Mapping pain-related EEG perturbation in high frequency range in migraine and non-migraine subjects

Marina de Tommaso, Iege Bassez, Katia Ricci, Marianna Delussi, Daniele Marinazzo
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.
Migraine attack

1. ↓ Mitochondrial ATP
2. Hyperresponsivity of sensory cortices
   - Deficient habituation of evoked potentials
   - Impaired EEG synchronization and connectivity
3. Thalamocortical dysrhythmia
4. Central sensitizing of pain processing
   - Potentials evoked by noxious stimuli
   - Nociceptive reflexes
   - Temporal summation of nociceptive withdrawal reflex
5. Limbic system
   - Amygdala, hypothalamus
   - Upper brain stem
   - PAG, monoaminergic nuclei
6. Metabolic strain
7. Cortical spreading depression
8. Amplifies and persists in chronic migraine

Aura

Trigeminovascular system

Headache
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,
  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.

(Browne and Thompson, 1973)
MIGRAINE IS AN “OSCILLOPATHY”

Abnormal synchronization of alpha rhythm during intermittent light stimulation.
**MIGRAINE IS AN “OSCILLOPATHY”**

**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** | HF0s and somatosensory evoked potentials. In healthy controls (panel 1), the N20–P25 component habituates, and early HF0s (reflecting thalamocortical drive) are greater than late HF0s (generated by intrinsic cortical activation). In patients with migraine between attacks (panel 2), habituation is absent and early HF0s are reduced, although late HF0s are normal. During a migraine attack (panel 3), habituation and early HF0s normalize. After 10Hz 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 HF0s increase. Abbreviations: HFO, high-frequency oscillation; HF-rTMS, high-frequency repetitive transcranial magnetic stimulation.
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

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

Lyudmila V Vinogradova
The real problem in clinical setting is to prevent chronic migraine.

Two main aspects of migraine:
1. Mechanisms predisposing to chronic evolution

Central sensitization may play a key role in many pathologic pain conditions.
ALLODYNA IS A SIGN OF CENTRAL SENSITIZATION
Fig 2.—Sensitization of central trigeminovascular neurons in nucleus caudalis mediates cutaneous allodynia. Adapted with permission.\textsuperscript{19}
Sensibilizzazione centrale

dopo attivazione intensa

afferente dolorifico primario
ganglio
neurone dolorifico midollare

Membrana presinaptica
Rec. NMDA depolarizzato
Rec. AMPA

Membrana postsinaptica

Ca²⁺

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

Changes in cingulate activation in chronic migraine

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.
LEPs are not a correlate of subjective pain sensation.....

3.3 Aim 3

In the entire group of healthy subjects, neither pain rating and threshold nor N2-P2 amplitude and habituation showed significant correlations at either the trigeminal or hand levels. The lack of significant correlations among these variables was also confirmed in the single age groups.
REDUCED HABITUATION TO REPETITIVE LASER STIMULATION: A SIGNATURE OF MIGRAINE AND CENTRAL SENSITIZATION PHENOMENA PREDISPOSITION

Valeriani et al., 2003

....but they could reflect a modality of pain processing
Reduced habituation of LEPs is present in childhood migraine and it is correlated with symptoms of central sensitization (allodynia).
Reduced habituation of LEPs is common among central sensitization syndromes.

Valeriani et al. 2003

Migraine

N2 habituation

0 2 4 6 8 10 12 14
I° II° III° I° II° III° I° II° III°

Face hand knee

Irritable bowel syndrome (de Tommaso et al., in preparation)

Central Sensitization may Play a key Role in Many Pathologic Pain Conditions

de Tommaso et al. 2011

Fibromyalgia

Chronic fatigue syndrome

IBS

T-T headache

CSS

Primary dysmenorrhea

PTSD

IC

MC S

PLMS

Restless legs syndrome

MPS

TMD

Vunnus, MB. Sem Arthritis Rheum 2007;56(6):1389-146. CSS = central sensitization syndromes; IBS = irritable bowel syndrome; ICD = International classification; MCS = multiple chemical sensitivity; MPS = myofascial pain syndrome; PLMS = periodic limb movements in sleep; PTSD = posttraumatic stress disorder; TMD = temporomandibular disorder; T-T headache = tension-type headache.
REDUCED HABITUATION OF LEPS COULD IMPROVE THE KNOWLEDGE OF TREATMENT MECHANISM AND RESPONSE
Effects of external trigeminal nerve stimulation (eTNS) on laser evoked cortical potentials (LEP): A pilot study in migraine patients and controls

Eleonora Vecchio, Eleonora Gentile, Giovanni Franco, Katia Ricci and Marina de Tommaso
IF LEPs ARE NOT A SIGNATURE OF SUBJECTIVE PAIN………..

