Electrophysiology in primary headaches

Pearls and pitfalls

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Why study electrophysiology?

Primary headaches
- = neurological diseases *without* structural lesions
- = *dysfunction* of the CNS at several levels
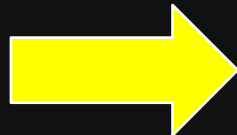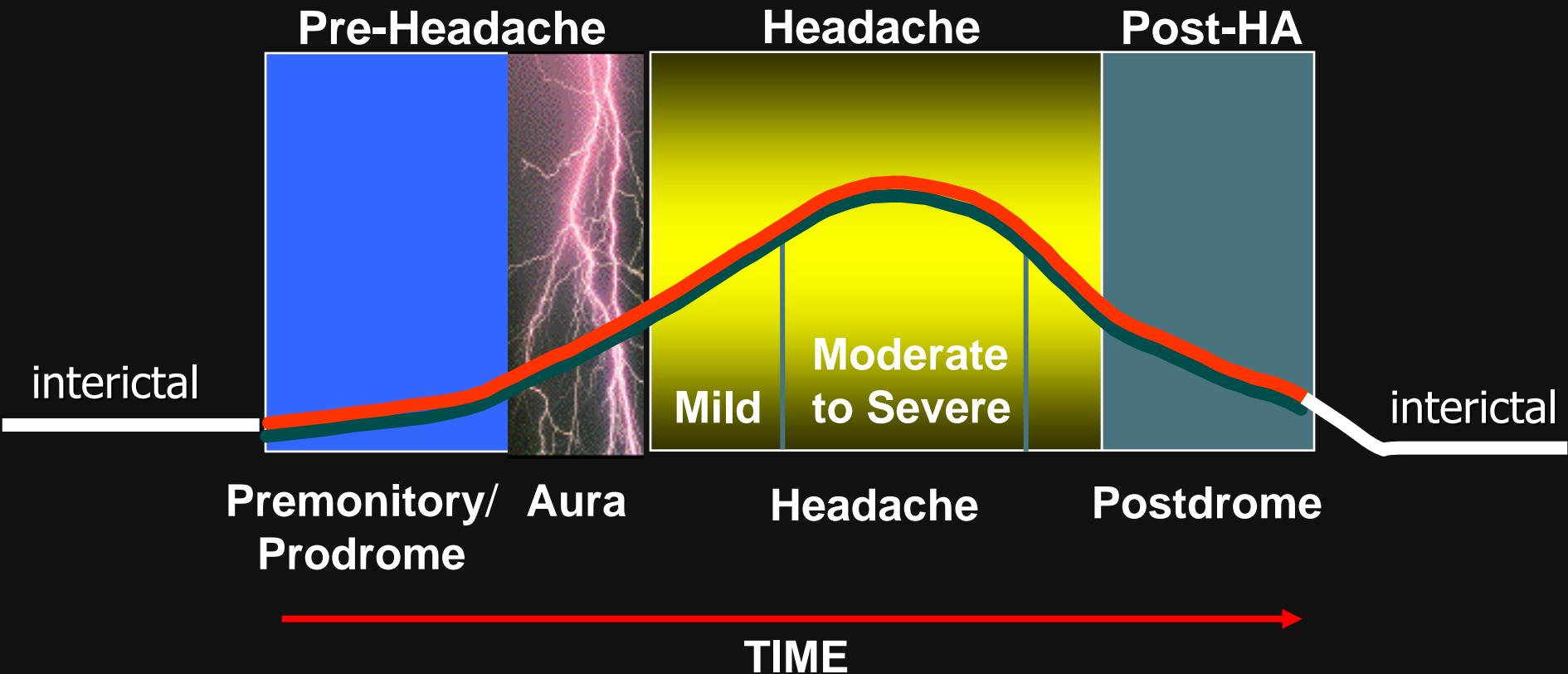- = *dynamic* pattern (ictal/interictal)

Electrophysiological recordings
- = reflect *current functionning* of underlying CNS
- = have high *interindividu*al variability

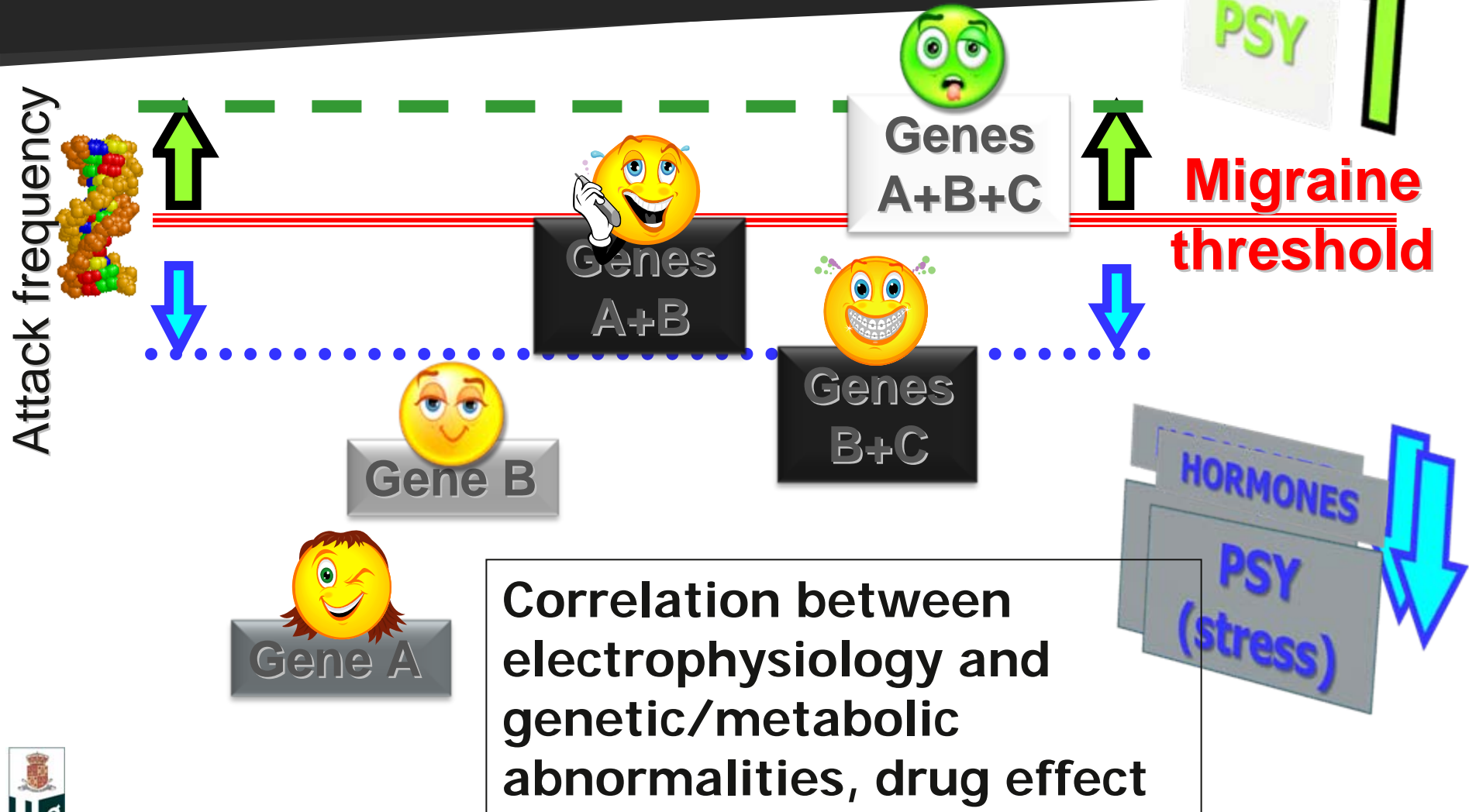✔ Pathophysiology   ✘ Diagnosis
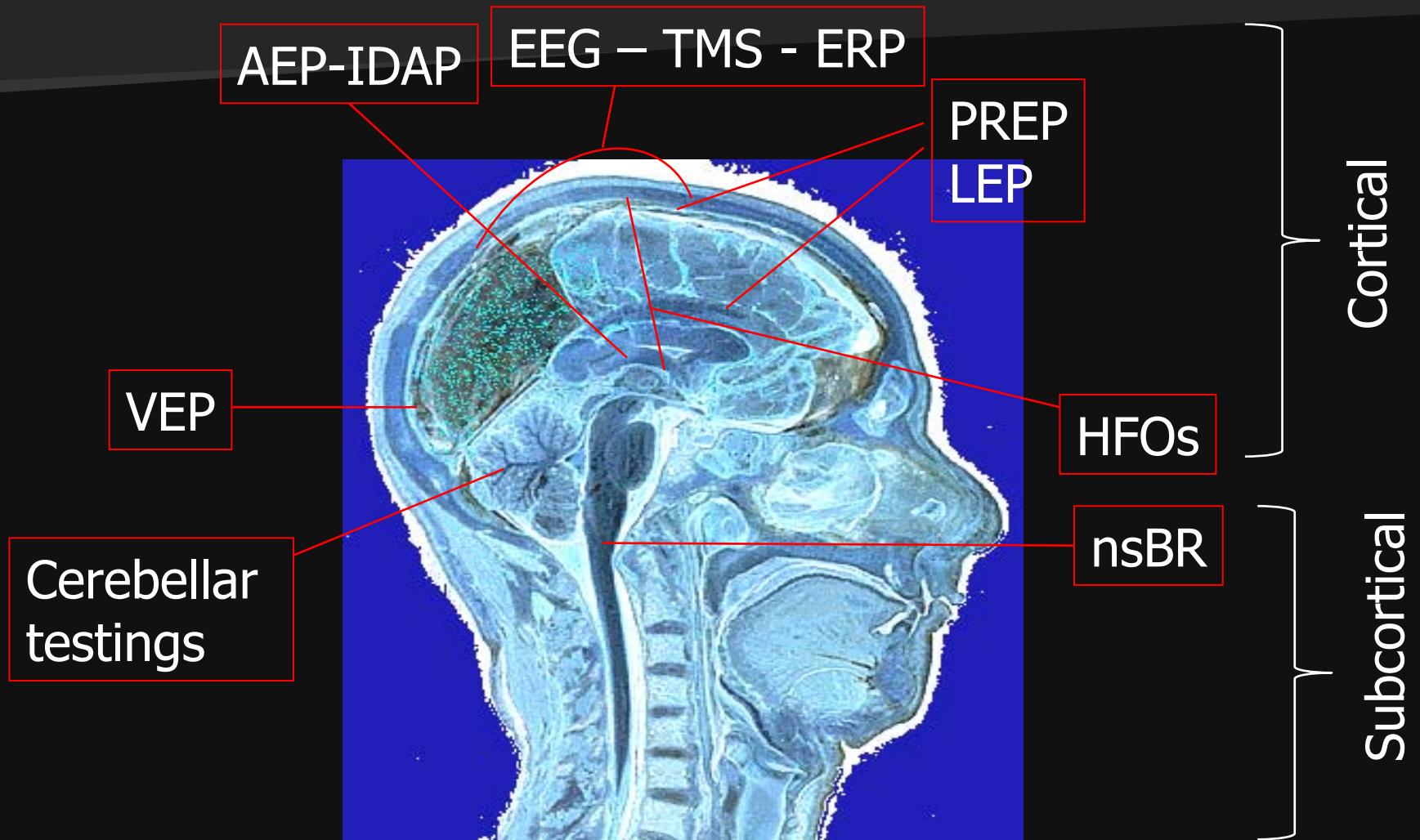✔ Treatment effects

