CON IL PATROCINIO DI
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SOCIETÀ ITALIANA DI NEUROLOGIA

UNIVERSITÀ
DEGLI STUDI DI BARI
ALDO MORO

Modulazione dell'eccitabilità corticale nel trattamento dell'emicrania con nuove terapie

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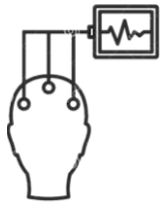

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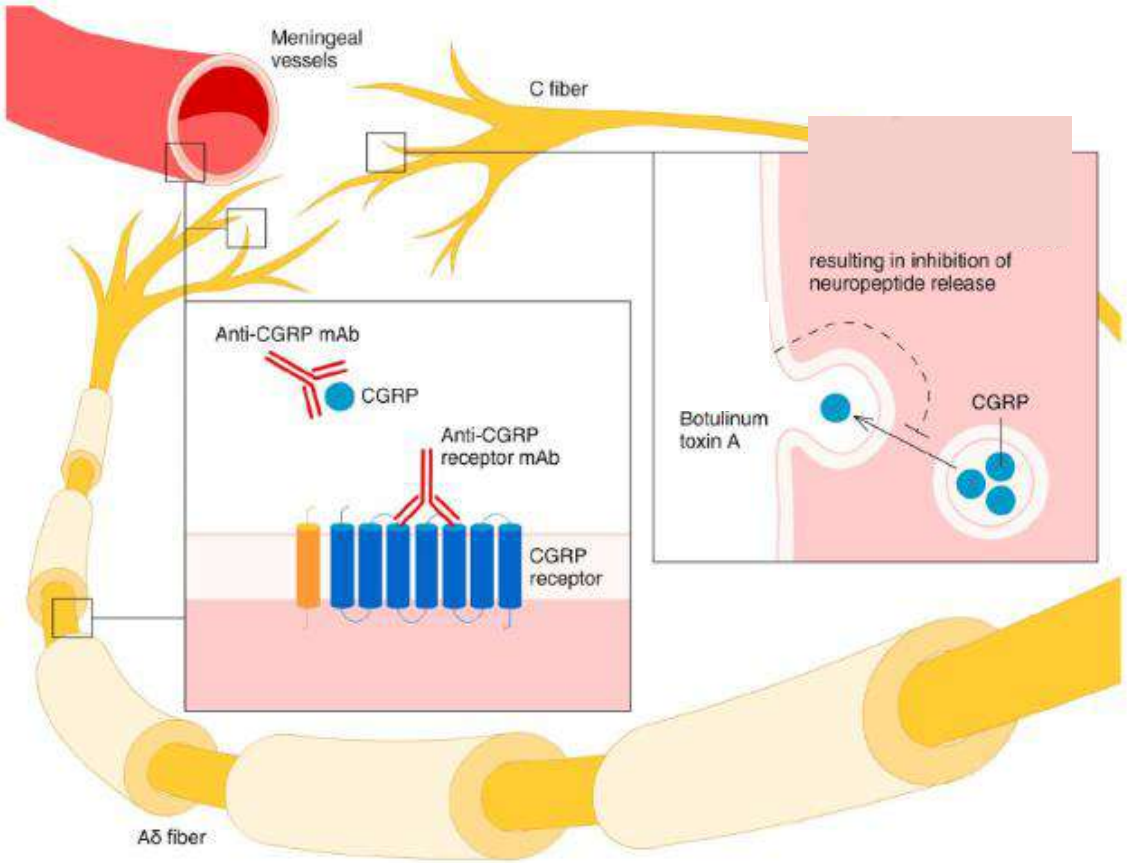
Introduction

The identification of Calcitonin Gene-Related Peptide (CGRP) as a possible target for migraine treatment has revolutionized the therapeutic scenario.

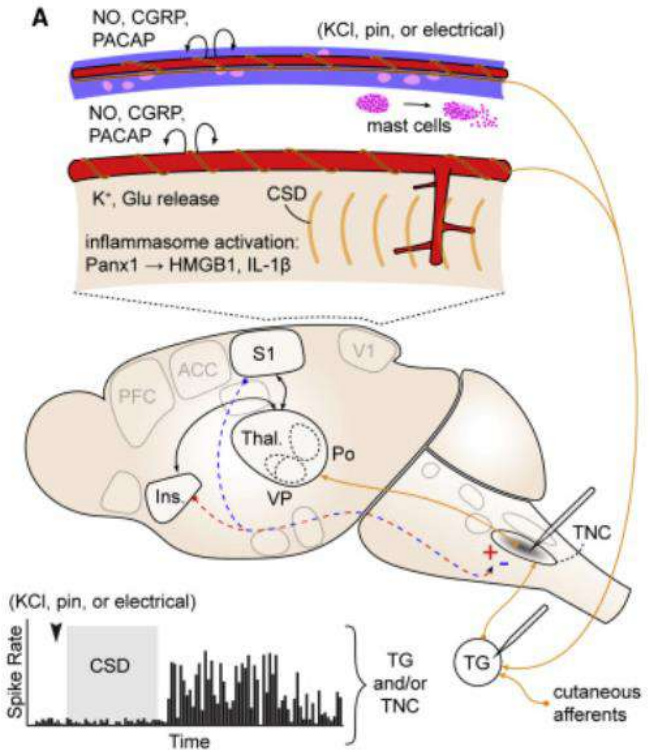


To date, all new therapies directed against CGRP or its receptor for the treatment of migraine have produced positive results.

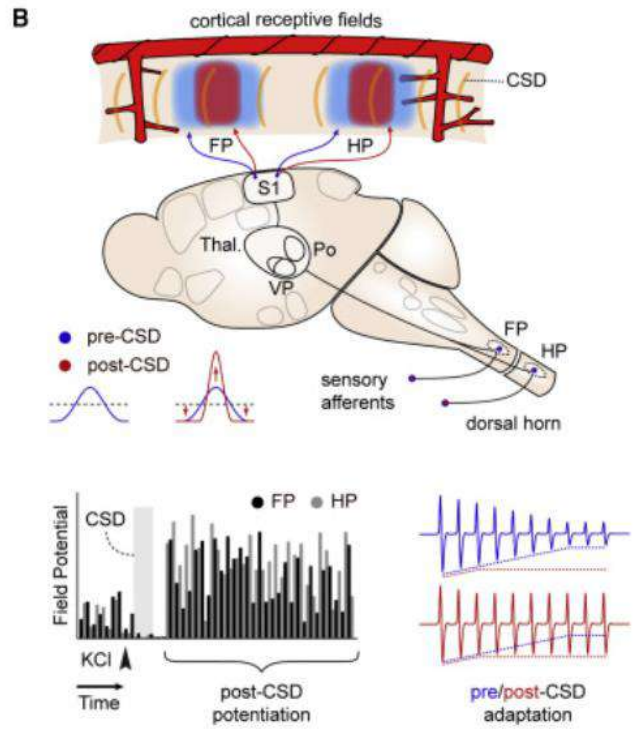
CGRP receptor antagonists (such as Erenumab) and monoclonal antibodies (such as Galcanezumab or GCA) have been shown to be effective in relieving migraine pain and reducing the frequency of attacks, supporting the hypothesis that CGRP plays an important role in the pathophysiology of migraine.