- COULD WE IMPROVE THE STUDY OF NOCICEPTIVE SYSTEM IN MIGRAINE USING LASER STIMULI?
Gamma Band Oscillations (GBOs) could reflect subjective pain rating, rather than stimulus salience.
They are not specific for pain (!), but they could reflect some aspects of cortical response to phasic noxious stimuli.
High-frequency brain activity and muscle artifacts in MEG/EEG: a review and recommendations

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CUBRIC, School of Psychology, Cardiff University, Cardiff, UK

GBO ➔ SOMATOSENSORY AREAS ➔ MUSCLE ARTIFACTS ➔ TEMPORAL REGIONS!!!
STUDY DESIGN

- LEPs 61 electrodes + 2 EOG
- Participants: 39 controls, 64 migraine patients
- Right forehead condition: 21 laser stimulations
  ISI 10 seconds → VAS (1-100)
- Right hand-back condition: 21 laser stimulations
  ISI 10 seconds → VAS (1-100)
Evaluation of gamma-band activity after painful laser stimuli in patients with migraine and healthy controls

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Automatic preprocessing pipeline in Matlab using EEGLAB and plug-in functions:

- **High-pass filter** the data at 1-Hz (for ICA, ASR)
- Remove line noise & artifacts using **NOTCH filter** (48-52 Hz and 98-102 Hz & 63-66 Hz, 73-77 Hz, 104-108 Hz)
- Reject bad channels and correct continuous data using **Artifact Subspace Reconstruction (ASR)** (clean_rawdata())
- Interpolate all the removed channels
- Re-reference the data to average
- EPOCH -3s to 2s to laser onset.
- Run ICA & **Remove artifactual ICs** with Multiple Artifact Rejection Algorithm → artifactual prob to be removed = 0.9
- If subjects has more than 15 trials → only keep the first 15 clean trials
Time-Frequency Analysis

pipeline 1: without Laplacian, Morlet wavelet (MW)
pipeline 2: with Laplacian, Morlet wavelet (MW-Lap)
pipeline 3: without Laplacian, Multitaper (MT)
pipeline 4: with Laplacian, Multitaper (MT-Lap)

For all pipelines, for every subject:
- mean over trials
- dB change from baseline
  Baseline: -2s to -1 s
- Average dB change between 70-90 Hz (gamma-band activity)

Details:
- Complex Morlet wavelets: min = 2 Hz, max = 100 Hz, 1 Hz freq. resol., 4 cycles for 2 Hz, 14 cycles for 100 Hz, 10ms temp. resol.
- Multitaper: 5.13 Hz freq. resol., number of tapers = 3, window = 200 ms, 10 ms temp. resol.

Statistical Analysis

Significant GBO separately in each group:
- H0: dB change = 0, Nonparametric permutation one-sample t-tests, Max T correction for multiple testing (nr of tests: 61 electrodes x 131 time-frames)

Association GBO [70-90 Hz, 150-350 ms (Schenal et al. 2011)] and subjective pain [VAS]:
- Correlational analysis with permutation, max correlation coefficient to correct for multiple testing (nr of tests: 61 electrodes)

Comparison MIGR-CONTR:
- Nonparametric ANCOVAs (group, gender & age) with bootstrapping and max stat correction for multiple testing (nr of tests: 61 electrodes x 131 time-frames)

Scatter plots to visualize possible associations GBO and clinical features
MIGRAINE-RIGHT HAND

N2 P2
GBO increase

```matlab
>> find(GBO_index > 0.05)
ans =    20    21    27
        61    63
```

Oz, O2, PO4, PO7

No temporal activity!
GBO decrease

>> find(GBO_index < -0.1)
ans = 30 47 51
CP5, C5, TP7
GBO: summary

RELIABLE TOPOGRAPHIC DISTRIBUTION (no temporal activity)

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<thead>
<tr>
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<th>Control</th>
<th>Migraine</th>
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<td><strong>Right forehead</strong></td>
<td><img src="image1" alt="Control" /></td>
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<tr>
<td><strong>Right hand</strong></td>
<td><img src="image3" alt="Control" /></td>
<td><img src="image4" alt="Migraine" /></td>
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A difficult comparison, as the GBO did not seem to be equally time locked to laser stimuli. Nevertheless, migraine patients showed higher GBO power over the central parietal regions.