The headache attack
A dynamic phenomenon

Pre-Headache   **Headache**   **Post-HA**

interictal

Mild

Moderate to Severe

interictal

Premonitory/ Prodrome   **Aura**   **Headache**   **Postdrome**

TIME

Electrophysiology can be repeated at several time points

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Primary headaches: complex disorders

MEDIC

PSY

Attack frequency

Genes A+B+C

Migraine threshold

Genes A+B

Genes B+C

Gene B

Gene A

Correlation between electrophysiology and genetic/metabolic abnormalities, drug effect

HORMONES

PSY (stress)

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Which tools are available?

AEP-IDAP

EEG – TMS - ERP

PREP
LEP

VEP

HFOs

Cerebellar testings

nsBR

Cortical

Subcortical

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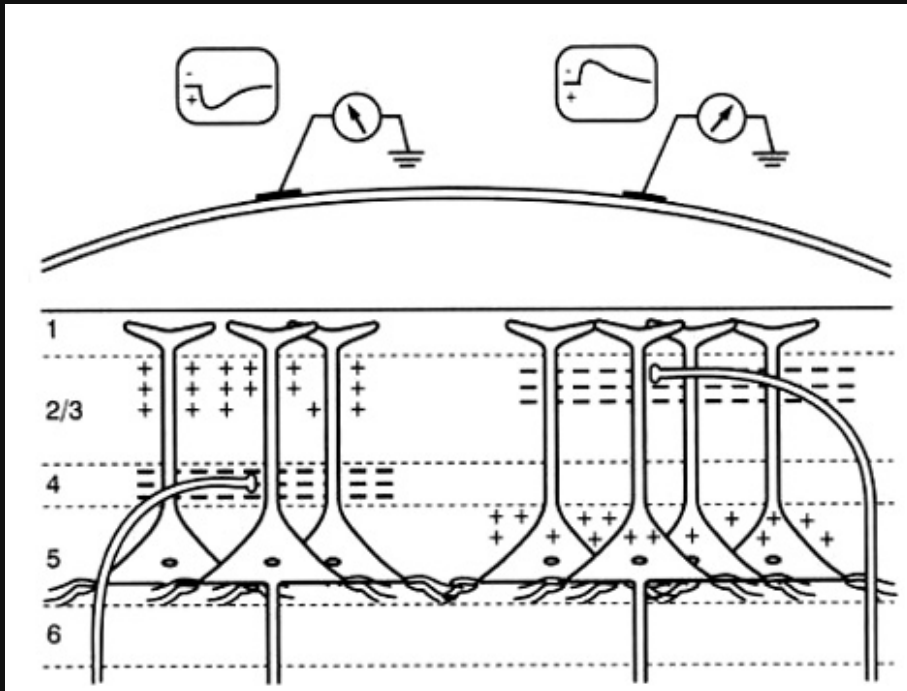
Cortical evaluation
Generalities

- Surface recordings

- Spontaneous activity or response to a stimulation

- Localisation of recording electrode will depend on the physiological process (sensorimotor etc.)

Cortical evaluation
## *Generalities (2)*

The recorded signal will be conditionned by

- (Pre) activation level of studied structure
  - inhibitory interneurons
  - thalamo-cortical loops
  - glia ?

- Depth of studied structure
- Geometrical configuration of studied structure
- Temporal synchronization of involved neurons
- Tissue conductivity
- Number of other co-activated structures

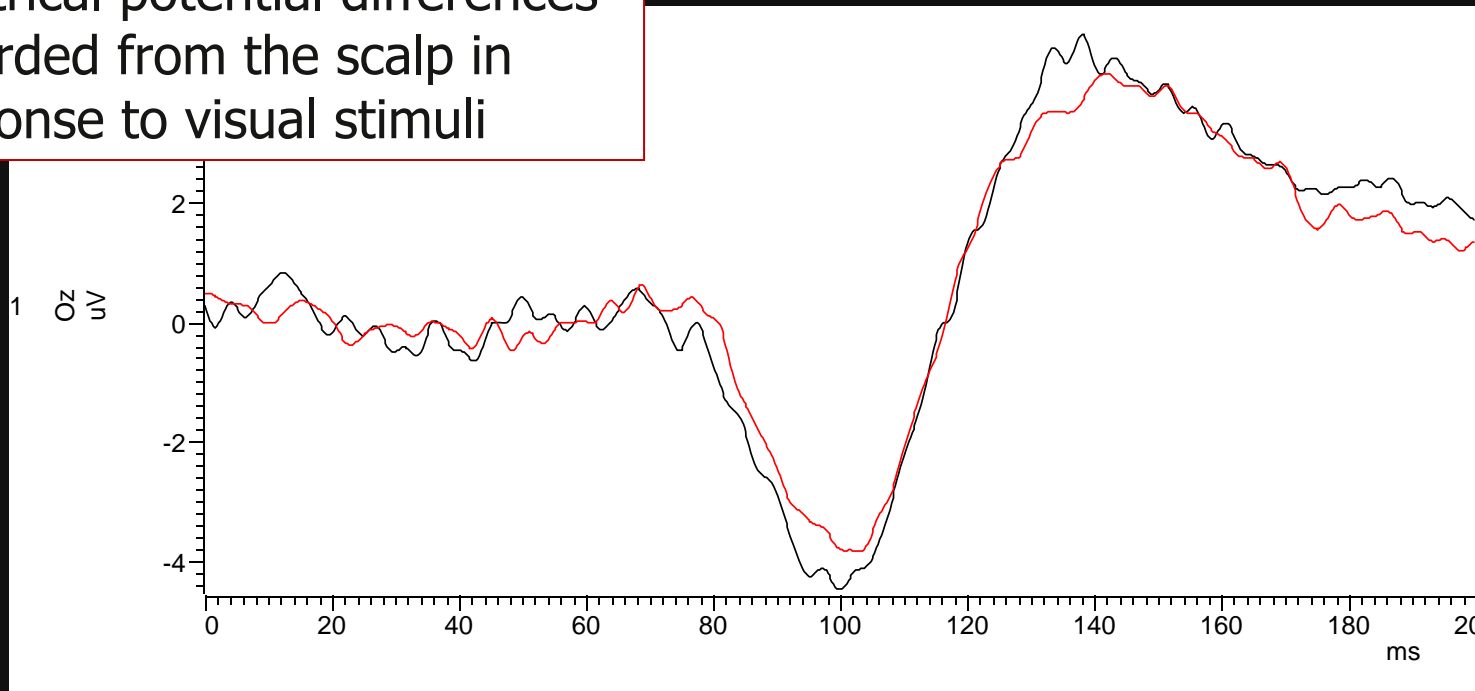# Cortical evaluation
30 years ago...EEG
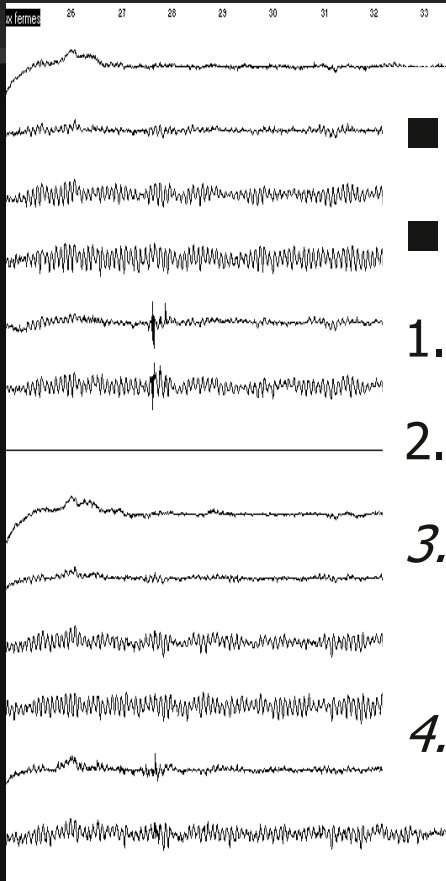
■ Activity of pyramidal cells (90%)

■ 4 EEG aspects in <u>migraine</u>:

1. Slowing of *background* rythm during attacks

2. Enhanced *photic* response (H-response)

3. *qEEG:* unilateral alpha activity reduction (MA, MO, MM) during attacks

4. *MEG:* direct current shifts during aura // CSD

Cortical evoked potentials
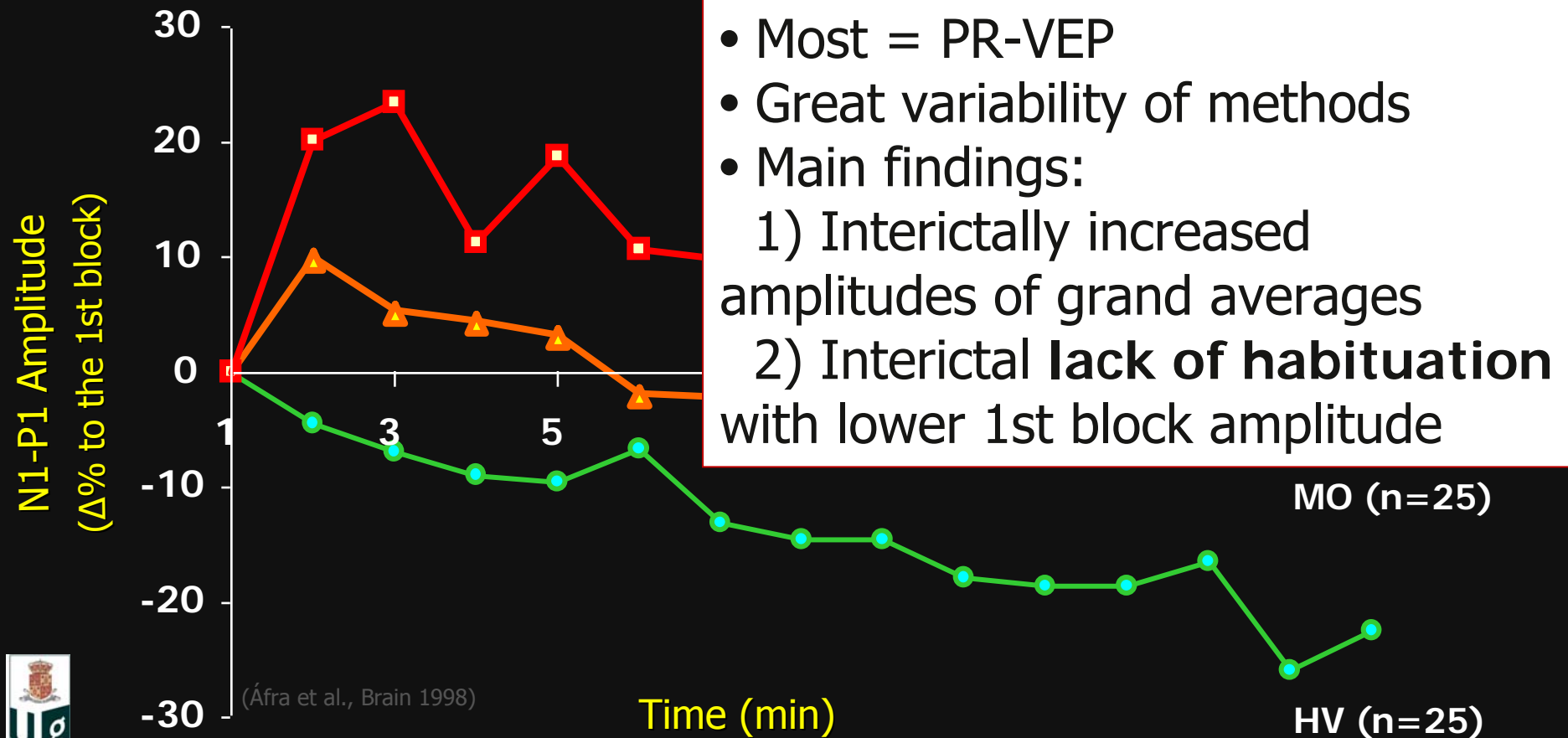## *Visual evoked potentials (VEPs)*

Electrical potential differences recorded from the scalp in response to visual stimuli
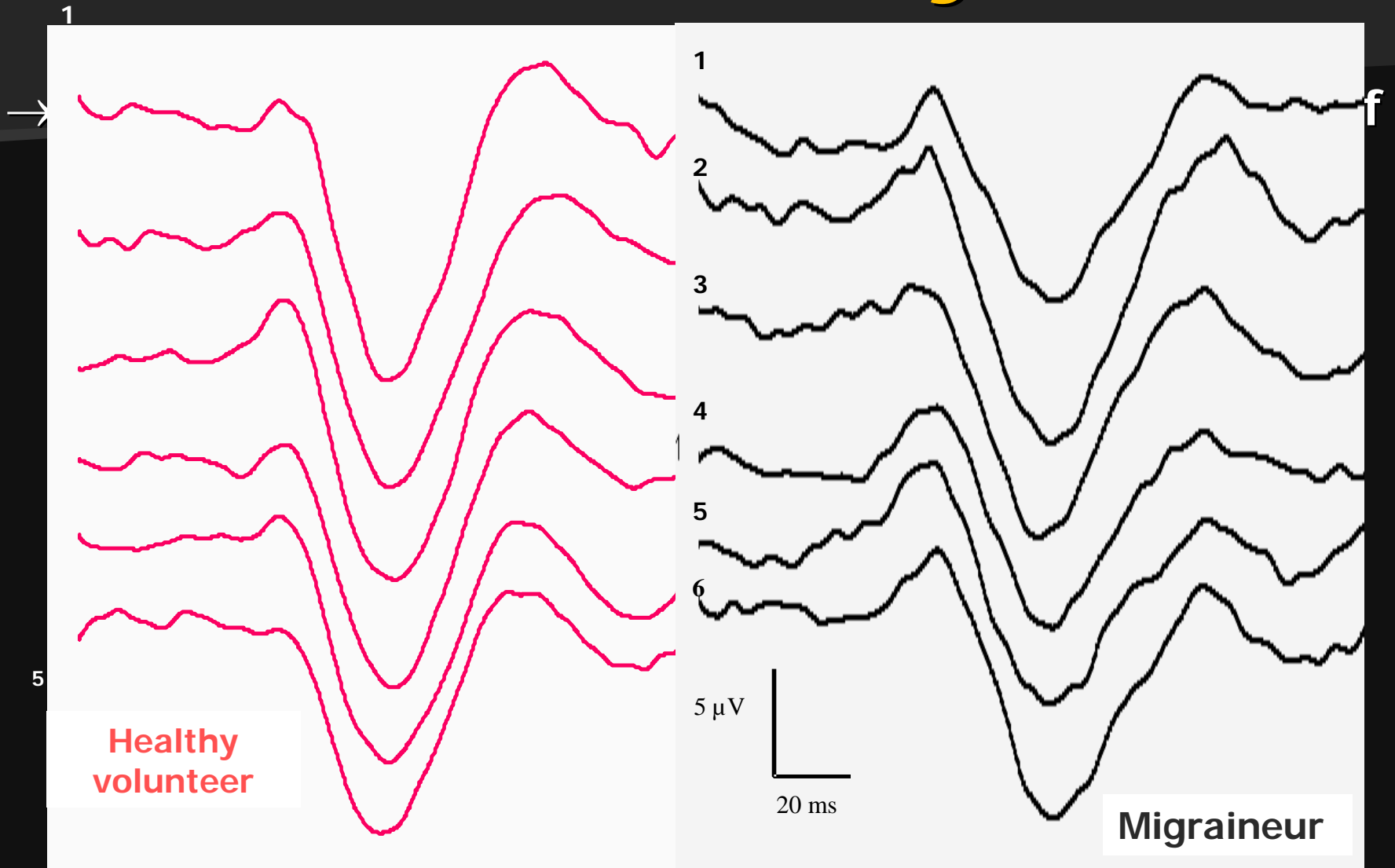

- VEPs at low stimulation rates = transient VEPs
- Elicited by unpatterned or patterned stimuli (PR-VEPs)
- VEPs above 3.5 Hz = steady-state VEPs = SVEPs

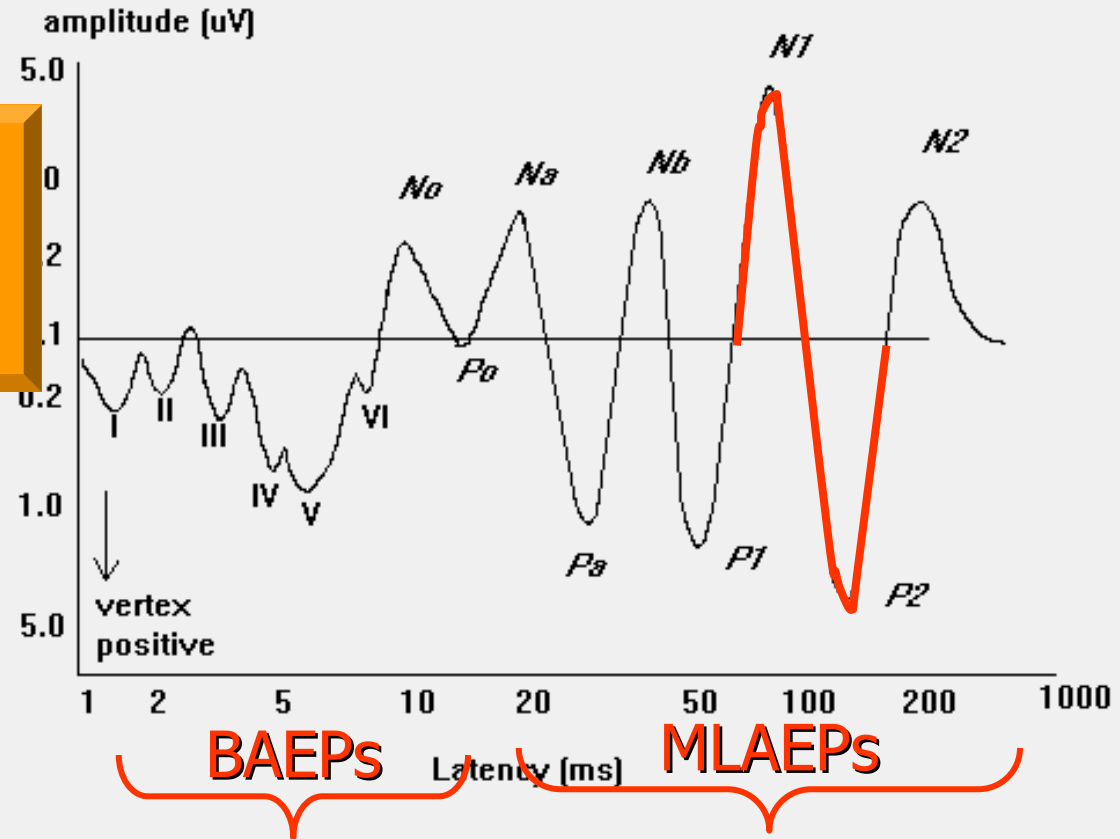D.Magis

VEPs : literature

VEPs in migraine: ~ 50 studies

- Most = PR-VEP
- Great variability of methods
- Main findings:
  1) Interictally increased amplitudes of grand averages
  2) Interictal **lack of habituation** with lower 1st block amplitude