Introduction

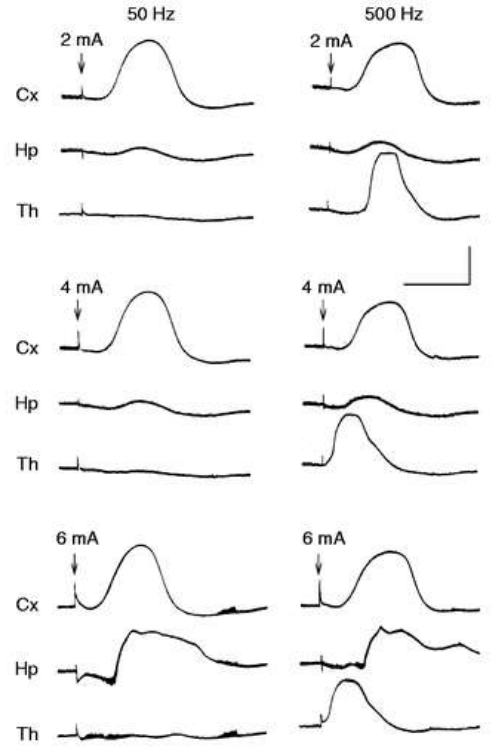
POSSIBLE MECHANISMS UNDERLYING CORTICAL SPREADING DEPRESSION (CSD): the role of occipital cortex in CSD generation, in C fiber activation and CGRP production



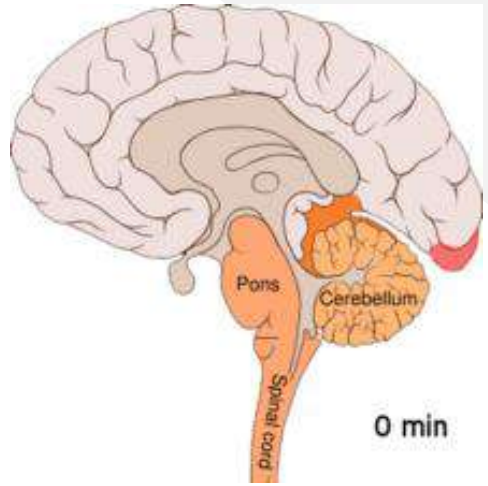
Spontaneous firing rate of trigeminal ganglion (TG) and trigeminal nucleus caudalis (TNC) neurons increases after experimentally induced CSD



CSD alters cortical sensory mapping



Initiation of CSD in the cortex (Cx), thalamus (Th) and hippocampus (Hp)



Animation of the propagation of the electrophysiological hyperactivity wave due to the CSD

A Systems Neuroscience Approach to Migraine

(K.C. Brennan and d. Pietrobon, Neuron, 2018)

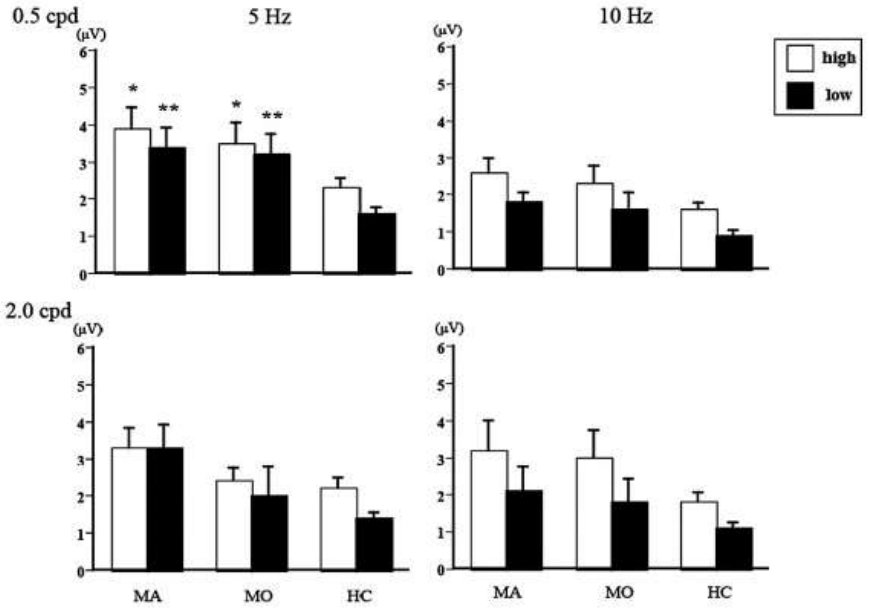
Initiation of CSD by synaptic and network hyperactivity: Insights into trigger mechanisms of migraine aura

(L. V. Vinogradova, Cephalgia, 2017)

Introduction

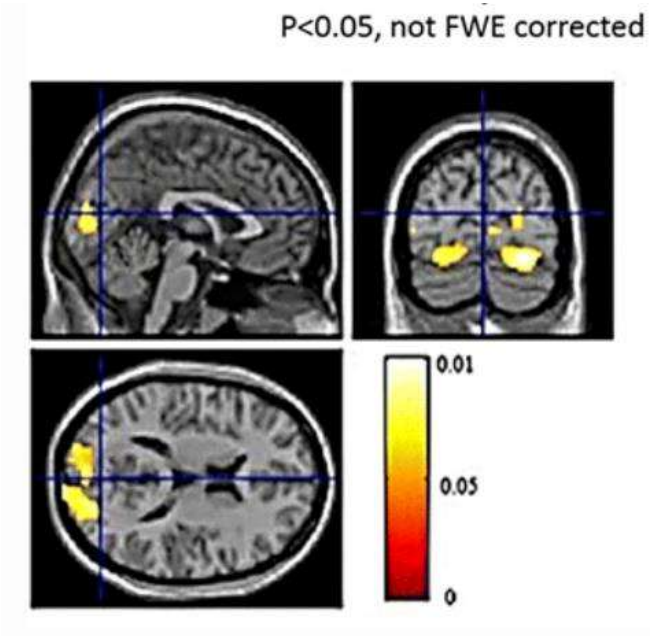
OCCIPITAL CORTEX IS A CRUCIAL SITE IN MIGRAINE: Increased amplitude of steady state visual evoked potentials, increased metabolic response and altered connectivity of occipital cortex were found

Abnormal visual processing in migraine with aura: A study of steady-state visual evoked potentials

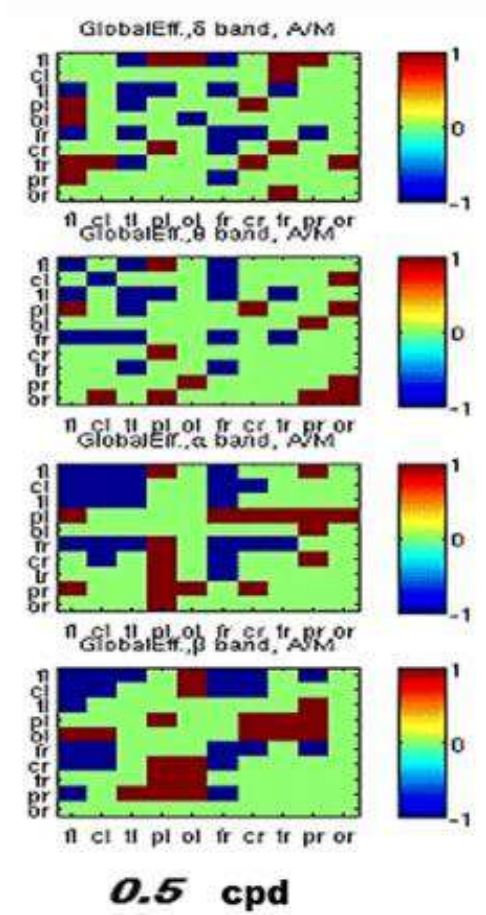


The mean amplitude at 5 and 10 Hz for 0.5 and 2.0 cpd and two different contrasts in migraine with aura (MA), without aura (MO) and healthy controls (HC)

(K. Shibita et al., Journal of the Neurological Sciences, 2008)



Statistical probability maps reporting the comparison of bold signal changes in migraine with aura vs migraine without aura



Comparison of global efficiency in migraine with aura vs migraine without aura

Brain networking analysis in migraine with and without aura

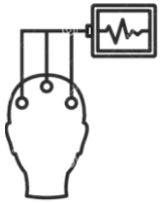
(M. De Tommaso et al., The Journal of Headache and Pain, 2017)

Introduction

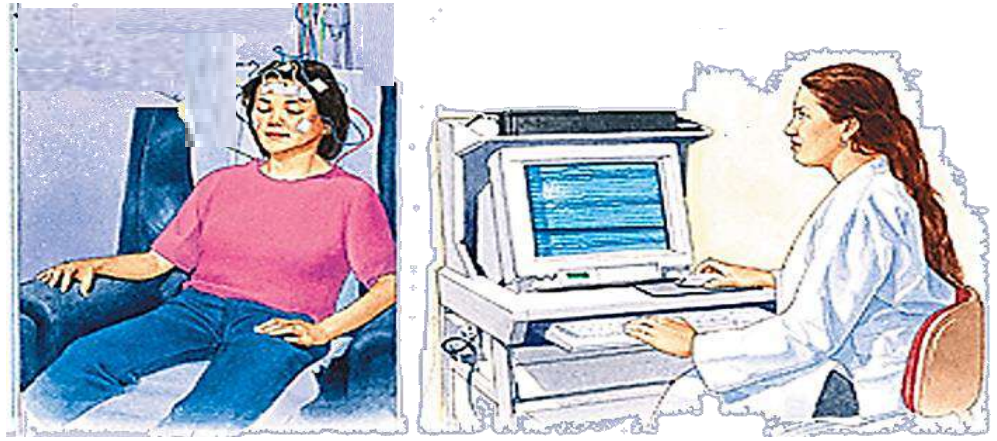
CGRP antagonists act at peripheral level. How could they modify occipital cortex excitability in migraine?

