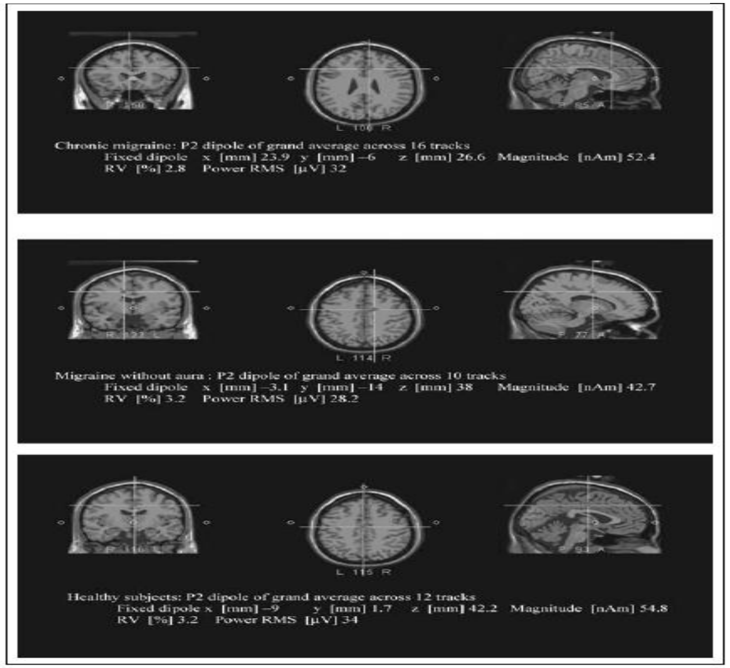



Fig. 3. An example of Laser Evoked Potentials (LEPs) elicited by the painful laser stimulation of the supraorbital skin ipsilateral to pain during the attack (black line) and after 92 h from the end of headache (gray line). The increased amplitude of cortical potential during the acute phase is evident.

## Changes in cingulate activation in chronic migraine

**Changes in Cortical Processing of Pain in Chronic Migraine**

Marina de Tommaso, MD; Luciana Losito, MD; Olimpia Difruscolo, MD; Giuseppe Libro, MD; Marco Guido, MD; Paolo Livrea, MD

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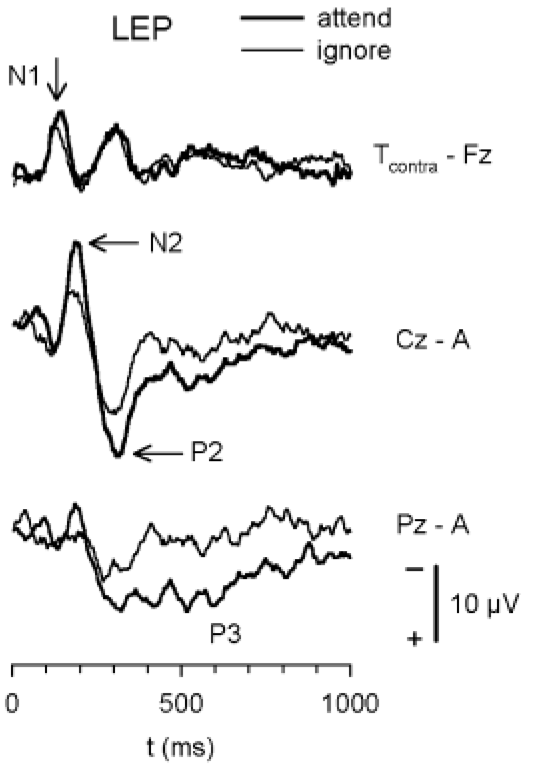


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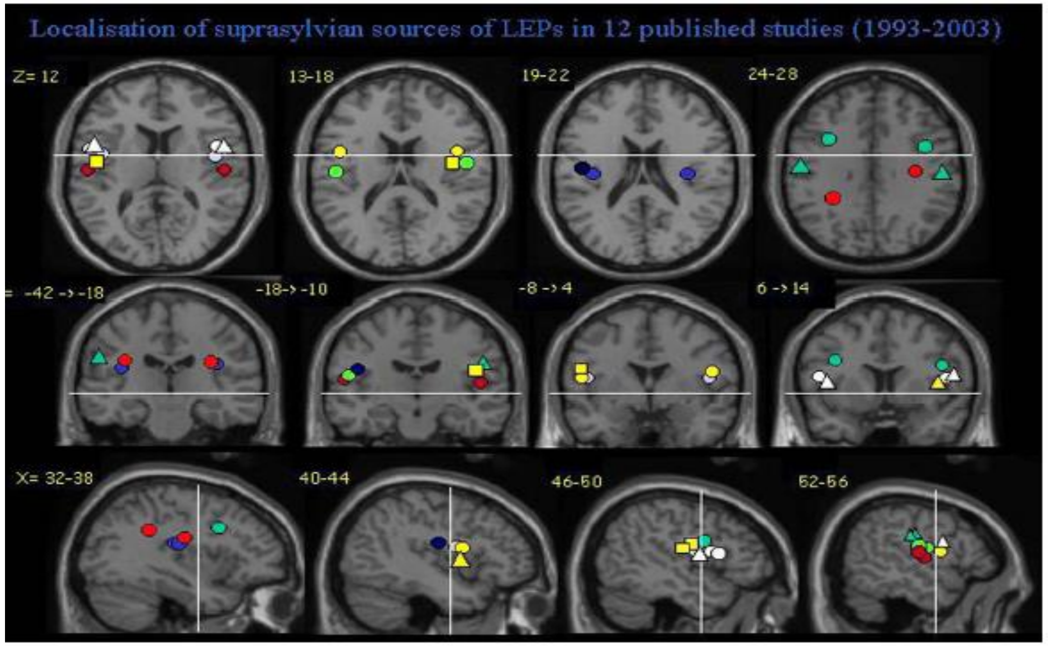
L. Garcia-Larrea et al. / Neurophysiologie clinique 33 (2003) 279–292 2



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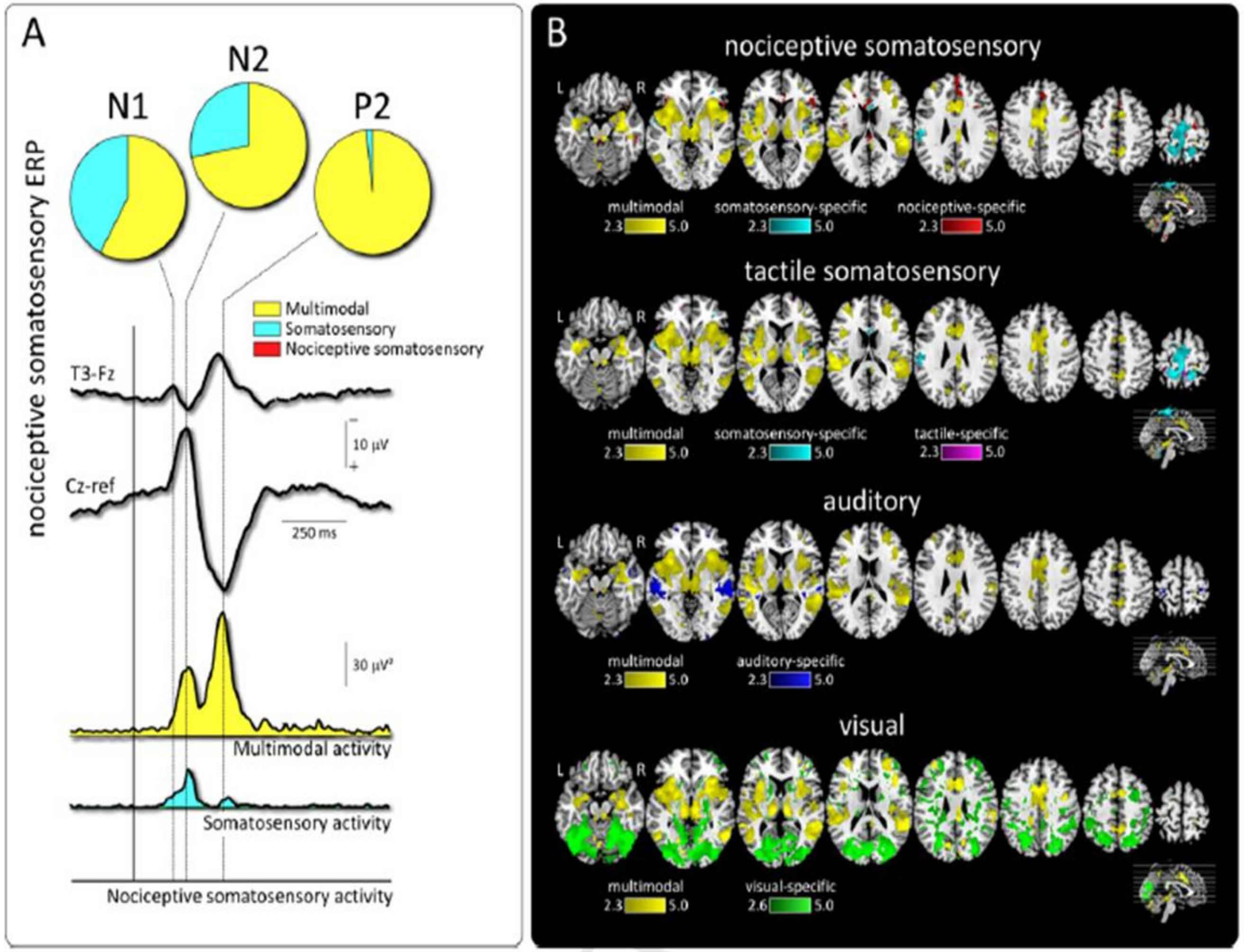
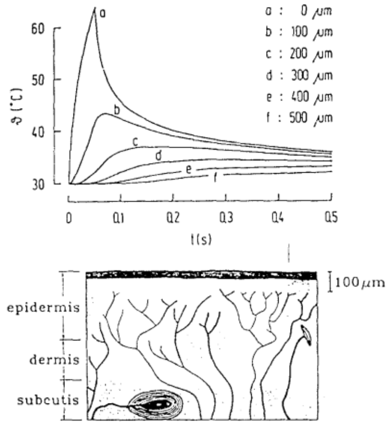
V. Legrain et al./Progress in Neurobiology xxx (2010) xxx–xxx 7