N1-P1 Amplitude (Δ% to the 1st block)

Time (min)

MO (n=25)

HV (n=25)

(Áfra et al., Brain 1998)

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Habituation deficit in migraineurs

Healthy volunteer

Migraineur

5 μV

20 ms

Cortical evoked potentials
Auditory evoked potentials

# *Auditory evoked potentials: literature*

- BAEP: heterogenous results in migraineurs, increased ictal latencies

- AEP in migraineurs:
  - Reduced gating of P50 response
  - Intensity-dependence of AEP (IDAP) is enhanced interictally and normalizes during attack
    - → Inversely related to central 5 HT transmission
    - → Familial influence
    - → Limited repeatability

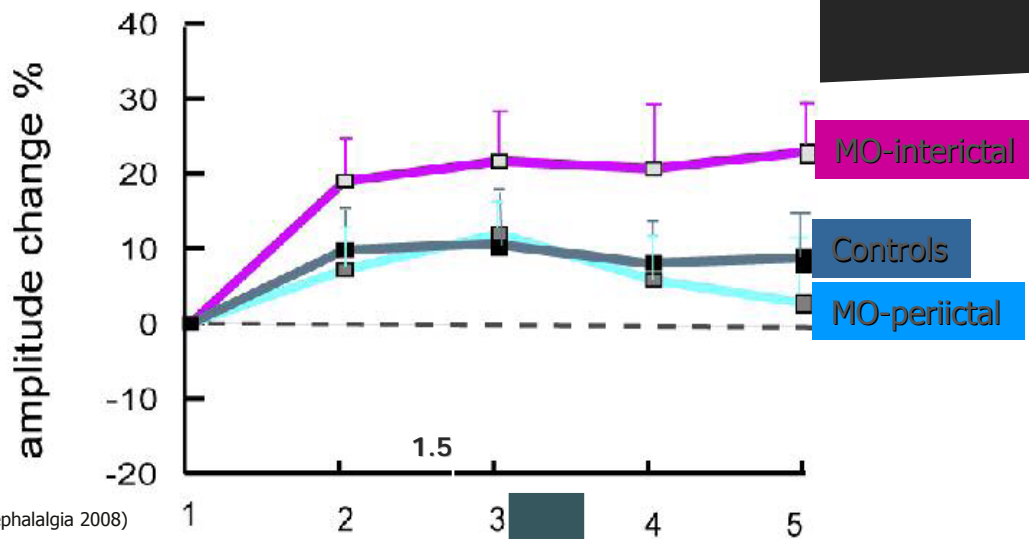IDAP and VEP habituation slopes are not correlated in a same patient
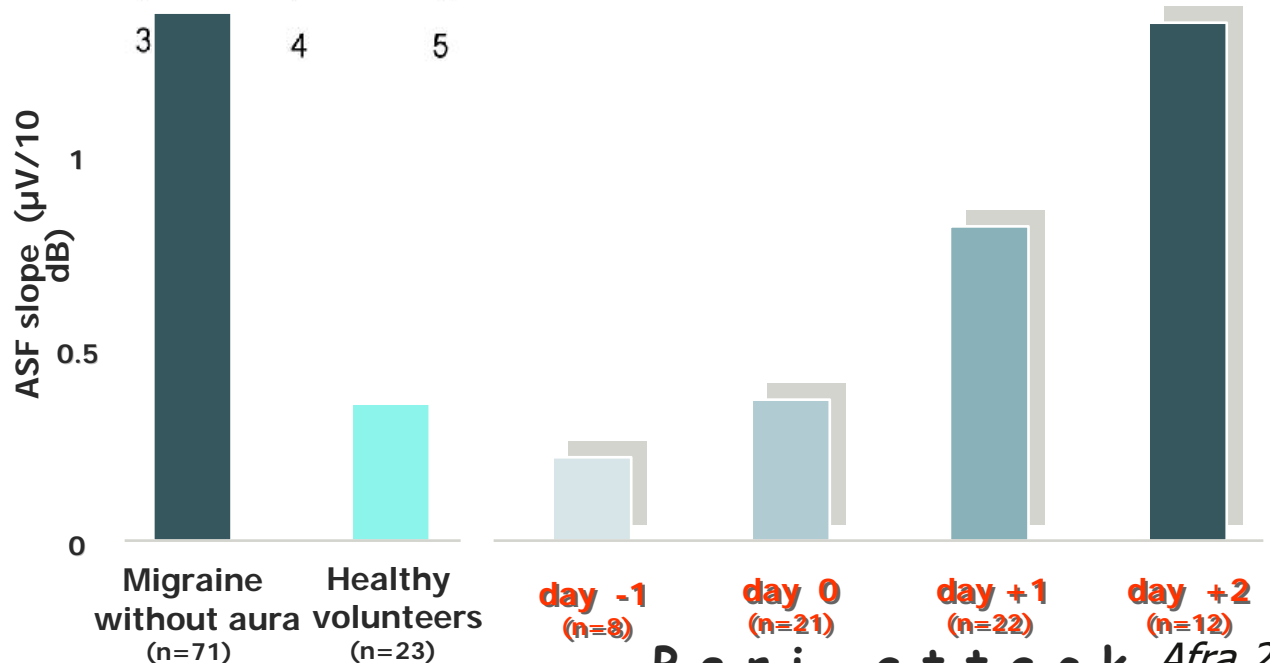
IDAP(Wang 1996)

Peri-attack interval


(Chen et al. Cephalalgia 2008)

MO-interictal

Controls
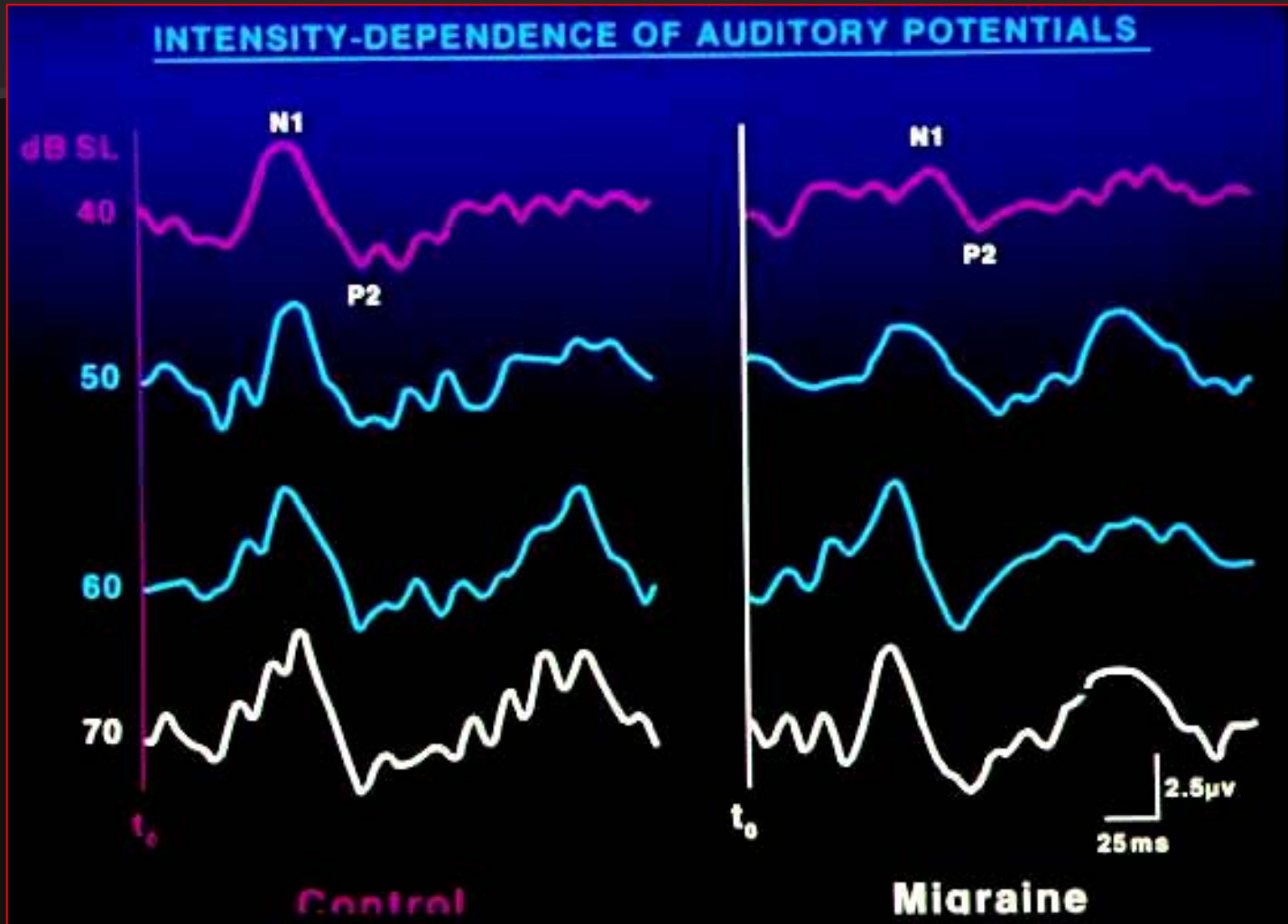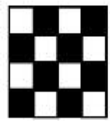
MO-periictal

Cortical excitability changes in periictal period

P e r i - a t t a c k *Afra 2000*

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Transcranial magnetic stimulation (TMS)