In this study, our goal has been to test the effect of 3 months GCA therapy on migraine patients by evaluating cerebral electrical (Steady State Visual Evoked Potentials -SSVEPs) and hemodynamic activities (functional near infrared spectroscopy, fNIRS) during checkerboard pattern-reversal stimulation at 5 Hz with spatial frequency of 0.5 cycle per degree.

Signal acquisition



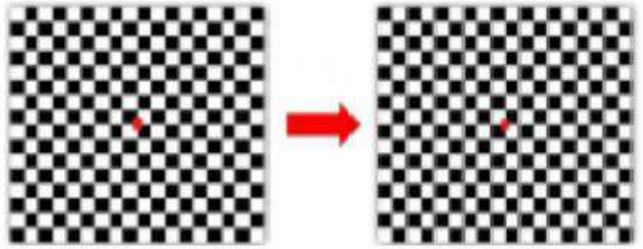
10 healthy volunteers and 13 drug patients were selected at the Headache Center of Applied Neurophysiology and Pain Unit of Bari Policlinico General Hospital from December 2020 to April 2021 during the routine clinical practice



Migraine patients underwent clinical and neurophysiological examination in basal condition (T0) , 1 hour after GCA injection (T1) and after 3 months of GCA treatment (T2). Controls were examined once.

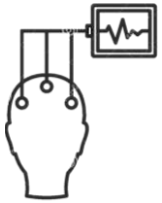
Patients received 240 mg of GCA the first time and then 120 mg monthly.

Checkboard pattern stimulations of 60s preceded by 60 s of resting state were performed for each patient and for each condition.



At the time of the study inclusion, patients were having 8 days or more with migraine / month in the last 3 months, were assuming symptomatic drugs for more than 10 days/month and were experiencing resistance to at least three preventive drugs.

Signal acquisition



	GENDER	AGE	DURATION	DIAGNOSIS	DRUGS	T0	DAYS/30	SIM/30	MIDAS	NRS	T2	DAYS/30	SIM/30	MIDAS	NRS
AI	F	29	20	MA	AED, AD, BB		13	13	79	10		17	16	113	10
BA	F	48	30	MA	AED, AD, BB,TB		12	12	26	7		8	8	12	4
DD	F	38	22	MA	AED,AD,CA		9	9	68	10		4	4	34	10
DE	F	47	25	CM	AED,AD,CA,TB		17	17	150	9		17	10	70	6
DI	F	48	25	MA	AED,AD,CA,BB		13	13	26	7		10	10	13	6
DL	F	47	24	MA	AED,AD		8	12	32	10		3	3	10	6
FA	F	57	40	CM	AED,AD,CA,TB		20	20	75	7		4	4	12	8
LE	F	42	30	CM	AED,AD,CA,BB,TB		27	27	30	8		6	6	10	6
MA	F	67	50	CM	AED,AD,CA,BB,TB		15	4	50	8		15	3	25	5
MO	F	47	30	CM	AED,AD,TB		25	25	56	8		12	10	25	7
MN	F	63	45	MA	AED,AD,CA,BB		10	12	5	6		5	0	0	4
PN	F	58	10	MA	AED,BB,AD		13	13	77	7		8	8	33	7
SM	M	56	30	CM	AED,BB,AD		15	15	108	10		5	5	50	8
Mean(SD)							15.5(8.7)	14.7(6.2)	60.1(39.2)	8.2(1.4)		8.7(5)	6.6(4.2)	31.3(31)	6.6(2)
T test							3.3	4.3	3.59	3.68					
p							0.006	0.001	0.004	0.003					

DAYS/30: average over 3 months of the number of headache days per month.

SIM/30: average over 3 month of the number of days per month with acute therapy

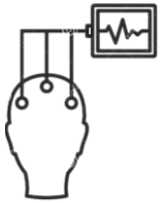
MIDAS: Migraine Disability Assessment, questionnaire measuring headache impact on patient's life.

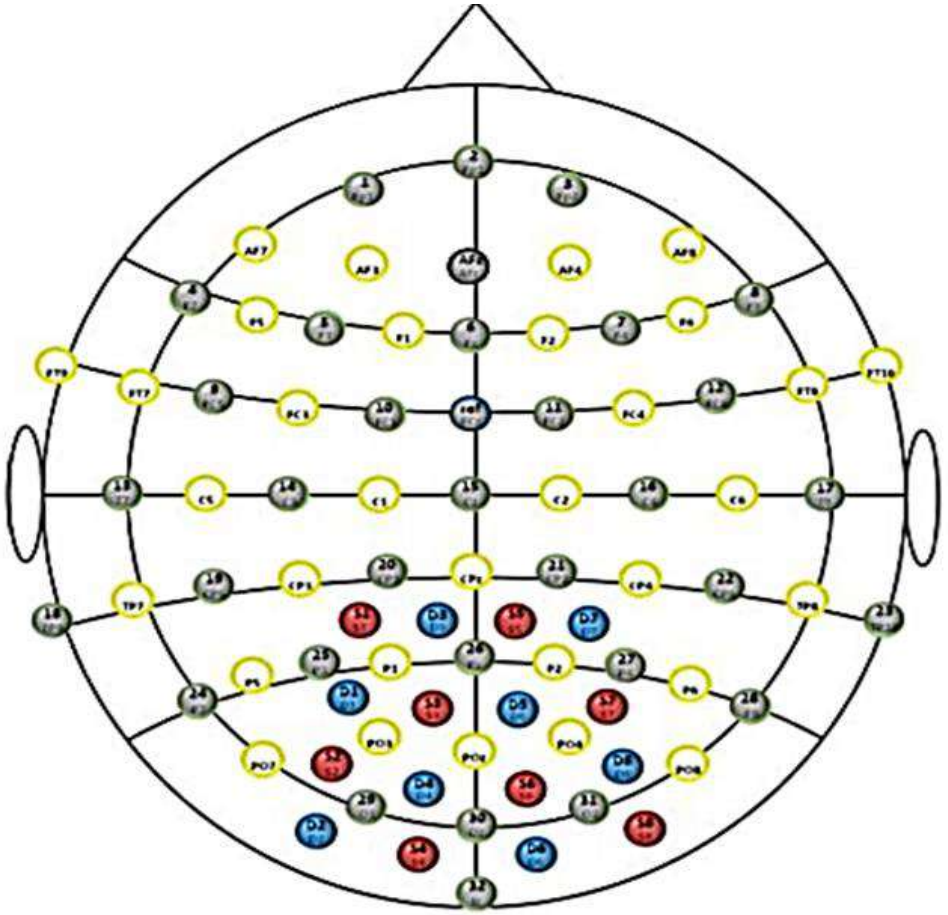
NRS: Numerical Rating Scale (from 0 no pain to 10 maximal pain) describing headache intensity.

AED: antiepileptics-topiramate and/or valproate
AD: antidepressants-amitriptyline
BB: beta blockers-propranolol or atenolol
CA: calcium channel blockers-flunarizine;
TB: Botulin Toxin

MA: episodic migraine without aura
CM: Chronic Migraine

Signal acquisition





EEG data were acquired simultaneously with fNIRS data, using a co-recording cap and a black over-cap to mitigate possible interferences generated by ambient light on the fNIRS acquisition.