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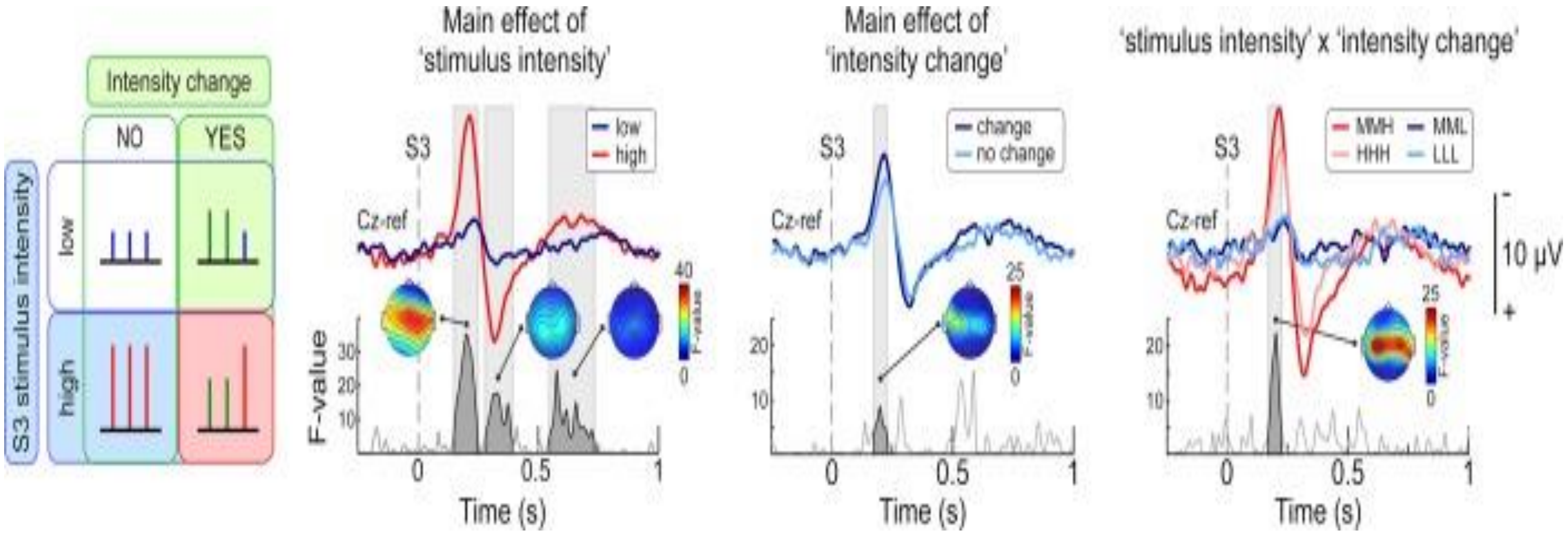

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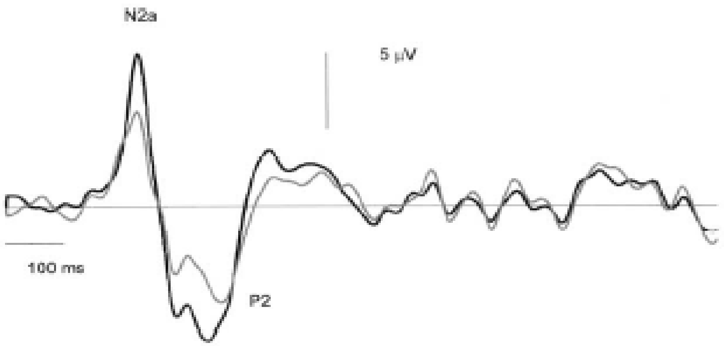


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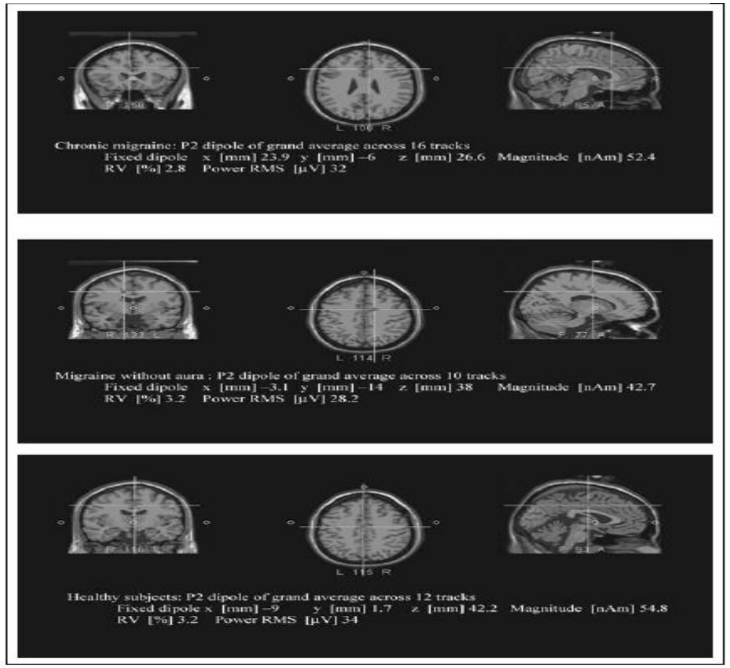


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Pain xx (2003) xxx–xxx

PAIN

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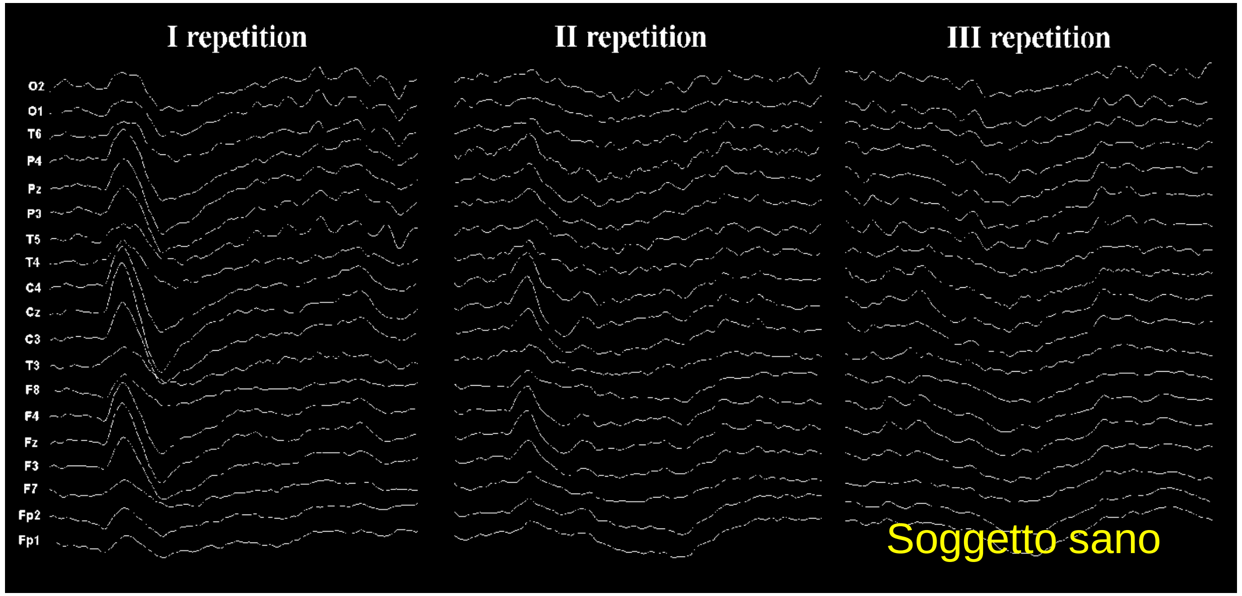
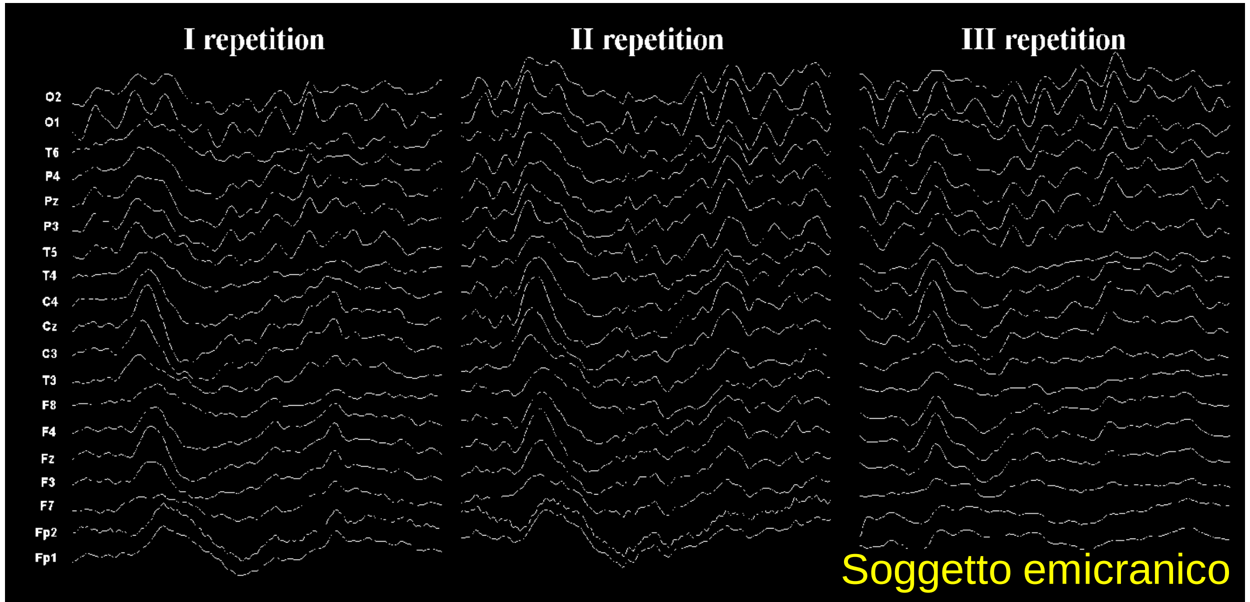
Reduced habituation to experimental pain in migraine patients: a $CO_2$ laser evoked potential study