TMS can non-invasively explore the excitability of certain cortical areas

- TMS of motor cortex in migraine
  - In general: motor threshold increased interictally
  - TMS of visual cortex in migraine
  - Results more conflicting (phosphene threshold)
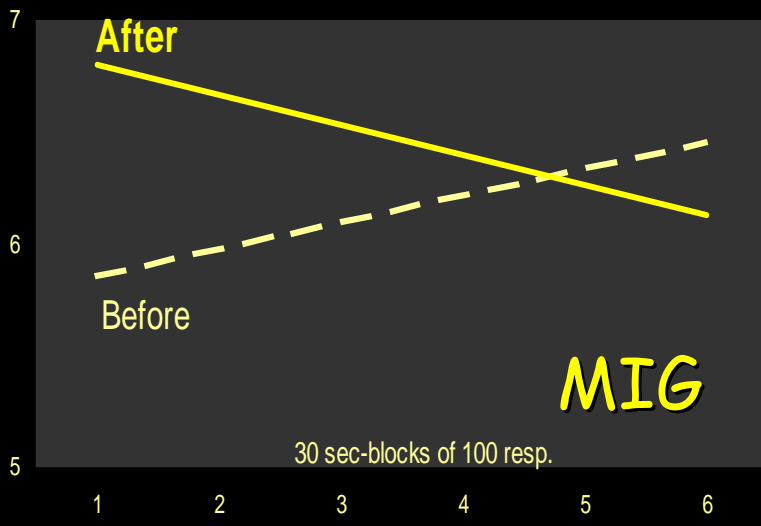
SINGLE PULSE

magnetophosphenes
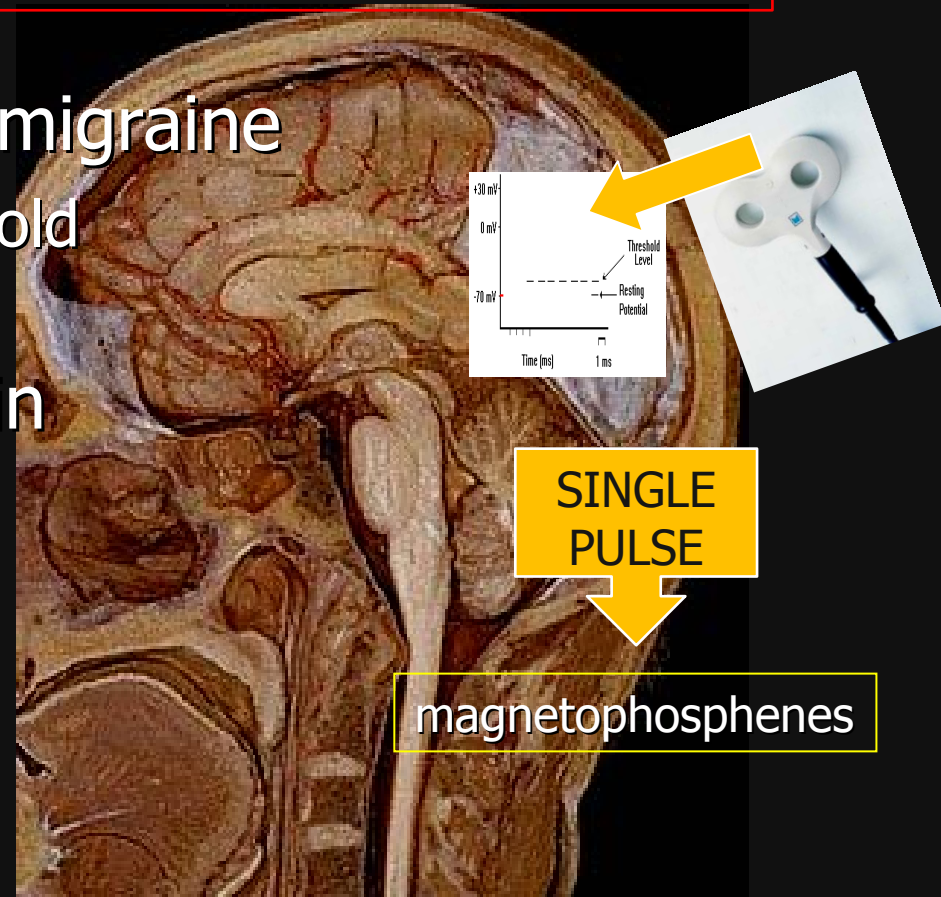
Repetitive transcranial magnetic stimulation (rTMS)

Can durably modify the excitability of certain cortical areas

Cortical activation at high (**10Hz**) stimulation frequency

Cortical inhibition at low (**1Hz**) stimulation frequency

After

Before

MIG

30 sec-blocks of 100 resp.

7

6

5

1 2 3 4 5 6

Successive VEP amplitudes before and after 10 Hz rTMS of the visual cortex
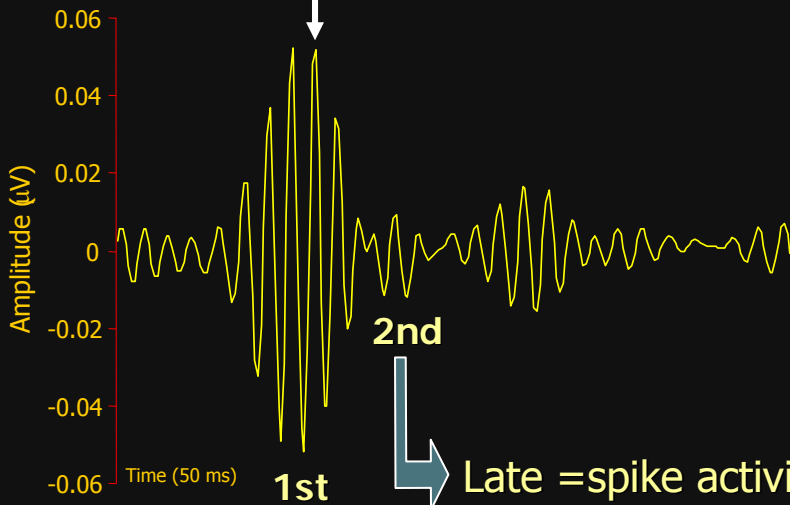→10 Hz rTMS normalizes VEP habituation in MIG
(Bohotin 2002)

→ Argument for a decreased preactivation of the migrainous brain

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High frequency oscillations (HFO) of SSEPs

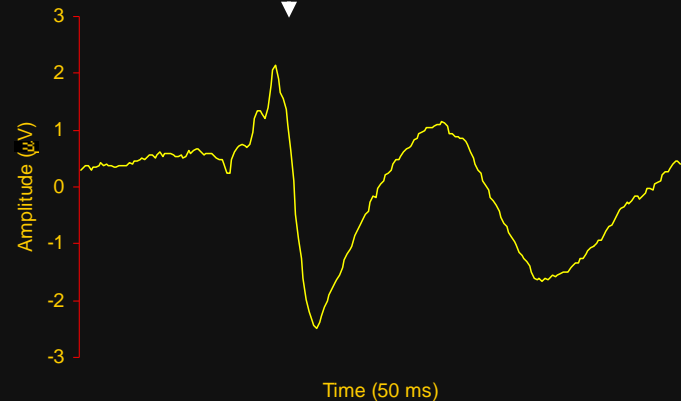**Electrical stimulation of median nerve at the wrist**

**Bursts of
high-frequency oscillations
(HFO)
(band-pass filter 450-750 Hz)**

**Low-frequency somesthetic
evoked potentials (SSEP)**

2nd

1st

Late =spike activity in cortical inhib. interneurons (? GABAergic)

Early = subcortical= spike activity in thalamo-cortical cholinergic fibers

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HFOs in migraine (Coppola 2005)

Healthy subject

1st

2nd

1st HFO maximal amplitude

P=0.037   P=0.011

0.06

0.060

0.049

0.044

0.03

HV (n=

1st HFO are

Time (50 ms)
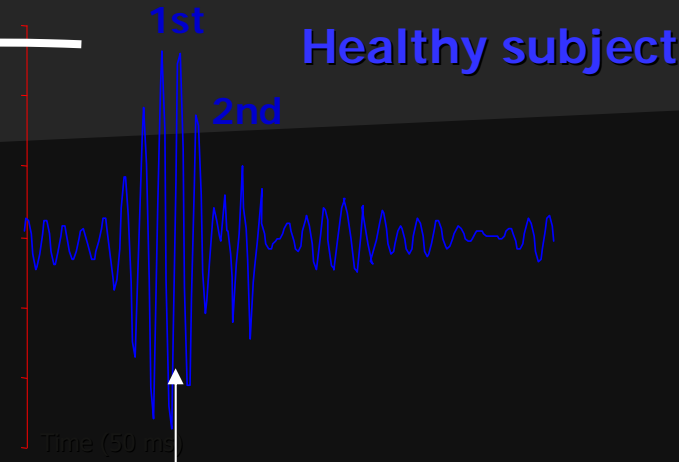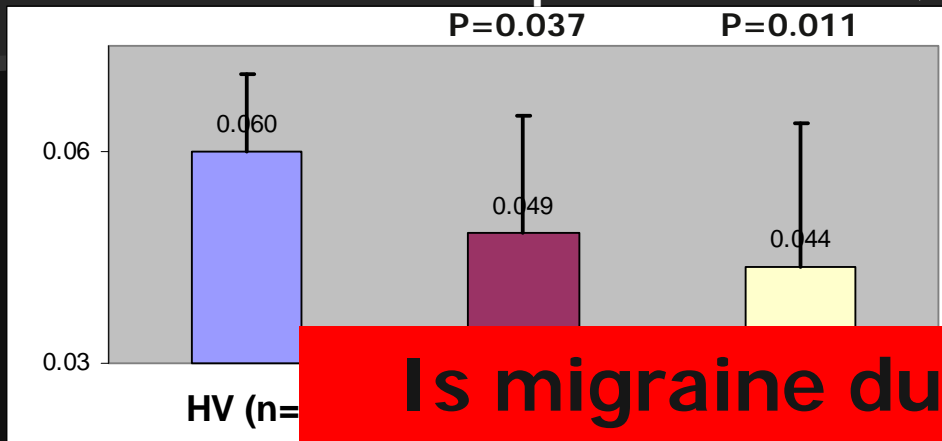
Is migraine due to thalamo-cortical dysrythmia ?