EEG data were recorded by 62 scalp electrodes, according to the enlarged 10–20 system (nasion as reference and Fpz as ground). Electrooculogram (EOG) was recorded, and EEG sampling rate was 256 Hz

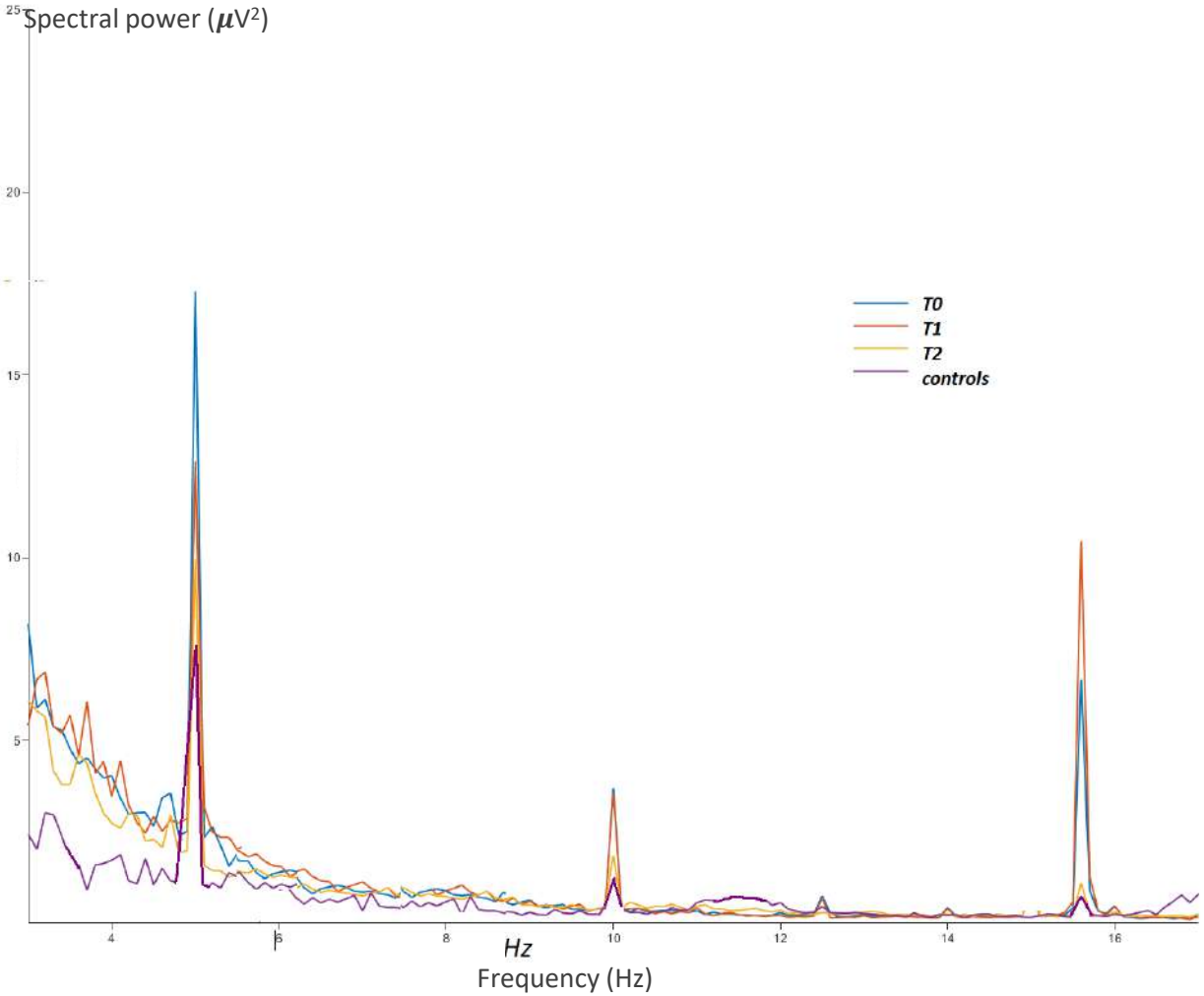
fNIRS data were recorded by 24 channels given by the arrangement of 8 sensors and 8 detectors. An inter-optode distance of 30 mm and a sampling rate of 7.8 Hz were used.

Each fNIRS recording was preceded by a calibration procedure to verify that signal amplification was in the range of 0.4 to 4.0 V that is considered an optimal range for the modulated raw signal level.

Statistical Analysis

EEG analysis

The spectral power of fundamental frequency (F) at 5 Hz, double frequency (2F) at 10 Hz and triple frequency at 15 Hz was averaged over the channels O1, O2 and Oz.



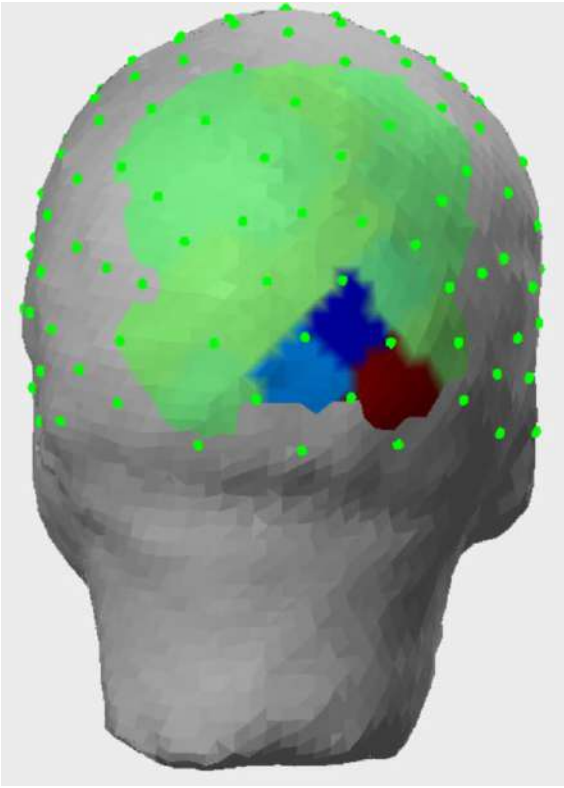
We performed an ANOVA test with Bonferroni correction to evaluate statistical differences in the spectral power computed among T0, T1, T2 and controls

Finally, We carried out a topographical analysis at F, 2F and 3F powers for the different conditions.

Statistical Analysis

fNIRS analysis

To compute the degree of hemodynamic activation of each channel compared with the baseline, we used a Generalized linear model (GLM), choosing the Hemodynamic Response Function (HRF) to model the response during the visual stimulation.



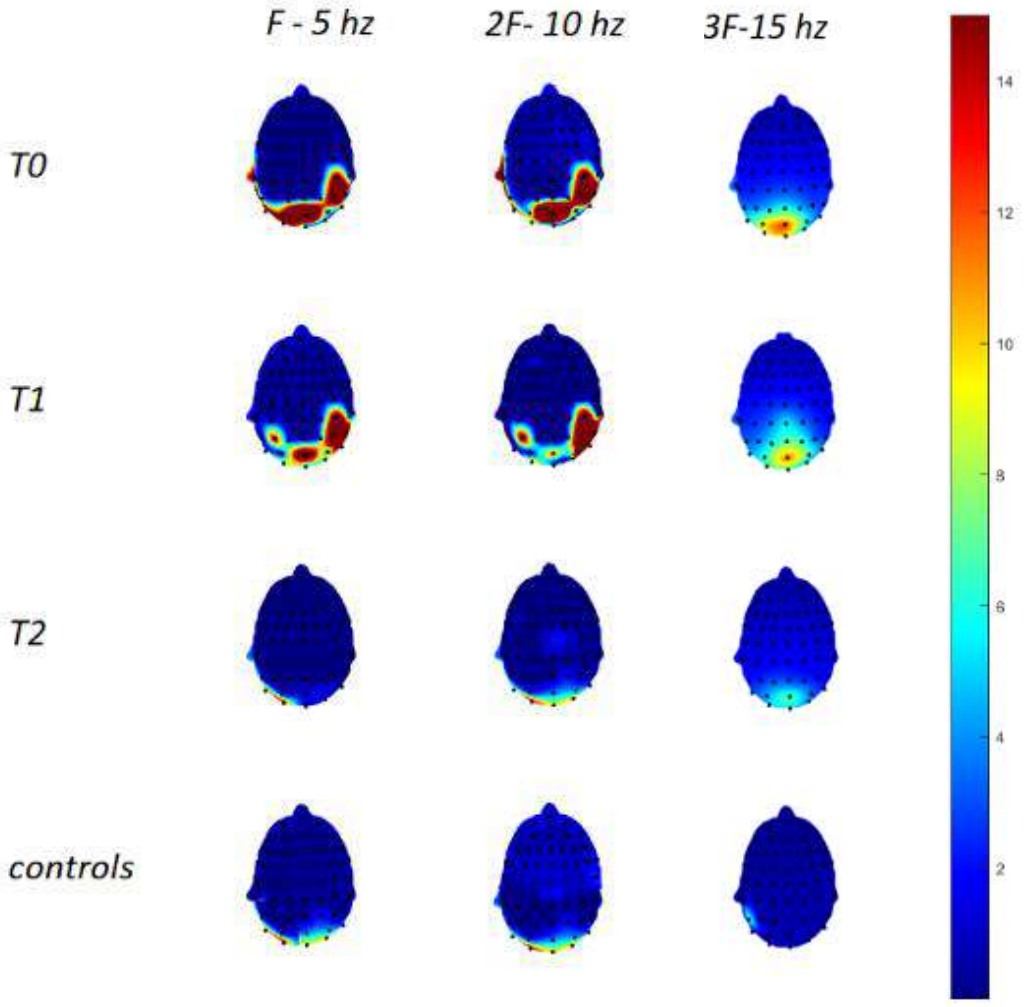
the results obtained from the GLM were used to evaluate, using the Student's t test, if there were fNIRS channels wherein oxy and deoxyhemoglobin changed in a statistically significant way (p-value < 0.05 corrected for multiple comparison) for the comparisons: T0 vs T2, T1 vs T2, Controls vs T2, Controls vs T0.