M. Valeriani[a,b,*], M. De Tommaso[c], D. Restuccia[a], D. Le Pera[a,d], M. Guido[c], G.D. Iannetti[e], G. Libro[c], A. Truini[e], G. Di Trapani[a], F. Puca[c], P. Tonali[a], G. Cruccu[e]

....but they could reflect a modality of pain processing

REDUCED HABITUATION TO REPETITIVE LASER STIMULATION: A SIGNATURE OF MIGRAINE AND CENTRAL SENSITIZATION PHENOMENA PREDISPOSITION




Valeriani et al., 2003

# Migraine patients show increased granger causality and information transfer under nociceptive stimuli

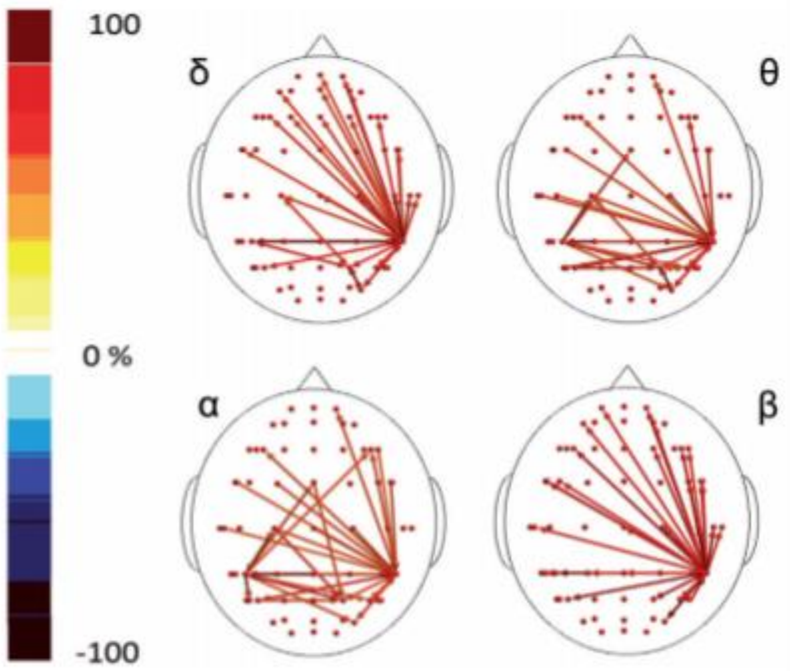



**FIGURE 6 | Percent differences of GC total activity between MIG vs CONT are reported.** The red colors express an increase and the blue colors a reduction of GC in MIG vs CONT. For the details regarding the statistical analysis, see Tables S7 and S8 in Supplementary Material.

frontiers in Human Neuroscience

ORIGINAL RESEARCH
published: 24 November 2015
doi: 10.3389/fnhum.2015.00640

# ..this is the counterpart of reduced habituation

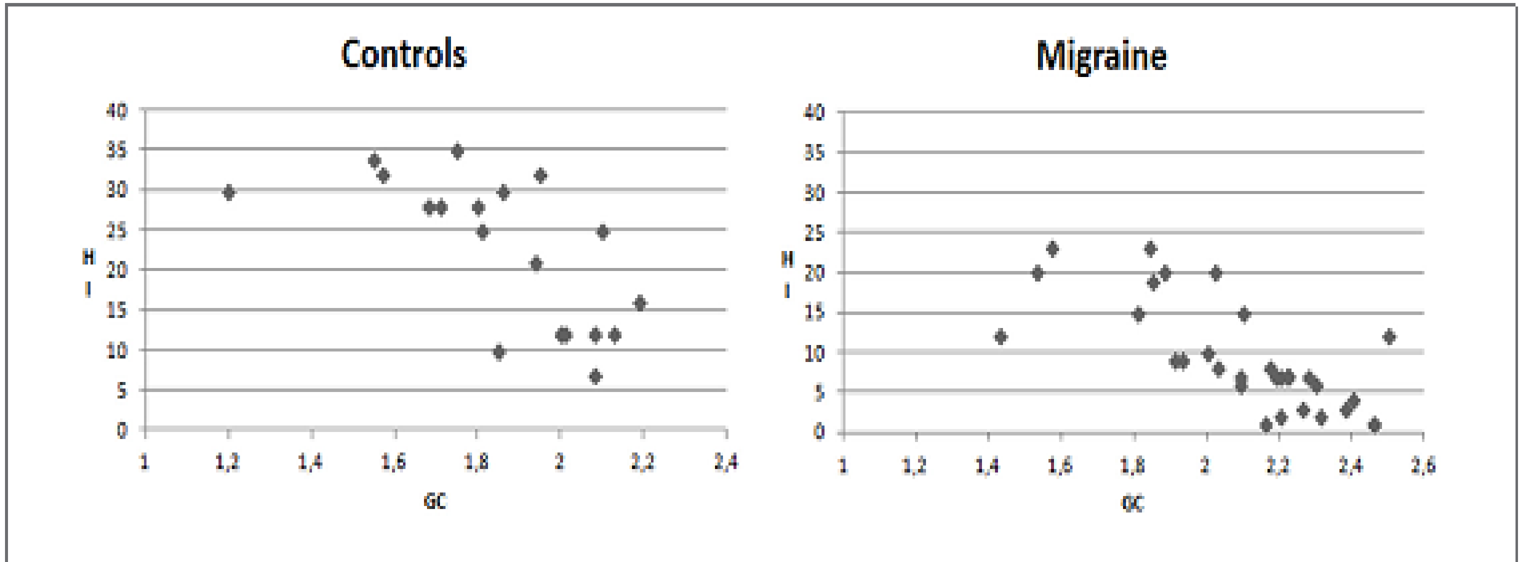
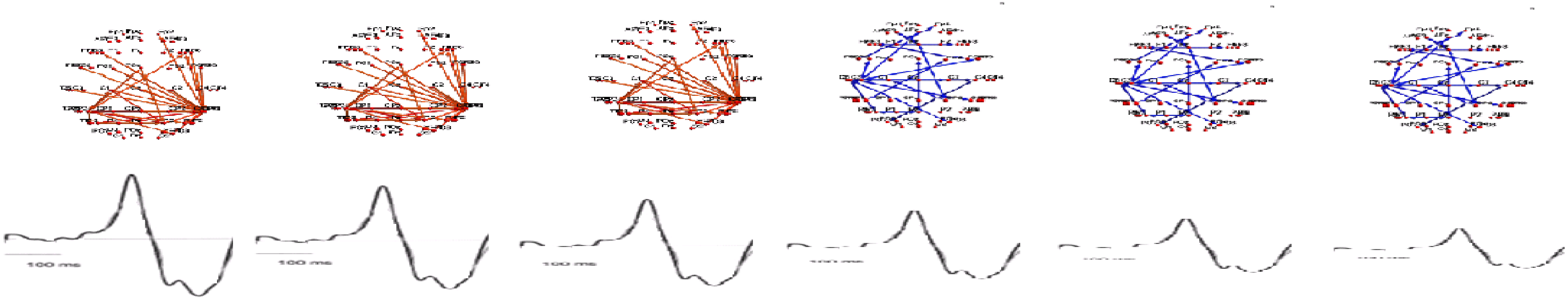


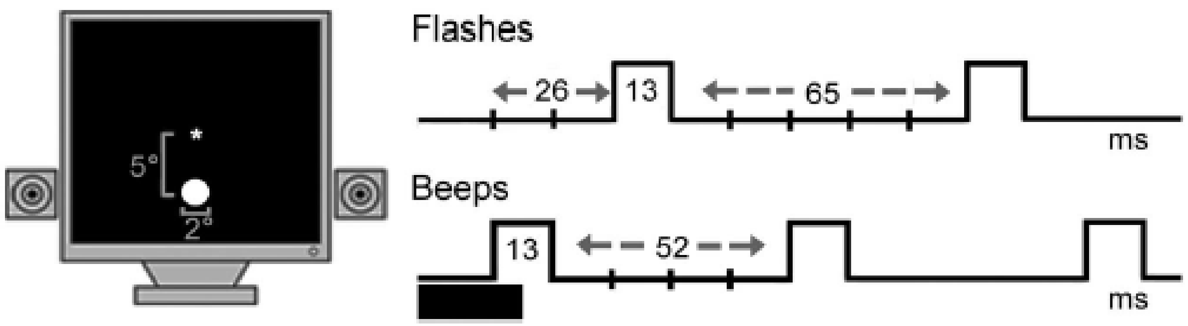

FIGURE 7 | *X–Y* charts showing the relationship between mean values of Granger causality (GC) and Habituation index (%) of N2P2 complex in



# 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

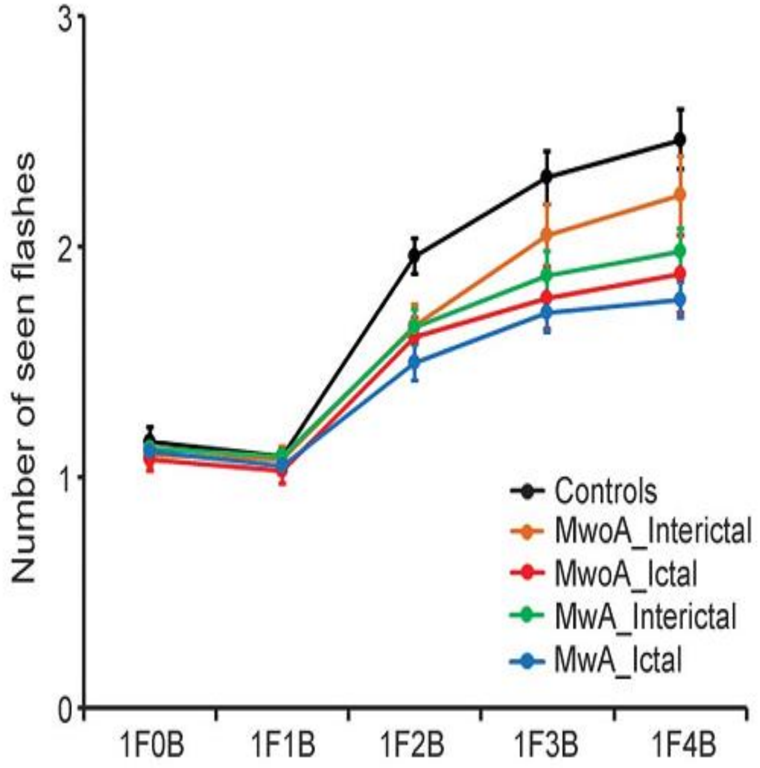
**Figure 1** **Experimental task**




Configuration of flashes and beeps and their timing.