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the laplacian method, reduces the significance of GBO change after laser stimuli. Relevant perturbation on fronto-central regions on the midline in migraine
In non migraine subjects, the GBO perturbation seems reduced with all methods.
Similar but attenuated pattern of GBO activation under hand stimulation in migraine
Similar of GBO activation under hand stimulation in controls
Forehead laser stimulation

- No significant differences between patients with migraine and healthy controls
Right hand laser stimulation

- No significant differences between patients with migraine and healthy controls
TECHNICAL CONSIDERATIONS

- THE GBO PERTURBATION SEEMS TO HAVE A SPATIAL DISTRIBUTION COHERENT WITH A CORTICAL NOT MUSCULAR SOURCE
- THE REDUCTION WITH LAPLACIAN FILTER COULD BE ATTRIBUTED TO A DEEP AND SPATIAL DISTRIBUTED GENERATORS
CLINICAL CONSIDERATION

- Lack of statistical significance between migraine patients and controls
- (Inclusion of chronic migraine?)
- The GBO are increased in migraine in respect to controls, but not in a relevant modality
- Clinical correlations?
ARE GBO A CORRELATE OF SUBJECTIVE PAIN INTENSITY

CONTROLS: YES

RIGHT FOREHEAD
thresholded corr GBO and VAS for HAND Control (MT)
ARE GBO A CORRELATE OF SUBJECTIVE PAIN INTENSITY

MIGRAINE: NO
IN MIGRAINE, GBO PERTURBATION BY HAND STIMULATION IS A CORRELATE OF ANXIETY, DEPRESSION and ALLODYNIA, BUT NOT OF ATTACK FREQUENCY.
IN MIGRAINE, GBO PERTURBATION BY FOREHEAD STIMULATION ARE IS A CORRELATE OF PAIN CATASTROPHIZING
THE DEFINITION THAT GBO REFLECTS PAIN PERCEPTION IS SEMPLICISTIC, AT LEAST IN PAIN SYNDROMES

THE DEFINITION THAT GBO REFLECTS THE ACTIVITY OF CORTICAL REGIONS SUBTENDING COGNITIVE ASPECTS OF PAIN SOUNDS GOOD IN LIGHT OF PRESENT RESULTS
THE METHODOLOGICAL APPROACH WITH MULTITAPER NOT LAPLACIAN FILTER SEEMS RELIABLE TO DETECT GBO PERTURBATION
IN MIGRAINE, CORTICAL GENERATORS OF GBO MAY BE INVOLVED IN MECHANISMS OF CENTRAL SENSITIZATION, AS SUGGESTED BY THE CORRELATION BETWEEN GBO PERTURBATION AND ANXIETY, DEPRESSION AND ALLODYNIA.

THIS WOULD BE AN INTRINSIC PATTERN OF ALLODYNIC MIGRAINE, POSSIBLY PREDISPOSING TO CHRONIC EVOLUTION (no correlation with migraine duration and attacks frequency).
Patients with more severe allodynia could respond with a different pattern of GBO perturbation under extra-cephalic stimulation.

Different thalamo-cortical inference evoked by yje extracephalic stimulation.
WHY THE CORRELATION BETWEEN TRIGEMINAL GBO AND PAIN CATASTROPHIZING?

Pain catastrophizing is a factor correlated to central sensitization.
LASER INDUCED GBOs IN MIGRAINE ARE A RELIABLE MEASURE OF ASPECTS OF PAIN PROCESSING

THEY ARE NOT A SIMPLE CORRELATE OF LASER PAIN PERCEPTION

THEY COULD EXPLAIN SOMETHING MORE ABOUT ELECTROPHYSIOLOGICAL CORRELATES OF CENTRAL SENSITIZATION AND FACILITATING FACTORS
NEXT METHODOLOGICAL APPROACH: DISTRIBUTED SOURCE ANALYSIS

CORTICAL CONNECTIVITY PATTERN

POSSIBLE APPLICATION: EFFECTS OF DRUGS

AMG 334 CGRP antibody for migraine: time to celebrate?