For both EEG and fNIRS data, we evaluated if there was association between neurophysiological changes (electrical and metabolic changes) and clinical data such as the migraine frequency reduction.

Results

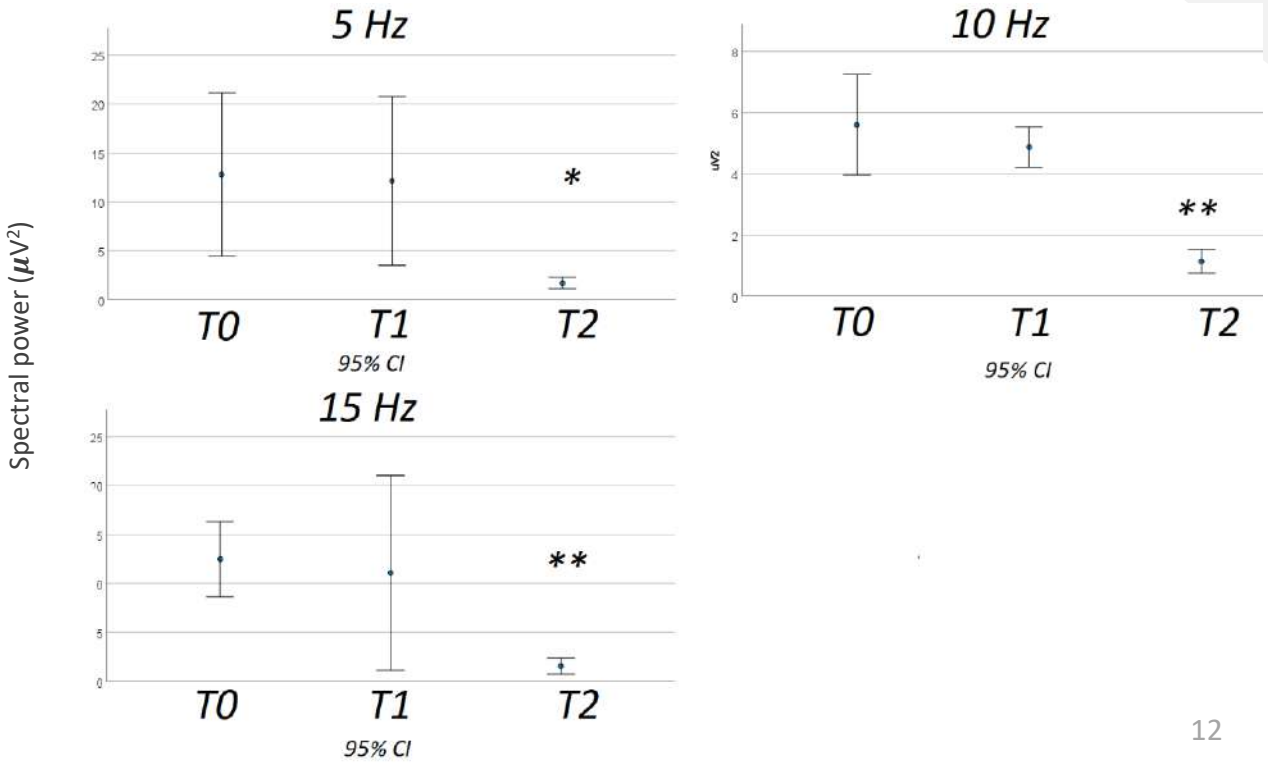
EEG results

(M. De Tommaso, M. La Rocca et al., The Journal of Headache and Pain, 2022)



We can observe a significant reduction of the spectral power at T2, as compared to T0 and T1 conditions for all the 3 frequencies (* p<0.05; ** p<0.01).

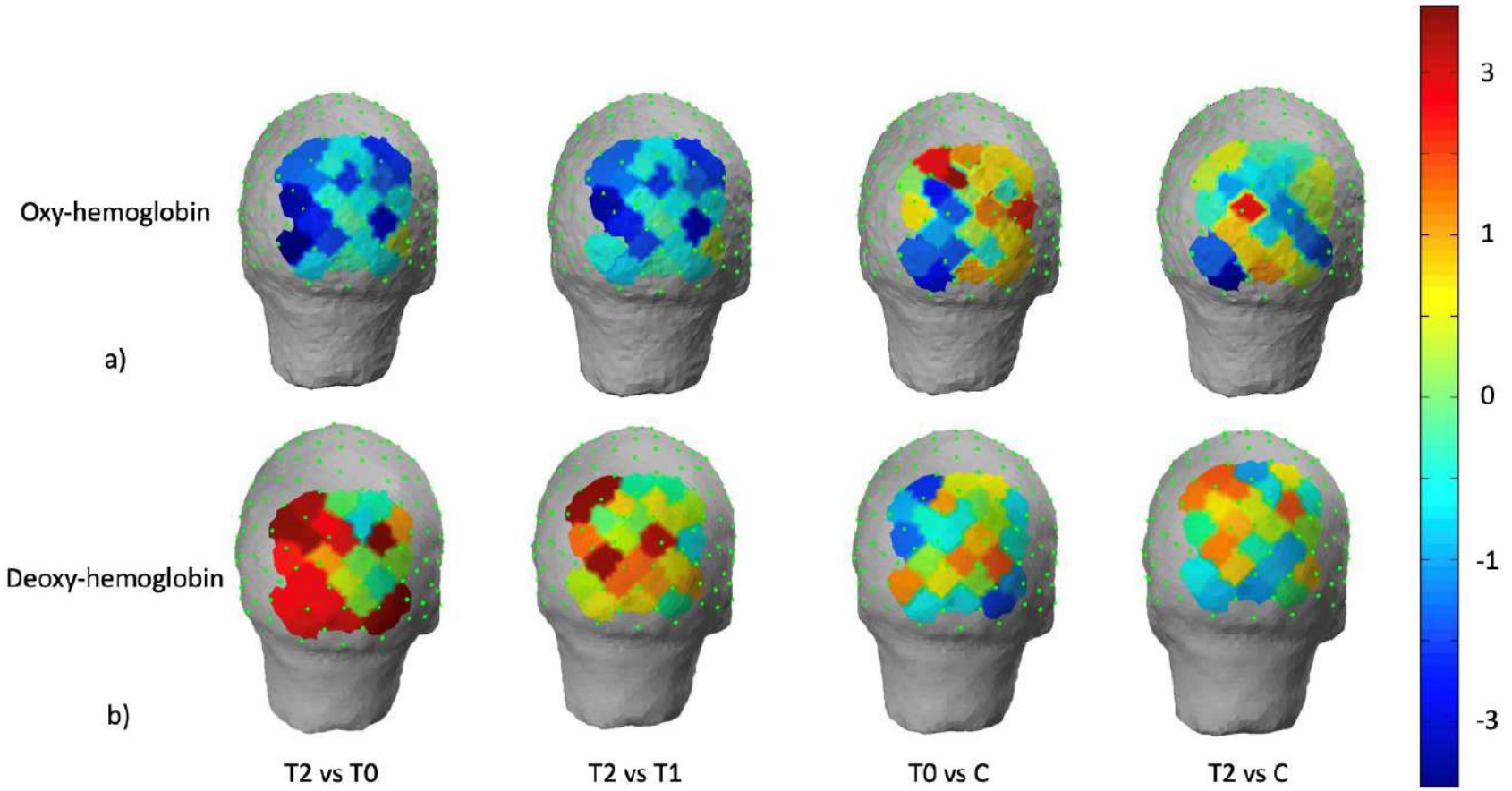
The spectral power was significantly lower also in controls compared with migraine patients at T0 and T1



Results

fNIRS results

(M. De Tommaso, M. La Rocca et al., The Journal of Headache and Pain, 2022)



T-statistic map of the brain regions wherein the significant increases and decreases in deoxy and oxyhemoglobin concentrations are indicated in intense red and in intense blue, respectively.