FLASH ILLUSIONS ARE REDUCED IN MIGRAINE AND FLUCTUATE ACROSS MIGRAINE CYCLE: IS THIS A SIGN OF VISUAL HYPER-EXCITABILITY, OR/AND DIFFERENT CONNECTIVTY BETWEEN CORTICAL SENSORY AREAS?

**Figure 2** **Fission illusion in migraineurs and controls**



Progress in Neurobiology 156 (2017) 164–188

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


Review article

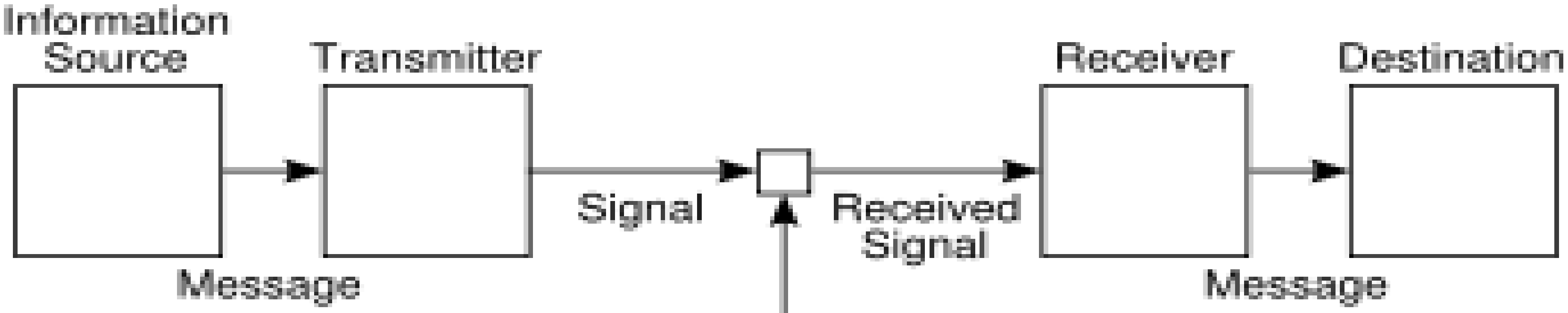
# Uncertainty and stress: Why it causes diseases and how it is mastered by the brain

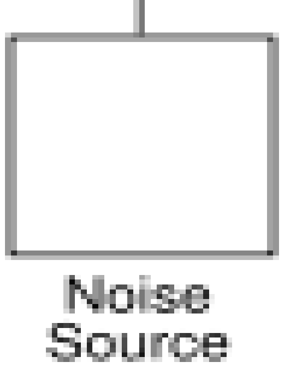
Achim Peters[a,*], Bruce S. McEwen[b], Karl Friston[c]

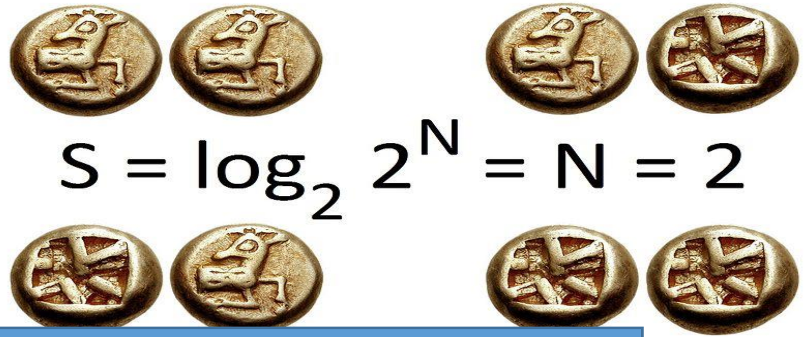
[a] Medical Clinic 1, Endocrinology & Diabetes, University of Luebeck, Luebeck, Germany
[b] Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY, USA
[c] The Wellcome Trust Centre for Neuroimaging, University College London, London, UK

# Shannon: 1948

Information is the reduction of uncertainty and entropy of solutions. The uncertainty is reduced with the reduction of entropy



$$S = \log_2 2^N = N = 2$$


Uncertainty theory

Conceptual bases of acquiring certainty and reducing stress

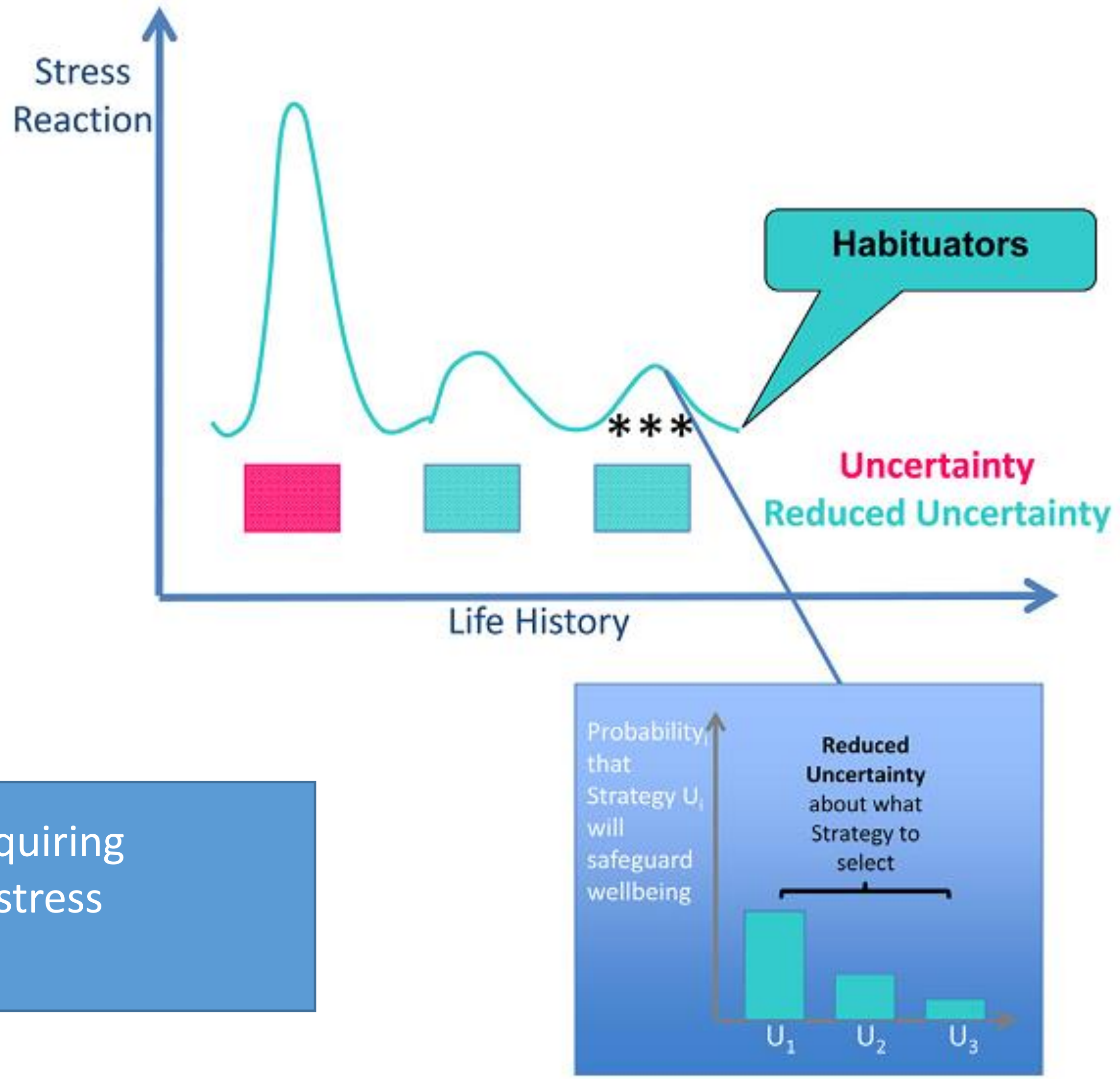



**Fig. 11. Stress habituation.** We define habituators as those who show repetition-induced-response attenuation (neuroenergetic, neuroendocrine, emotional and cardiovascular), when being chronically exposed to an inhospitable environment. When habituators are repeatedly exposed to the same homotypic stressor, they can reduce their uncertainty about which strategy they should select by redefining their goal states (***).