0.00006

P=0.027   P=0.013

4.55094E-05

3.58501E-05

0.000045

3.33394E-05

Time (50 ms)

MA patient

0.00003

| HV (n=15) | MO(n=14) | MA(n=15) |

Time (50 ms)
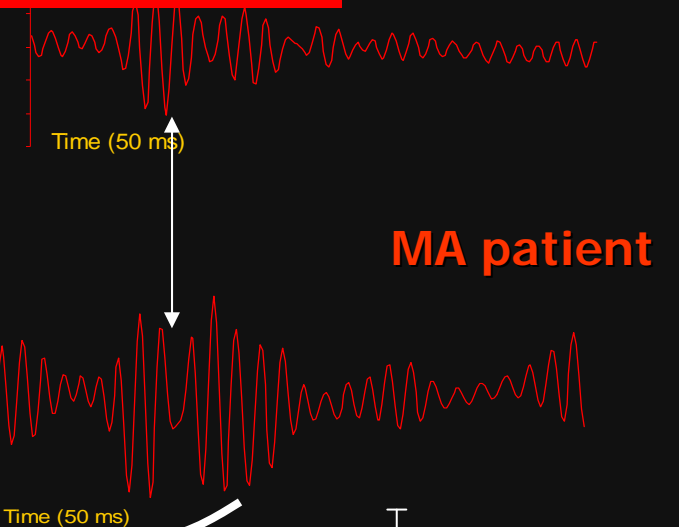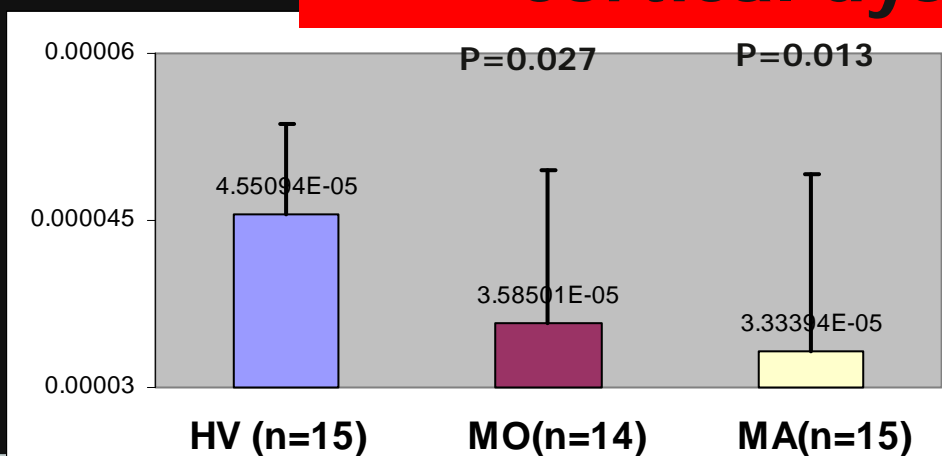
• **2nd HFO : no significant group difference**

Time (50 ms)

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Cortical evoked potentials
Conflicting results

- VEP

  - No lack of habituation: Sand and Vingen, Oelkers-Ax

    - TMS

      - Phosphene threshold <u>lower</u>: Aurora, Mulleners...

      - PT increased by 1Hz rTMS: Brighina...

    - HFOs

      - Early component <u>increased</u> in MIG: Lai 2011

 → Cortical hyperexcitability in MIG ??

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Migraine heterogeneity
Examples

• Ambrosini 2011: effect of <u>light stimulation</u> on IDAP

→ 2 subgroups of migraineurs with same clinical profile

      1) Normal IDAP – Increase with light

      2) High IDAP – Decrease with light

→ Underscores migraine pathophysiological heterogeneity

→ Light interference could improve phenotyping

• Hansen 2011: habituation is <u>greater in FHM</u> than HV

• Magis 2007: NO VEP habituation deficit in patients with MTHFR C677T TT homozygoty

Familial hemiplegic migraine

Visual Evoked Potentials - N1P1
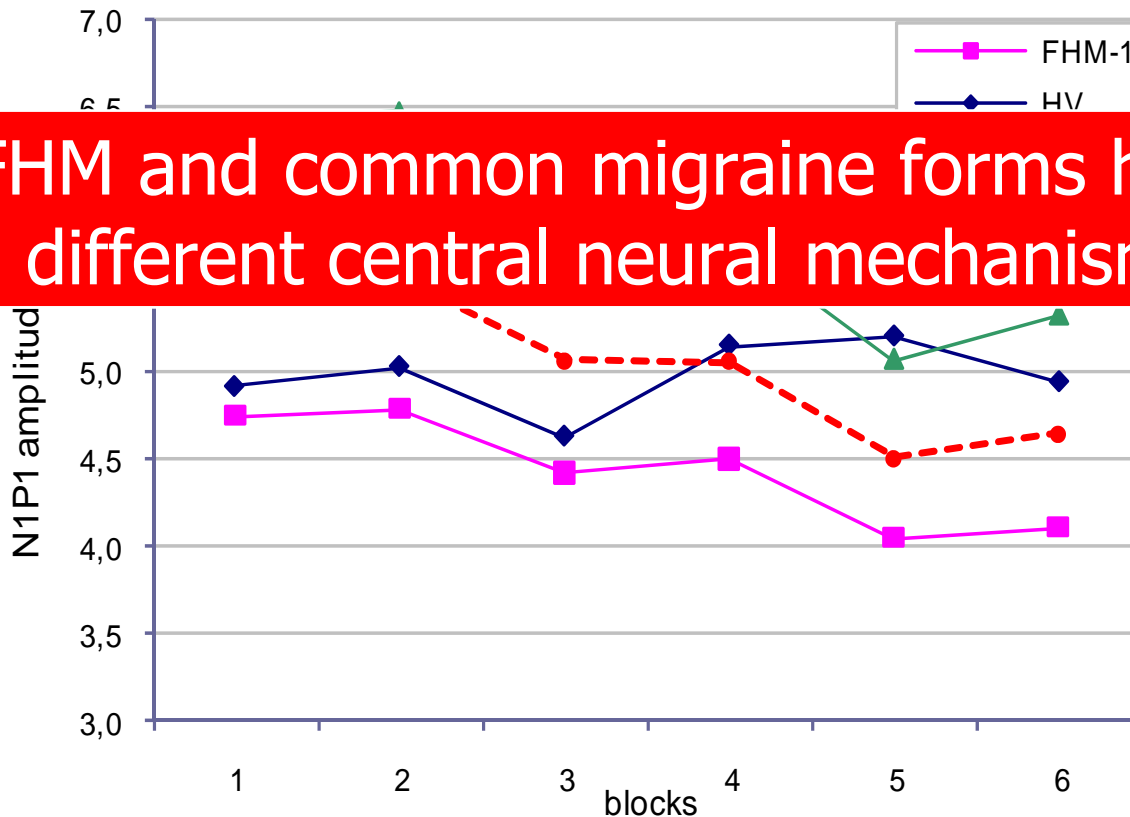
FHM and common migraine forms have different central neural mechanisms

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Cortical evoked potentials
Common interests and limitations

(+)

- non invasive

- replicable at different time points
- portable devices
- correlation with metabolic and genetic studies, effect of drugs

(-)

- lack of inter and intraindividual reproducibility data

- heterogenous migraine genotypes and pathophysiology, effect of drugs

- need for better standardization

    - Ex: habituation of PR-VEP: 1°8' spatial frequency, 3.1 Hz stimulation frequency…
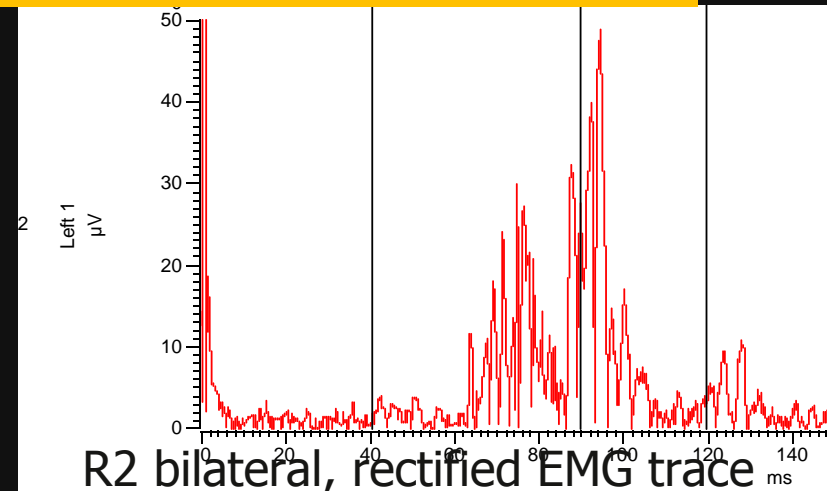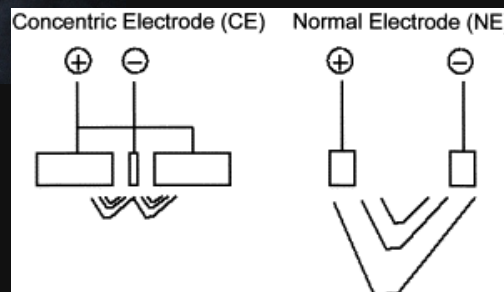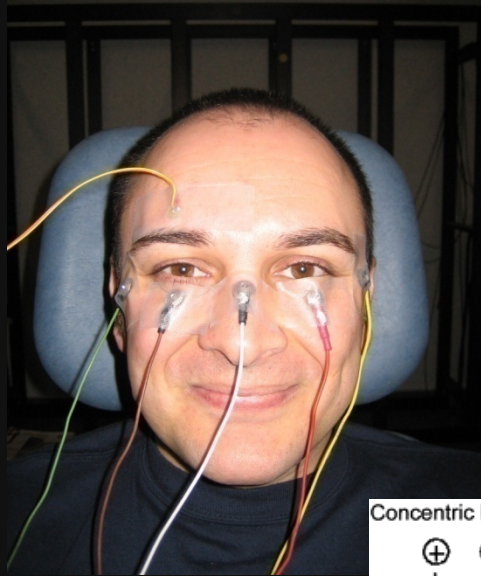
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Cortical evoked potentials
Critical variables