The paired Student's t test showed a general reduction of the oxyhemoglobin concentration at T2 compared with T0 and T1 , with significance ($p<0.05$) and a general increase in deoxyhemoglobin at T2 on different occipital channels.

For both EEG and fNIRS data, we did not observe significant association between clinical data and the neurophysiological changes.

Connectivity study

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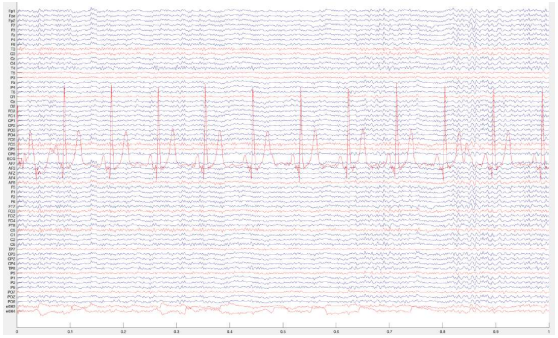
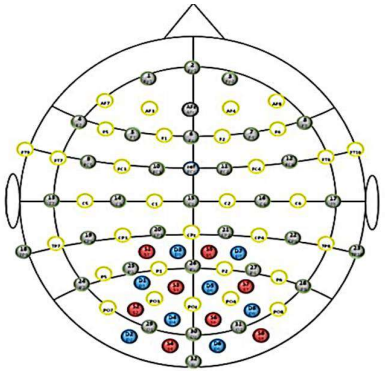
EEG analysis pipeline

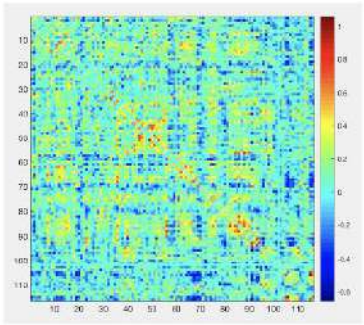
Processed EEG signal

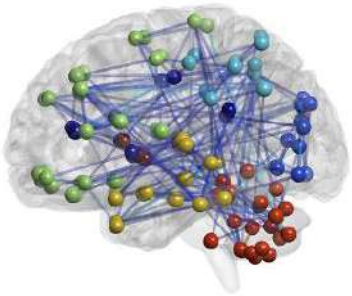


EEG electrodes to define network nodes

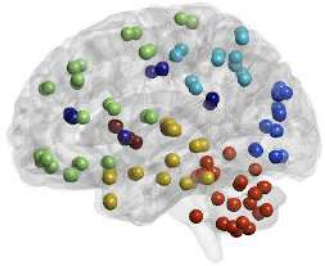


magnitude squared coherence was used to define network links





Network metrics:
Strength
Global Efficency
Clustering Coefficient

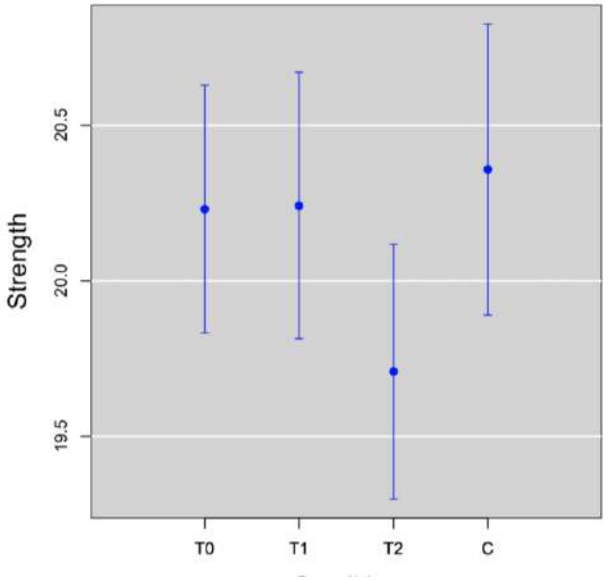


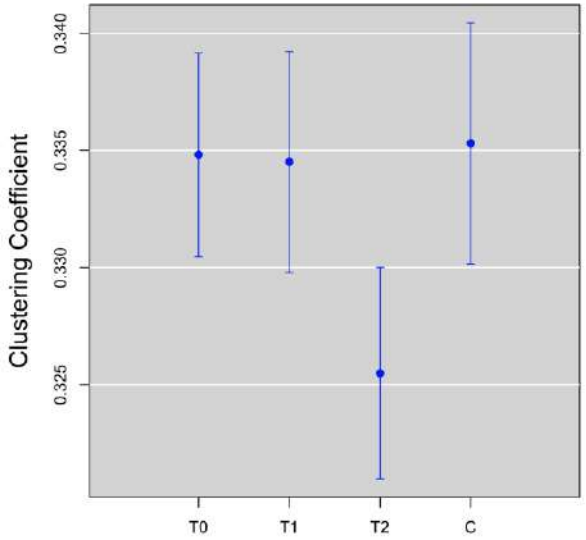
For each EEG frequency band (delta, theta, alpha, beta), we built a weighted network

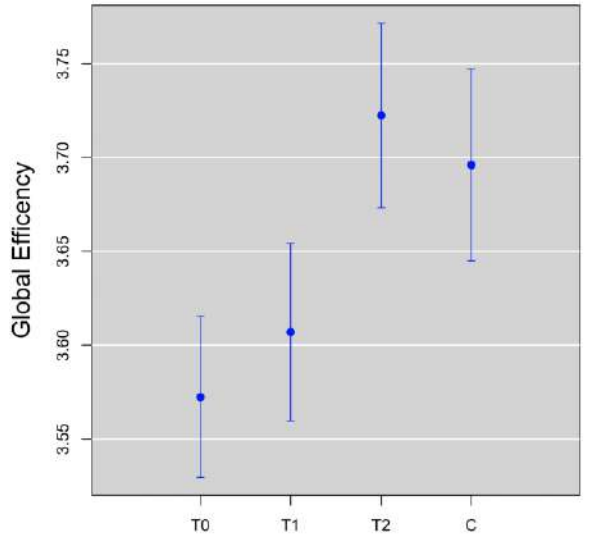
Migraine case study

EEG connectivity

Theta band (4-7 Hz)