Conceptual bases of acquiring certainty and reducing stress

A. Peters, B.S. McEwen / Neuroscience and

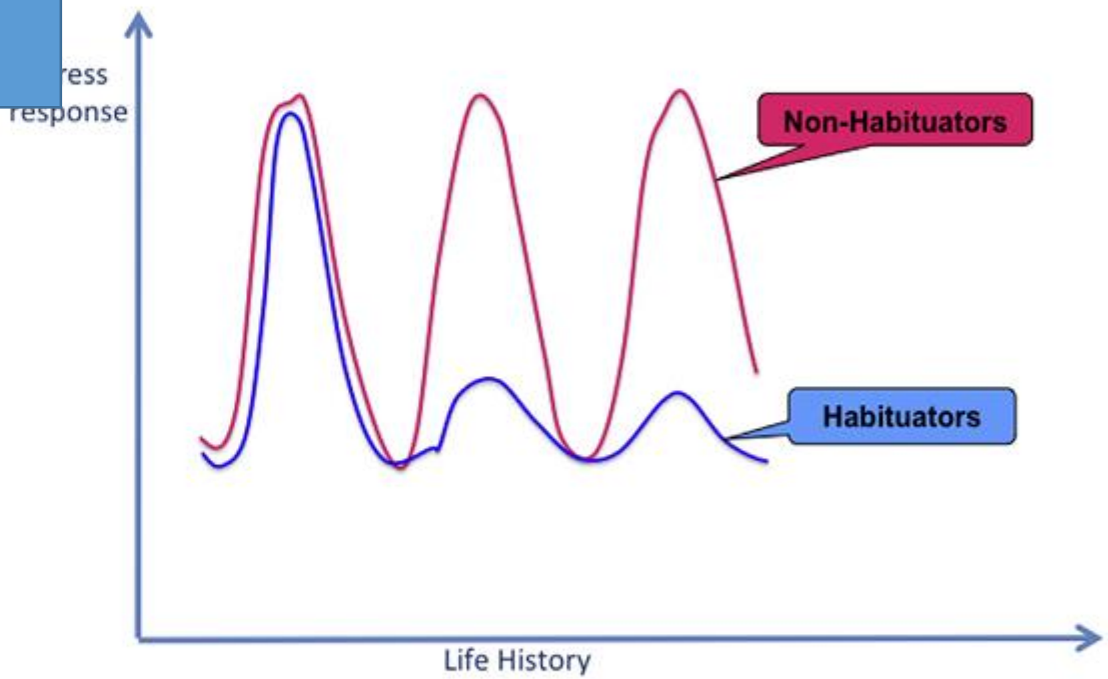
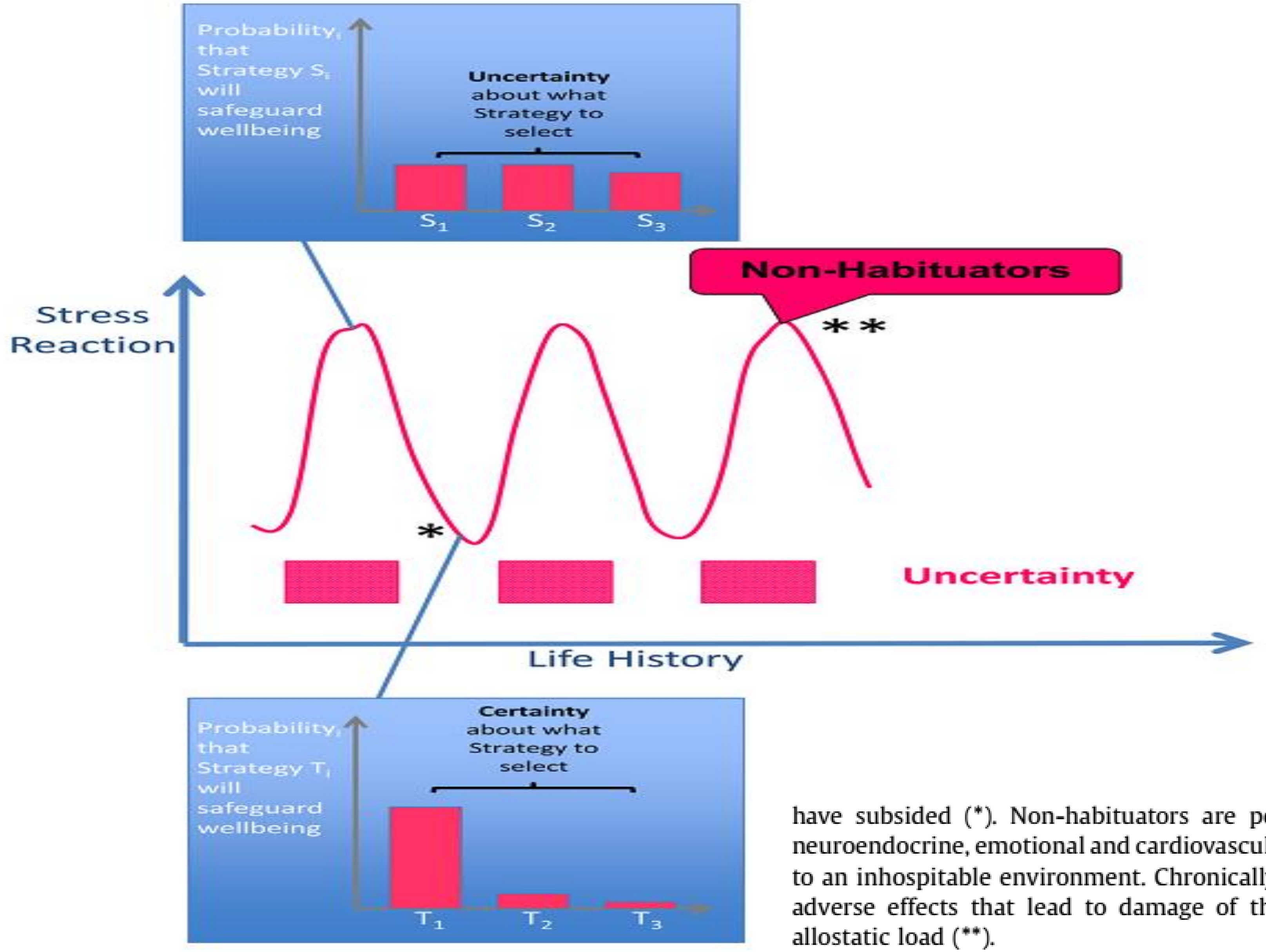



**Fig. 1.** *Differential modifications of stress reactivity.* We define 'habituators' as those who show repetition-induced response attenuation (neuroendocrine, cardiovascular, neuroenergetic, and emotional), when being chronically exposed to an unsafe environment. Over time, they develop a low 'stress reactivity'. In contrast, we define 'non-habituators' as those who do not show such a modification of responses. They uphold their high stress reactivity, when continuously being exposed to an unsafe environment. With repeated experimental stress challenges (TSST), subjects have been shown to *either* habituate *or* not habituate in their cortisol response

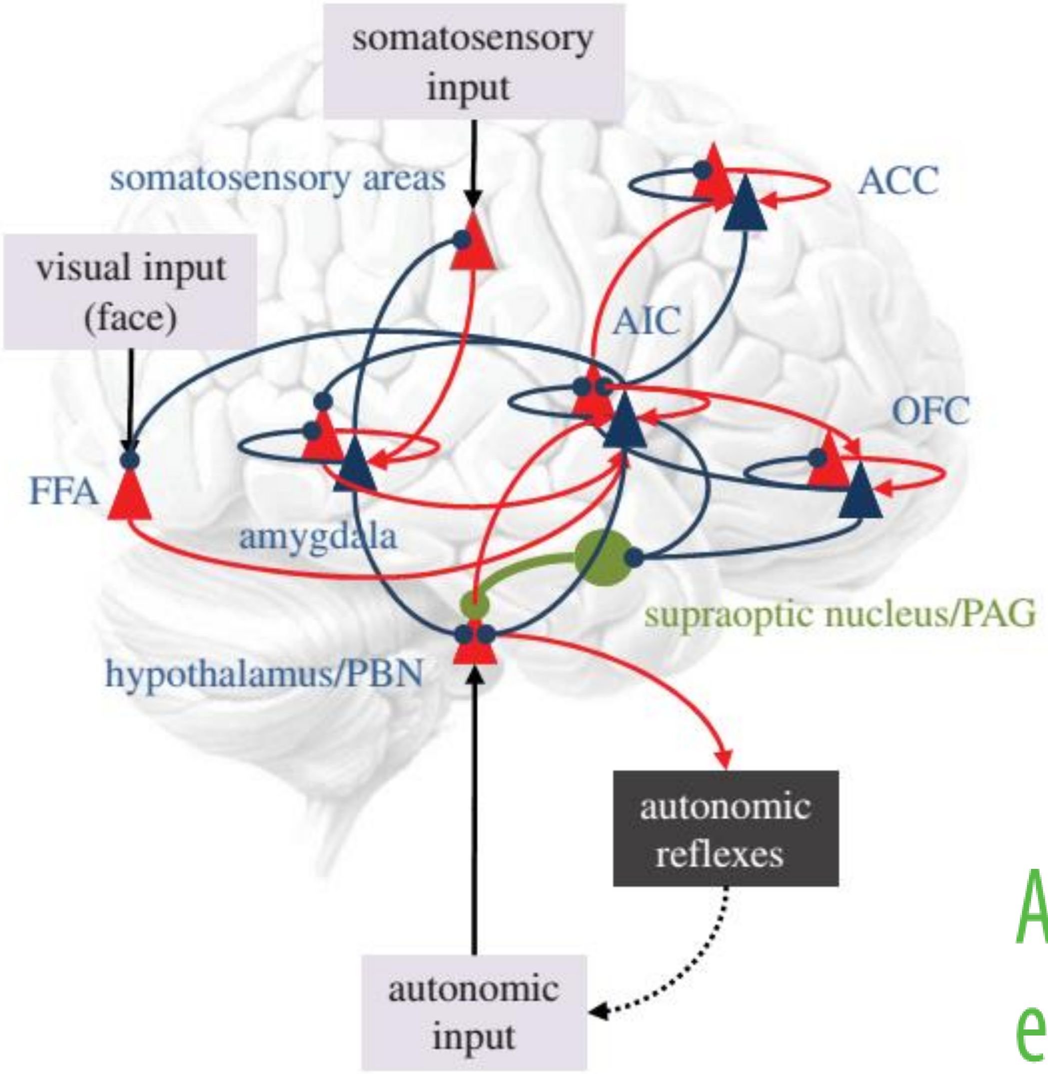
A. Peters, B.S. McEwen / Neuroscience and Biobehavioral Reviews 56 (2015) 139–150




Migraine as a perfect model of failure in acquiring certainty

have subsided (*). Non-habituators are people who show full neuroenergetic, neuroendocrine, emotional and cardiovascular responses when repeatedly exposed to an inhospitable environment. Chronically activated stress responses also exert adverse effects that lead to damage of the body and the brain-referred to as allostatic load (**).