- method-dependent :

stimulation parameters : VEP spatial & temporal
      frequencies, number of averagings…

- patient-dependent :

optimize intraindividual reproducibility,
      heterogeneous pathophysiology, drug intake…

- disease-dependent :

timing of recording in relation to the
      previous and next attack

Nociception-specific blink reflex
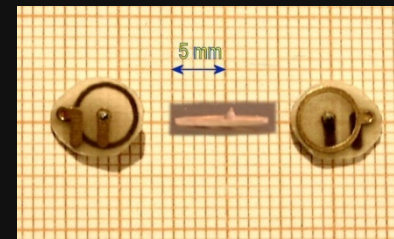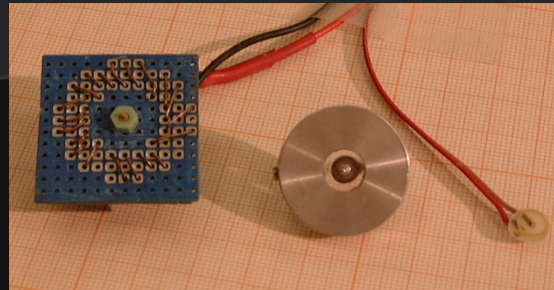
Concentric electrode delivering a high-density current selectively activating Adelta fibers
(Kaube 2000)

R2 bilateral, rectified EMG trace

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nsBR
Interest: evaluation of trigeminal nociception in humans

VII Motor nucleus

VII Motor nucleus

Bulbo-pontine R2 interneurons

Aβ-Aδ

R2

R2

S

S

Aδ,C

Parameters:
1.5 PT 0.3 ms
Exclude 1st trace
15-17 s ISI

Trigeminal nucleus caudalis

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nsBR
Migraine

- Ictally: R2 increased, latency decreased

→ Reflects trigeminal sensitization

- Interictally: R2 habituation deficit (Katsarava…)

- Pathophysiology

  - Correlation between nsBR and VEP habituations *(Di Clemente 2005)*

  - Habituation deficit in subjects « at risk » *(Di Clemente 2005)*

  - Habituation deficit after NTG in HV *(Di Clemente 2009)*

nsBR
habituation in HV « at risk »

Habituation deficit: a presymptomatic marker of the disease?

Di Clemente 2005
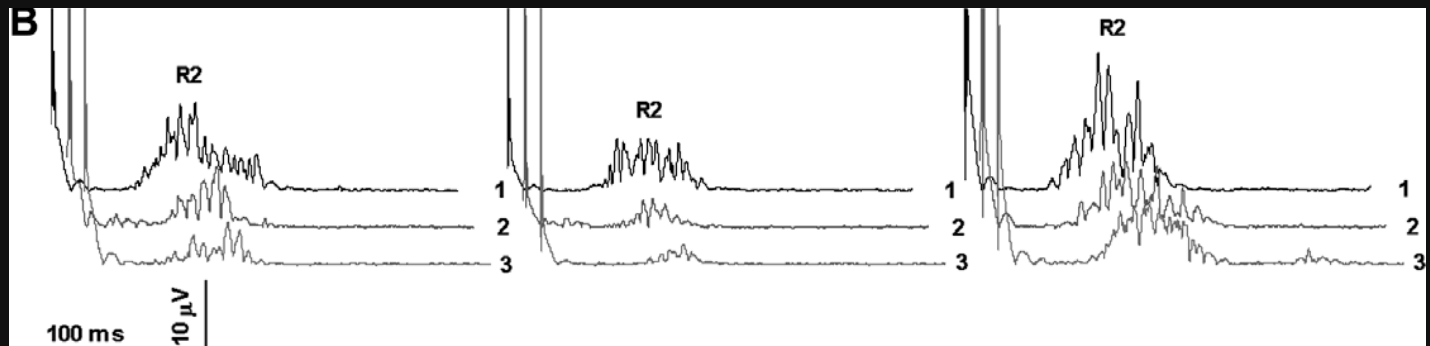
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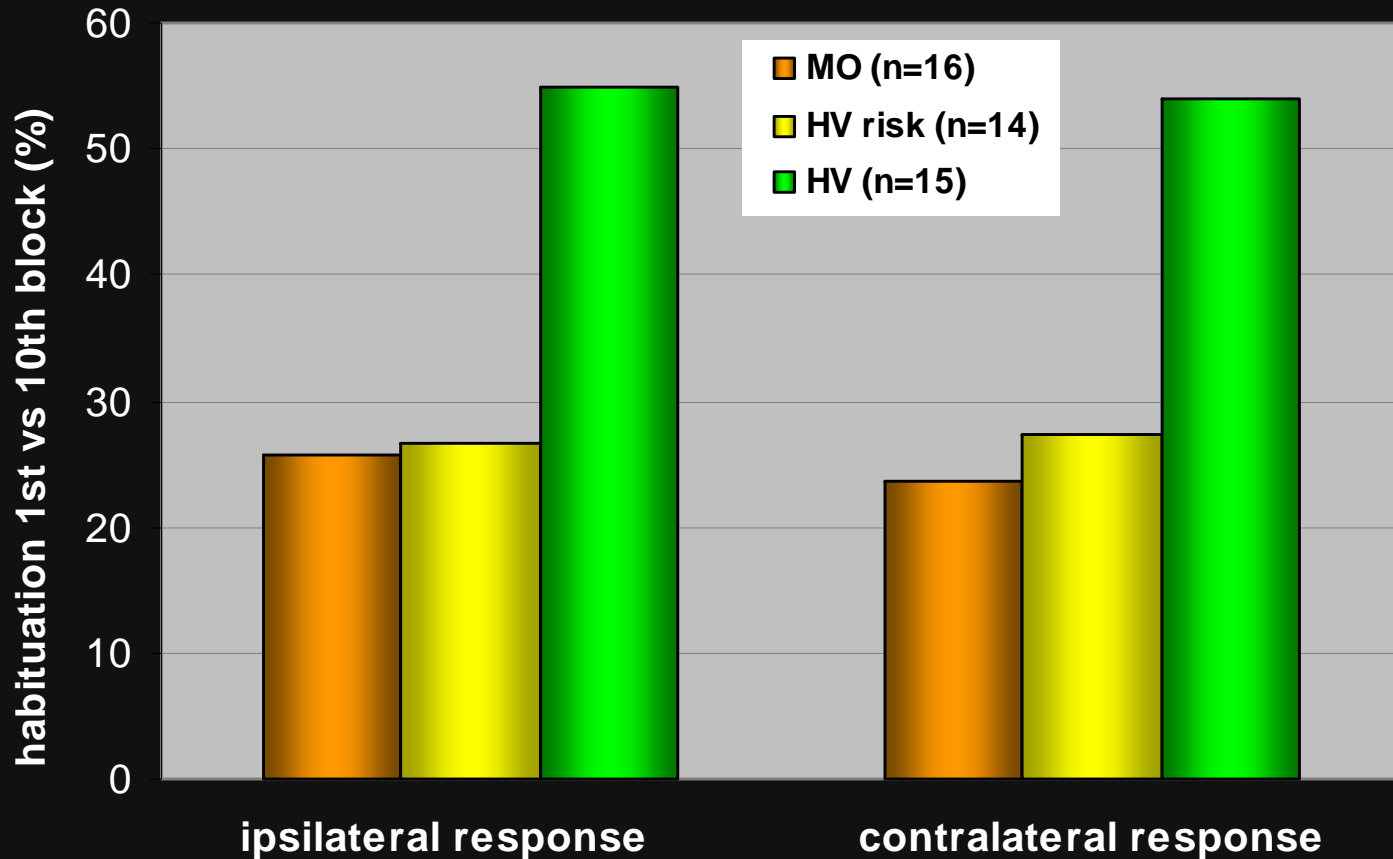
nsBR
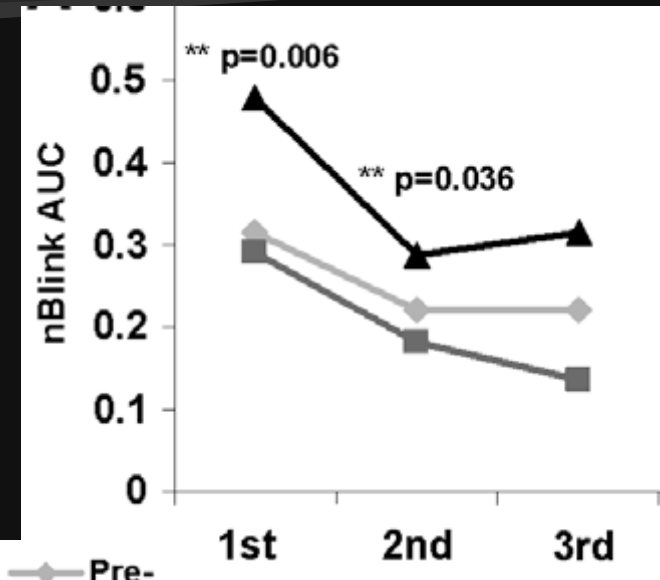## *Nitroglycerin effects in HV*