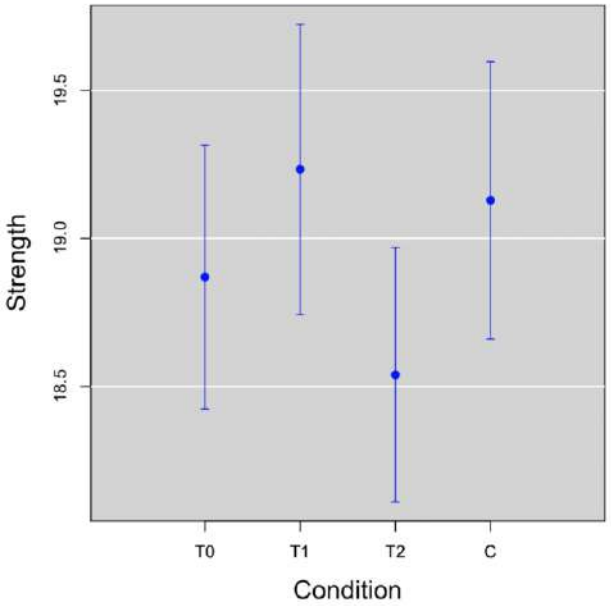


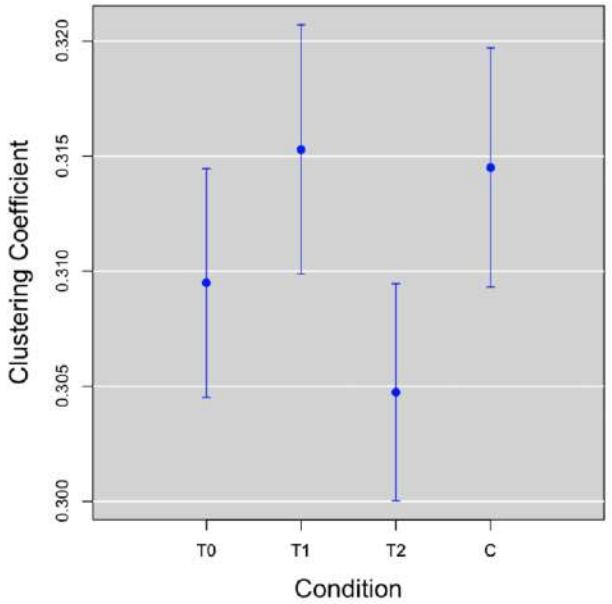


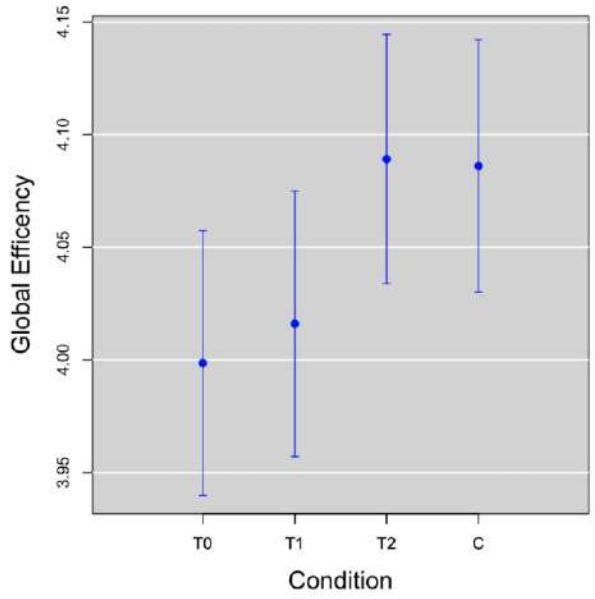


For both bands, GCA has the effect to increase network integration and decrease node coeherence and network segregation.

Alpha band (8-12 Hz)





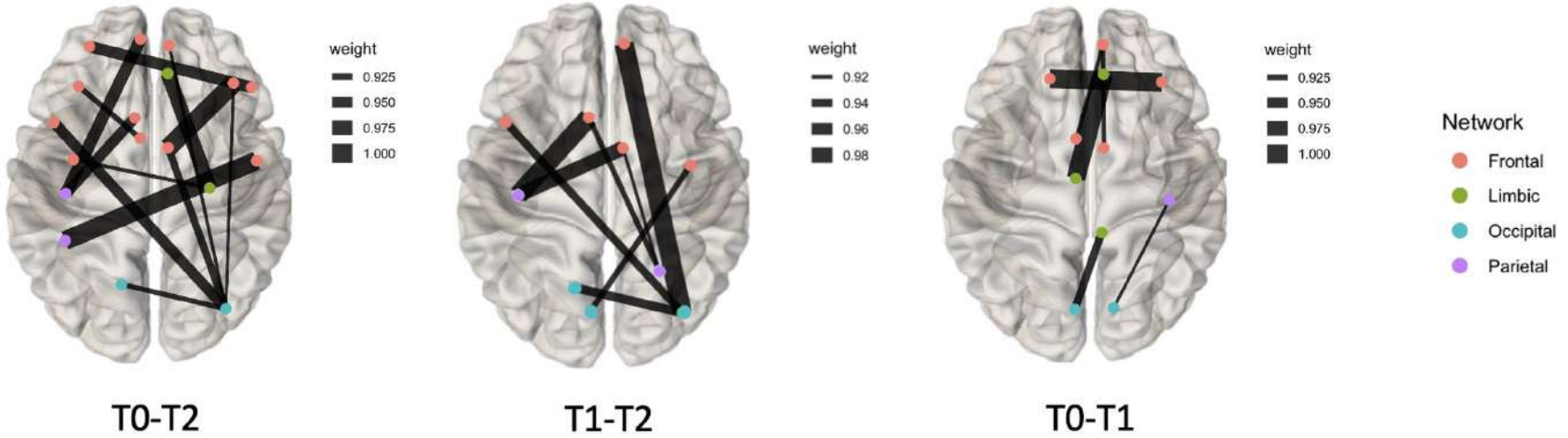


The beneficial effect seems to be due to the increase of the communication efficency of the network

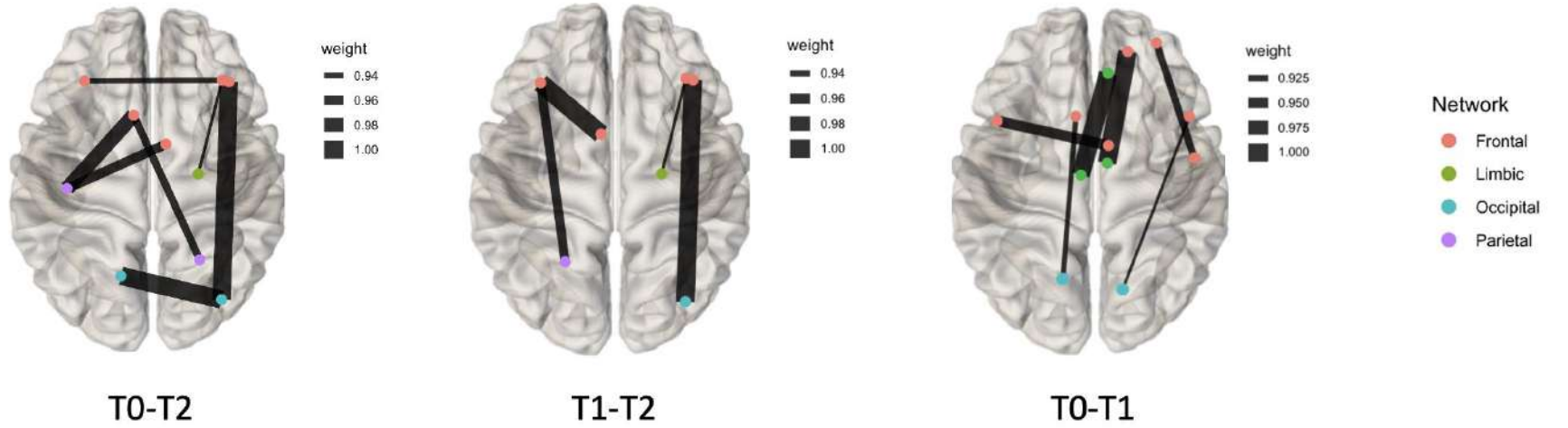
Migraine case study

EEG connectivity

Differences in coherence between conditions greater than the 90th percentile of the distribution of the differences



Theta band (4-7 Hz)



Alpha band (8-12 Hz)

The differences between T0 and T2 and T1 and T2 tend to be more intense, more numerous and for these differences the more intese links tend to connect the frontal and the occipital cortex confirming the role of the occipital cortex in migrine pain

Conclusions and future steps

- This is the first study attempting to evaluate the effects of GCA in migraine patients by studying the electrical and metabolic activity of the occipital cortex (crucial site for migraine pathogenesis) using EEG and fNIRS data.

- After 3 months of treatment, we observed a significant decrease in EEG spectral power and in the oxyhemoglobin levels in different areas of the occipital cortex suggesting a medium-term effect of GCA on cortical regions hyper-activated during visual stimulations because of migraine .

- From the comparison with the control group, we observed that abnormal electrical and hemodynamic activity revert into normal ranges with GCA. This could open a new scenario on the central effects induced by the peripheral modulation of CGRP transmission.

- Our patients showed on average a reduction in headache days, acute drug consumption and disability. However, the association between clinical and neurophysiological effects of GCA was not significant.

- The lack of correspondence with clinical efficacy after 3 months may be explained by the fact that the possible central effect of GCA could be slower than the peripheral mechanisms.

- To shed light on this aspect and best investigate GCA short and long effects, we are going to acquire more data and we plan to consider a longer and a shorter follow-up.

- We plan to carry out the same connectivity study used for EEG also for fNIRS data in order to have a comparison between two modalities.