Progress in Neurobiology 156 (2017) 164–188



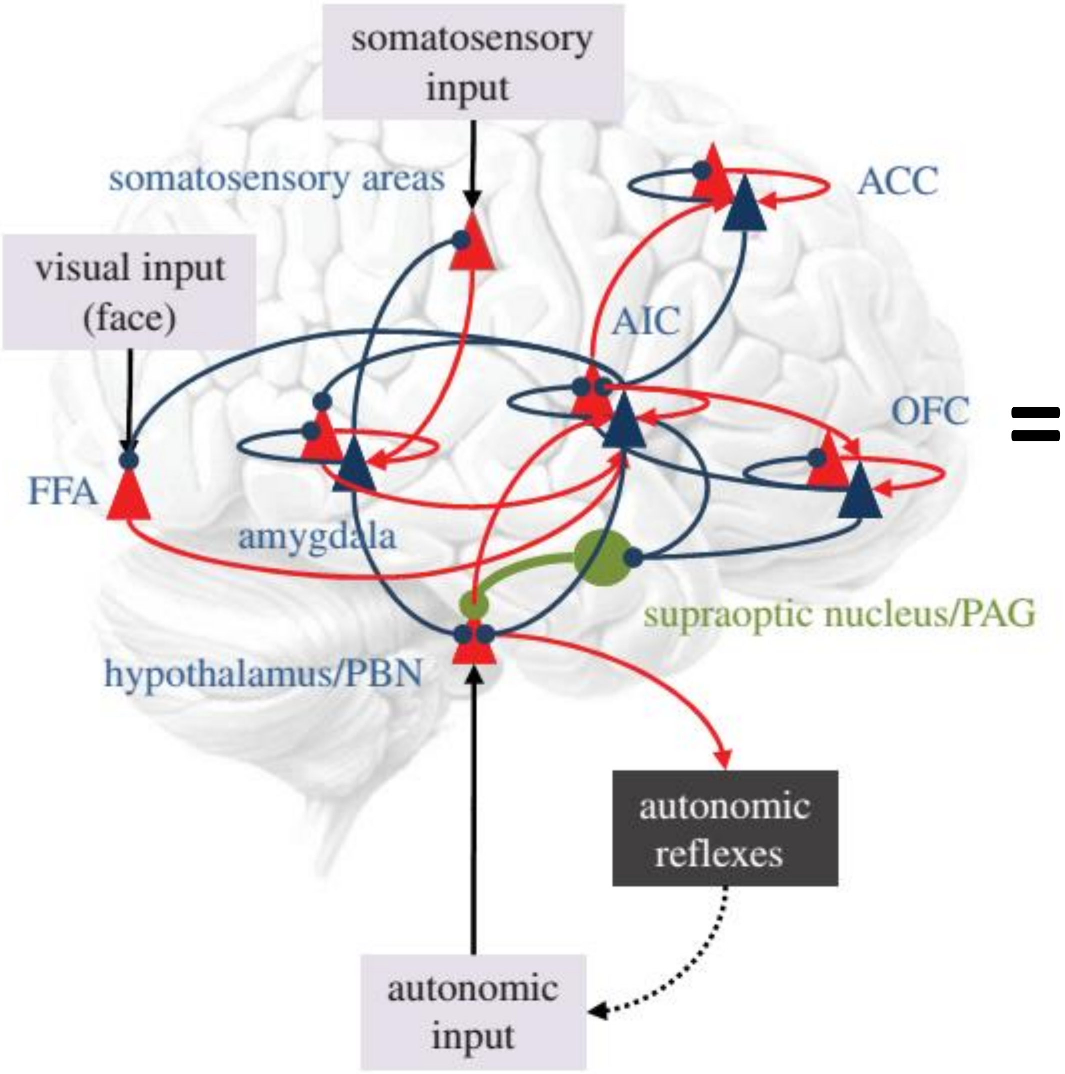

*Phil. Trans. R. Soc. B* **371**:

With respect to an input stimulus, the "uncertainty" network encodes the error of prediction, the waiting and the arousal and activates the motor and reflex behavioral reaction
Exciting circuits in red Inhibitors in blue

# Active interoceptive inference and the emotional brain


Anil K. Seth[1] and Karl J. Friston[2]

In migraine the altered cortical excitability induced in the «salience networks» by different enviromental stimulation and emotional events,characterized by reduced habituation, could generate a top down activation of trigemino-vascular system, with a flaw of nociceptive inputs directed again to the same cortical areas.

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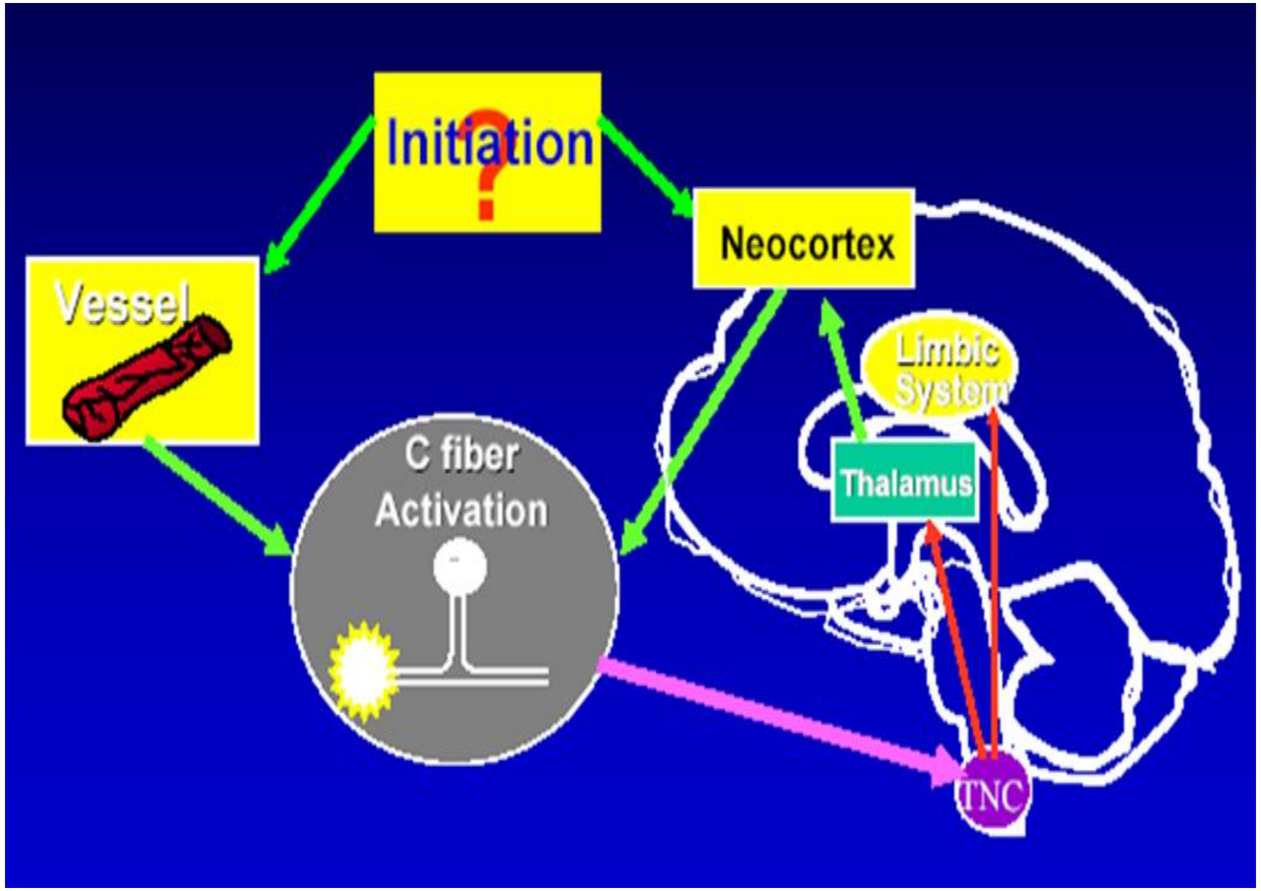
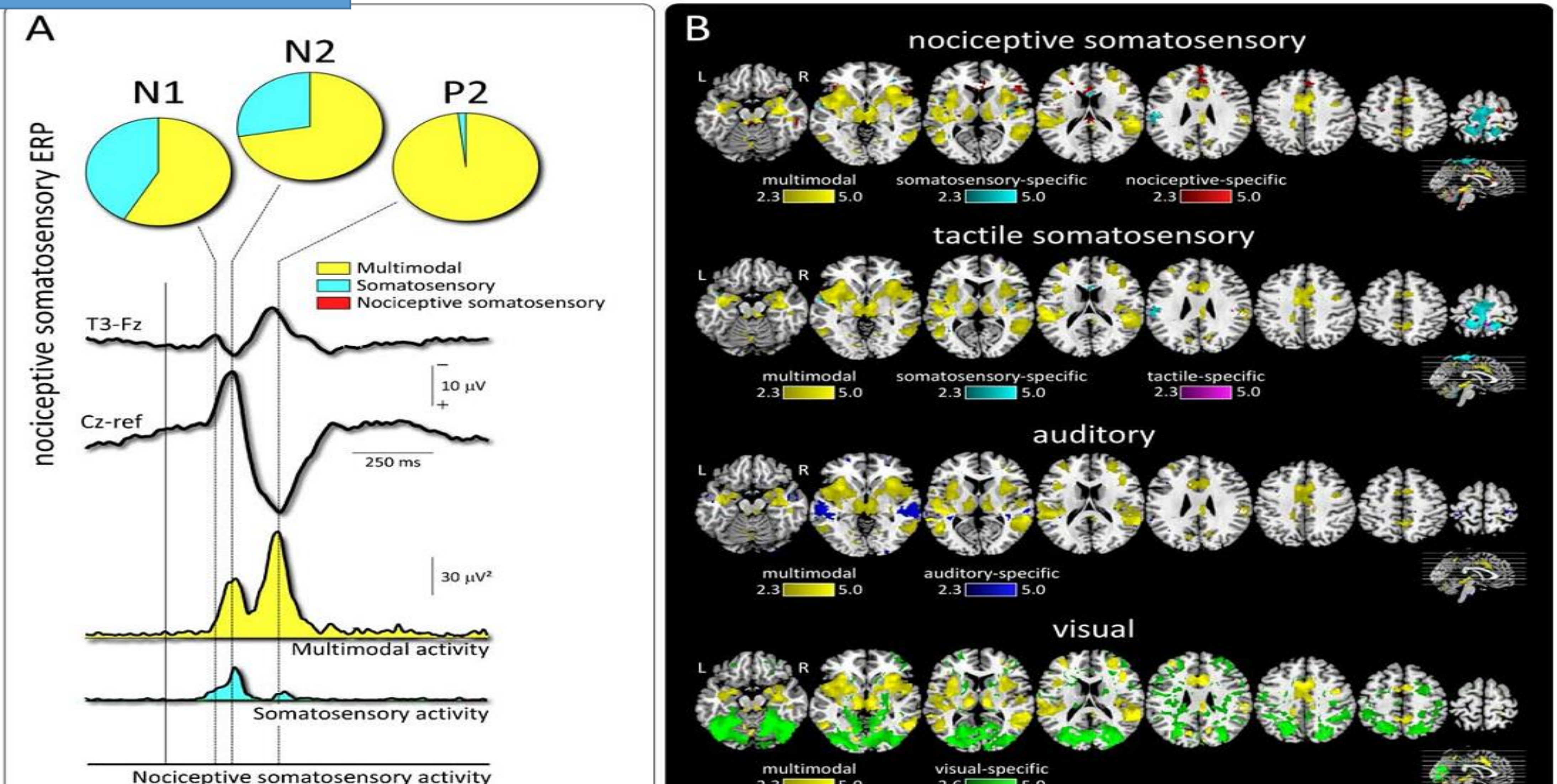