NTG in humans:
- Immediate headache, bilateral
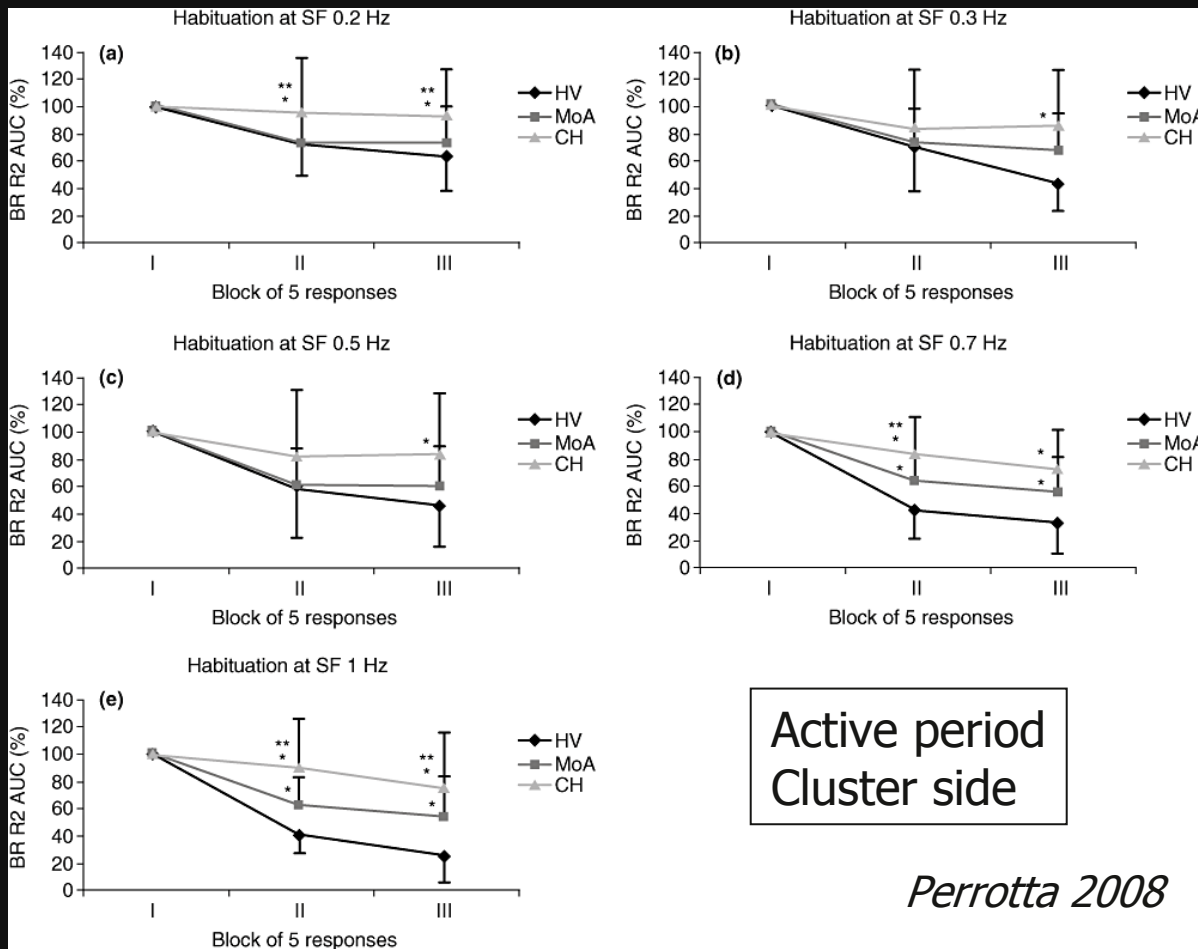- Delayed headache (4-6h) MIG features

NTG 1.2 mg vs. placebo
Similar changes than in MIG during attack:
- R2 AUC increase
- R2 latency decrease

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Di Clemente 2009

BR
Reduced habituation in cluster headache



Perrotta 2008

Active period
Cluster side

Habituation deficit in cluster headache:

- Suprasegmental mechanisms ? (Hypothalamo-trigeminal)

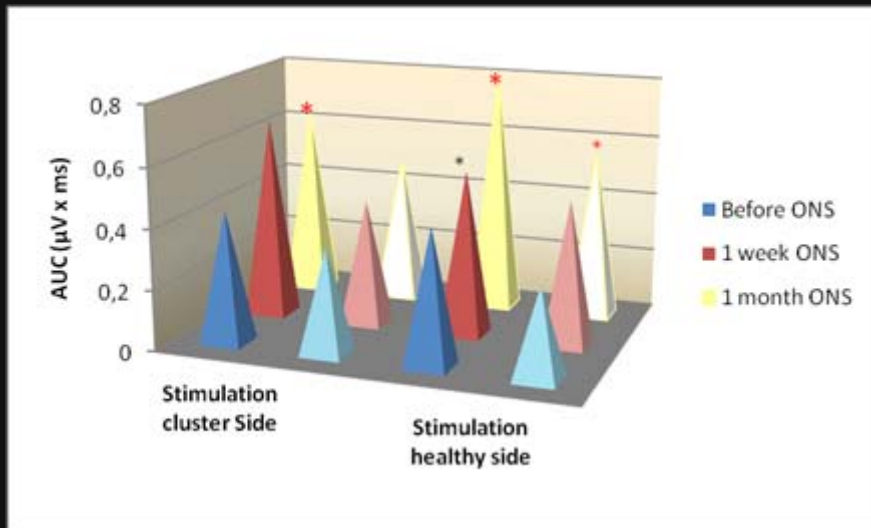- Segmental mechanisms? (Trigeminal sensitization)

nsBR

Demonstration of functional connections between visual cortex and trigeminal nociceptive system
(Sava IHC 2011)

Study of nsBR before and after 1Hz / 10Hz rTMS applied over the visual cortex ; and 8Hz flash
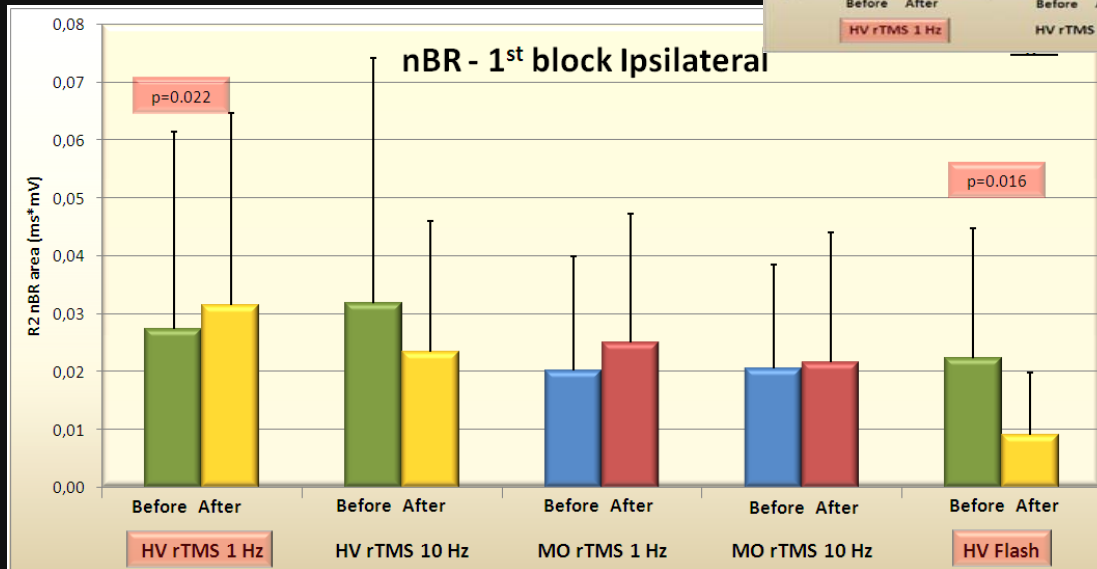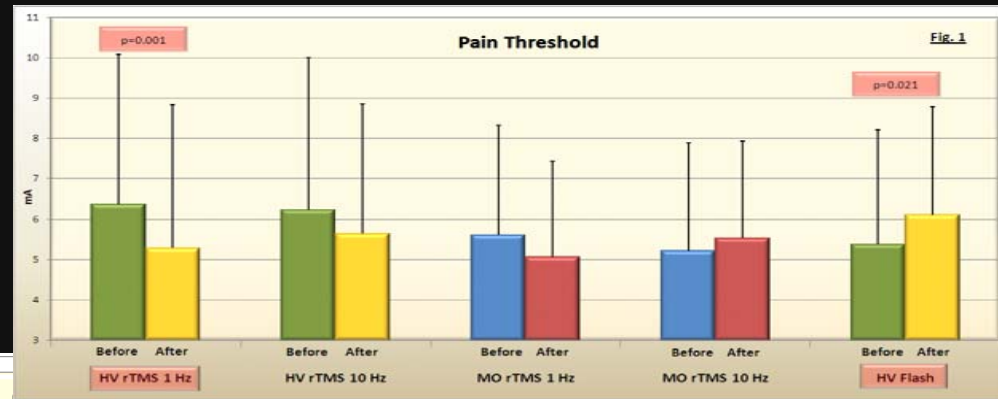
nsBR
Treatment mode of action
Example of neurostimulation in chronic cluster headache

→ R2 AUC increases with DBS and ONS durations

(Schoenen et al. 2005, Magis et al. 2007)

• Suggests long-lasting plastic changes in trigeminal nucleus caudalis
• Argues against a direct analgesic effect

nsBR
Interests and limitations

(+)

- simple way to explore trigeminal nociceptive

system at brainstem level

- replicable at different time points
- correlation studies
- parameters homogeneity of available studies
- concentric electrode: alternative to laser ?

(-)

- habituation definition varies: blocks vs. single sweeps

- custom-built electrodes (!!Anode width)

- pain threshold: a subjective component

Electrophysiology in headaches
Conclusions

Interests

- Easy access, relatively low cost
- Directly reflects what happens in the CNS
- Many applications in headaches except diagnosis
  - Pathophysiology – correlation studies
  - Treatments' mode of action
  - Follow-up studies
  - Can be combined together or with other investigation techniques

Electrophysiology in headaches Conclusions (2)

Limitations

- Need for standardized research protocols
- Lack of reproducibility data
- High artefact sensibility, some protocols may be laborious for the patient and the investigator
- Headache heterogeneity under a same clinical presentation could explain discordance between studies
- Insufficient blindness could influence results (cursors position) → anonymization?

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