Migraine as a perfect model of failure in acquiring certainty.

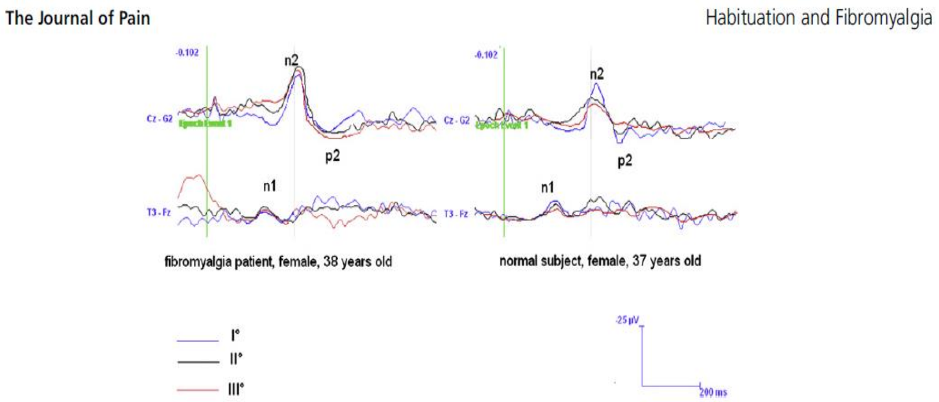
Pain matrix, salience matrix and uncertainty matrix: the same cortical areas process relevant stimuli for a behavioral strategy. The painful stimuli are «salient» for definition and recruit mandatorily the cortical network

Uncertainty matrix, pain matrix and salience matrix



Reduce habituation to pain is intrinsic to the general dysfunction of the network of "uncertainty and salience" and underlies central sensitization syndromes, as migraine, fibromyalgia, irritable bowel syndrome

Uncertainty matrix, pain matrix and salience matrix




fibromyalgia

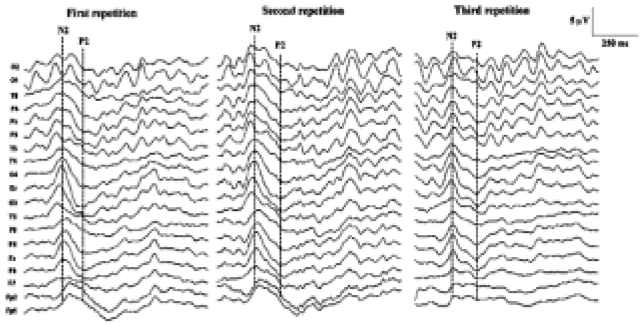
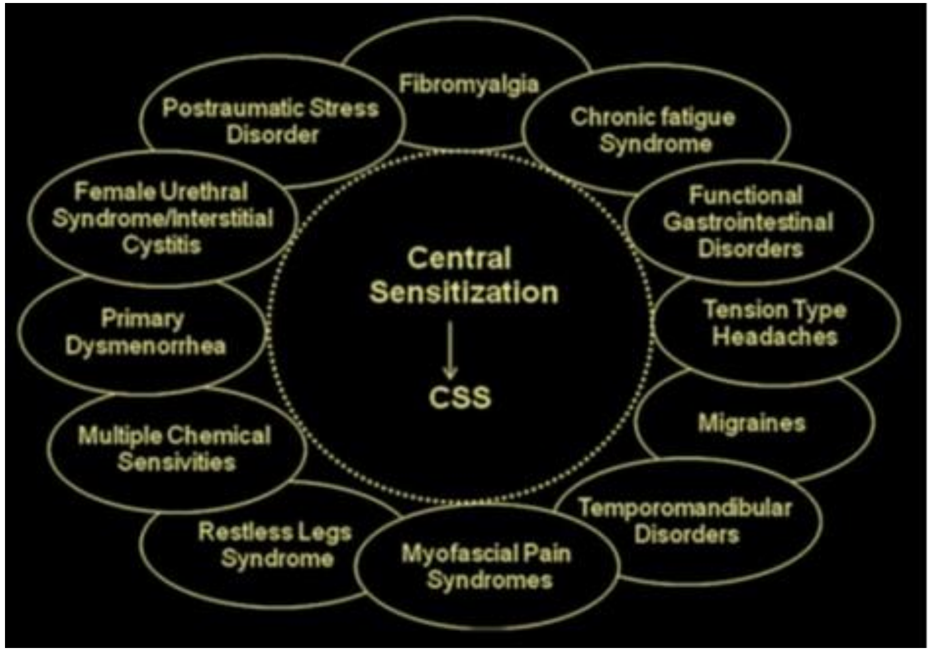


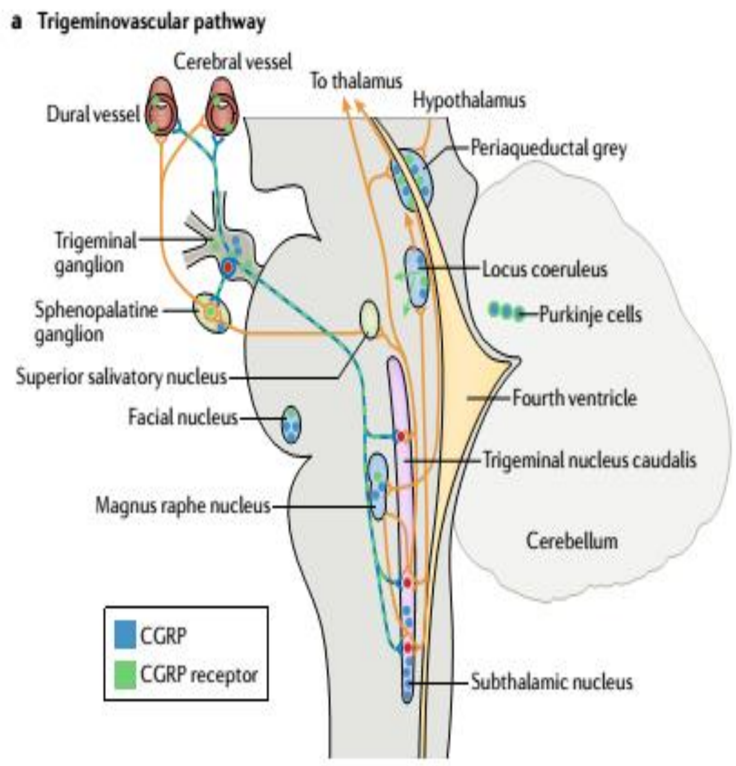

Fig. 2. LEPs recorded from 19 scalp electrodes in a representat … and P2 potentials is only slightly reduced in the second and third repetition.

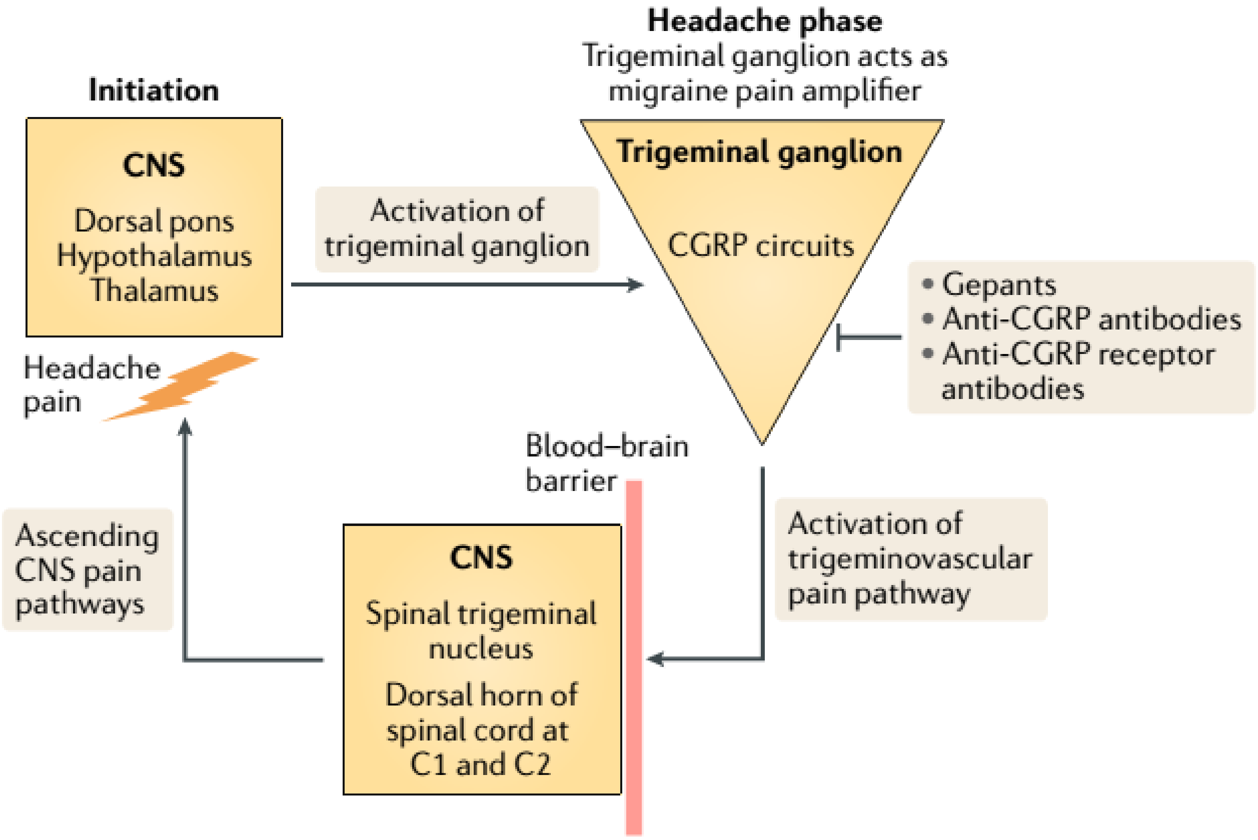
migraine




Central sensitization syndromes share a common etiologic mechanism and frequently present with overlapping epidemiologic, clinical and psychological features

# How drugs could acc on the uncertainty-salience-pain matrix?




Edvinsson, 2018

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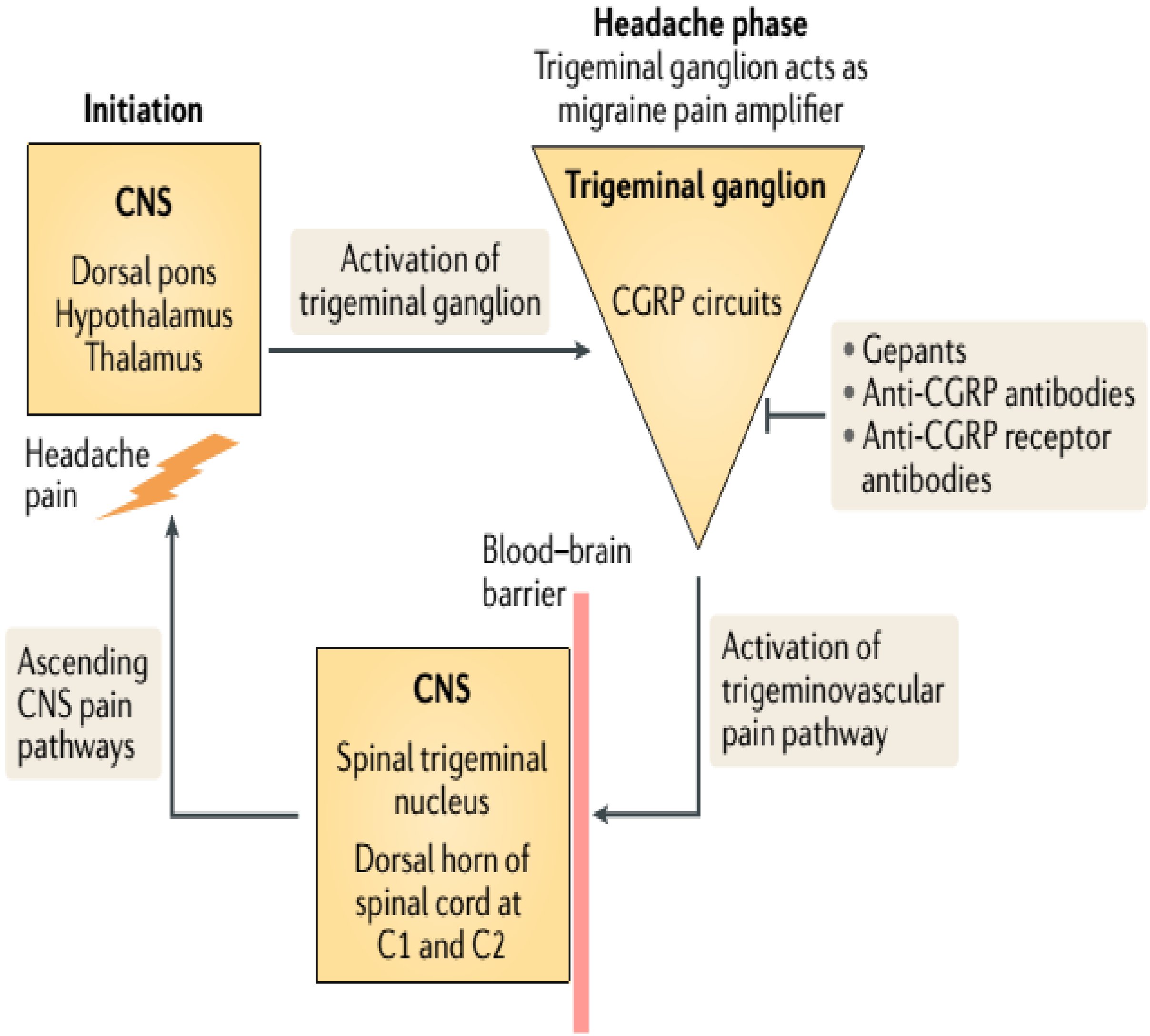


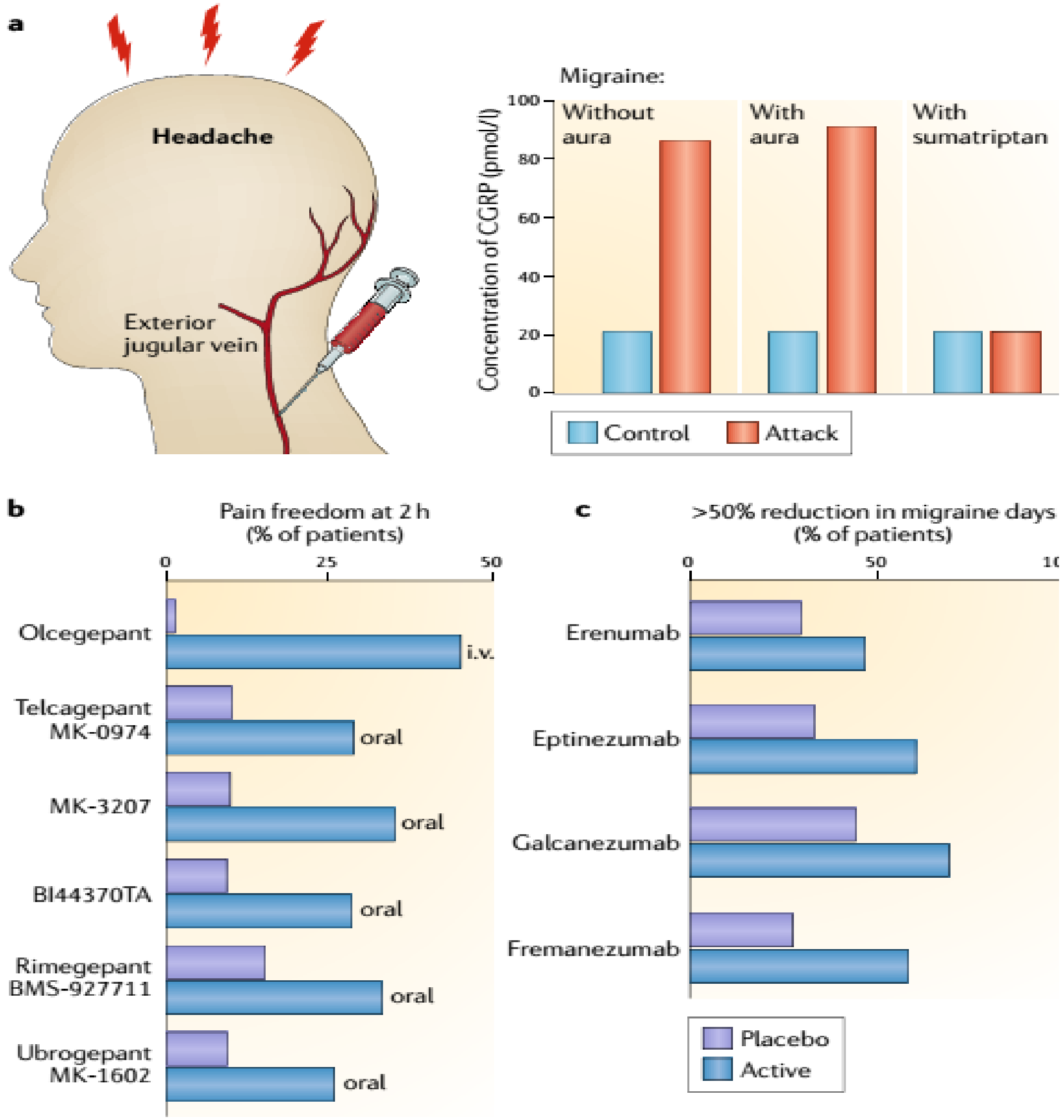


Could the «new CGRP approach» resolve the puzzle of migraine?