UNIBA team

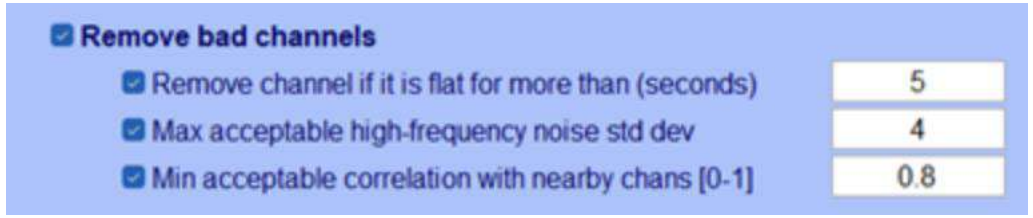
Bari Policlinico

Physics Department
“M. Merlin”

Thank you for your attention

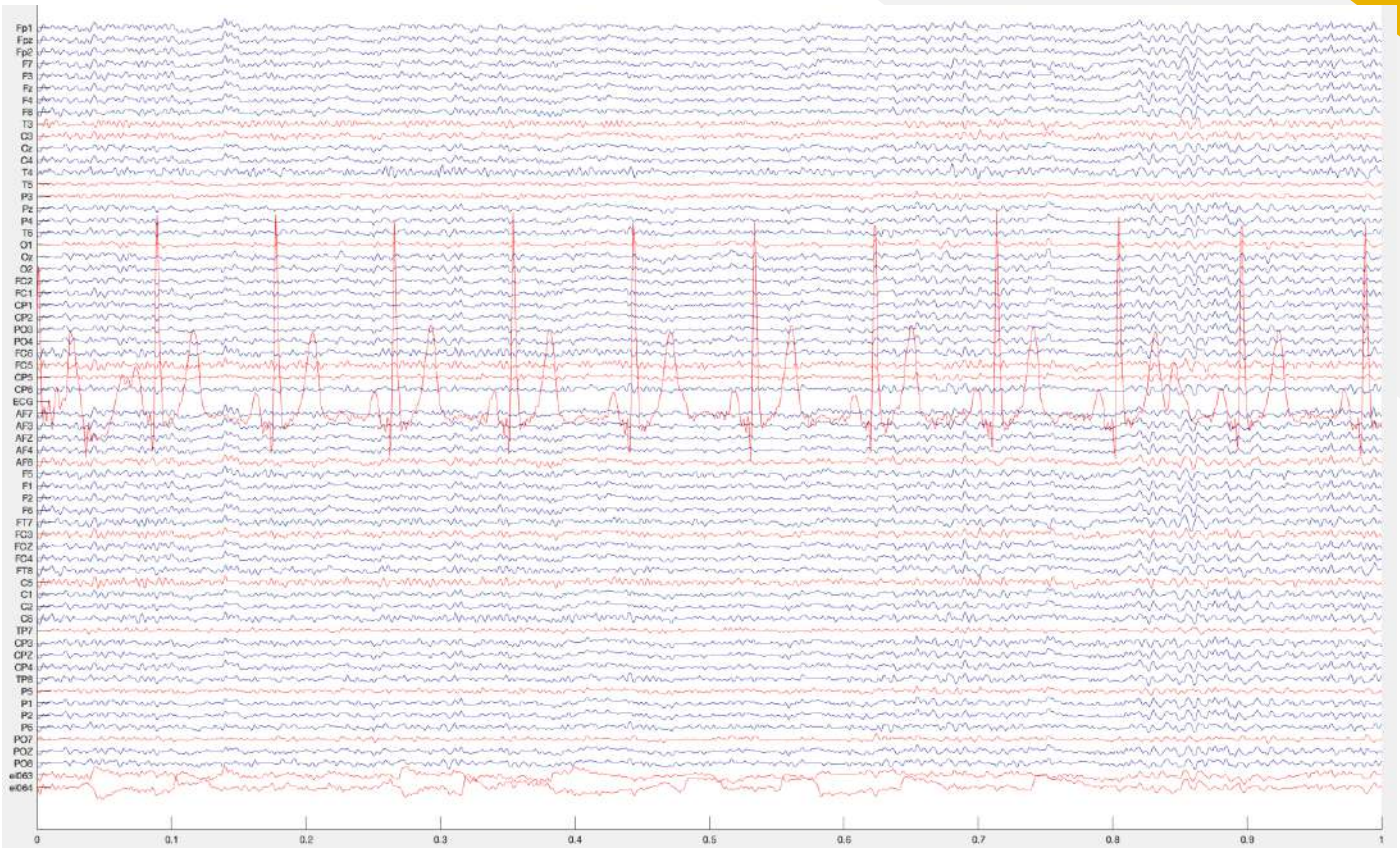
Data processing

EEG processing



Bad channels were identified and removed. Channels presenting distributions far away from the Gaussian distribution were also deleted.

Ocular artifacts recorded on EOG channels were removed and a notch filter at 50 Hz was applied.



We estimated the spectral power using the Fast Fourier Transform (FFT), averaging 10 sec samples from the recording session. Then, we applied a baseline correction in the frequency domain.

Data processing

fNIRS processing

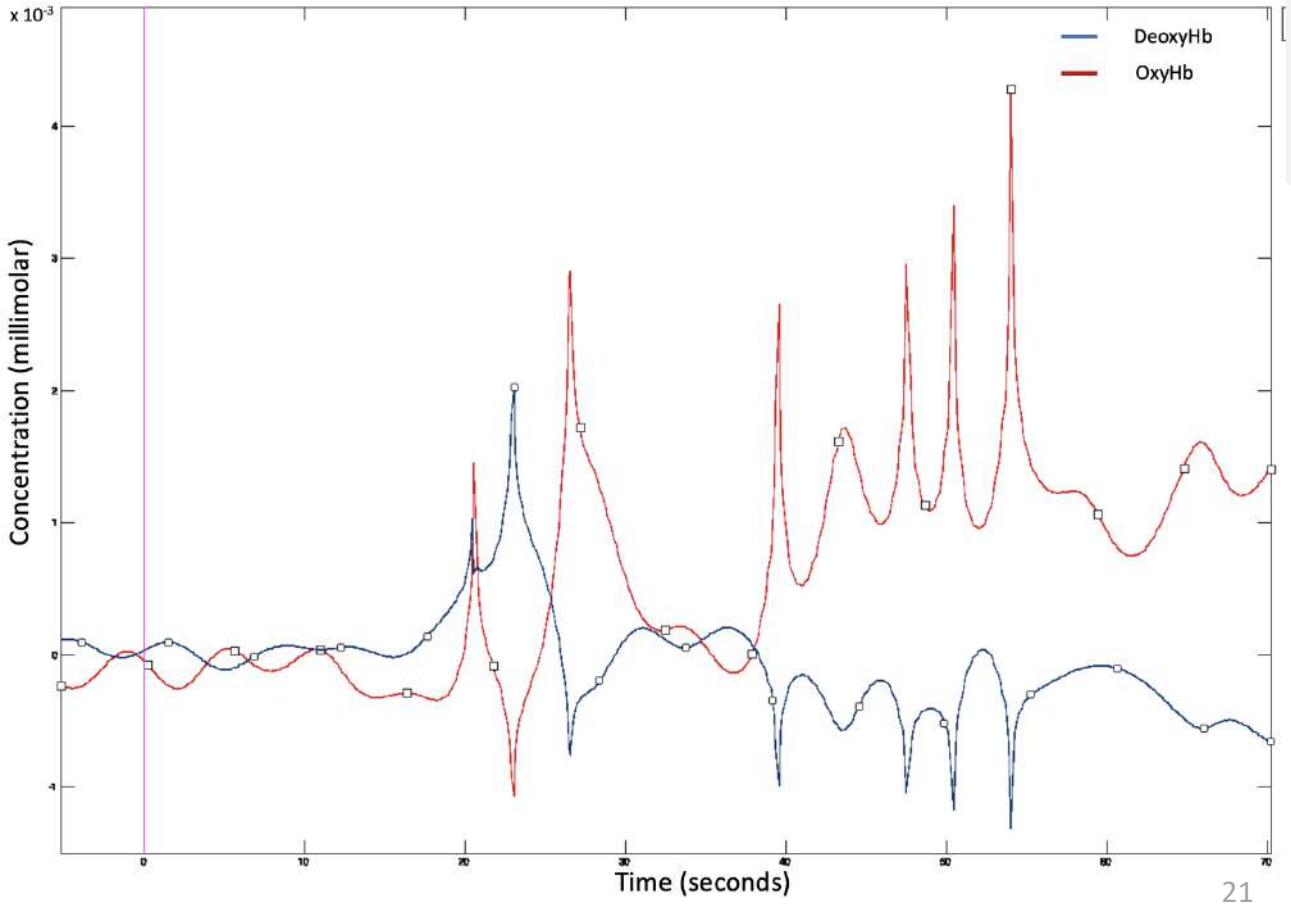
Signal quality was evaluated by checking two thresholds chosen during the calibration phase:

- the gain factor < 8 (how much photo-current is amplified)
- the coefficient of variation < 7.5 (the ratio between 100 times the standard deviation and the mean of the signal)

We automatically removed discontinuities, identified and removed common fNIRS artifacts and filtered data in the band-pass 0.008-0.2 Hz

The signals were converted to optical intensities using the Gratzer method and the optical intensities were converted to oxy and deoxyhemoglobin concentration changes using the modified Beer-Lambert law.

Finally, we carried out a correction of the baseline defined as the first 20 seconds out of 60 seconds of resting state recorded before the visual stimulation.



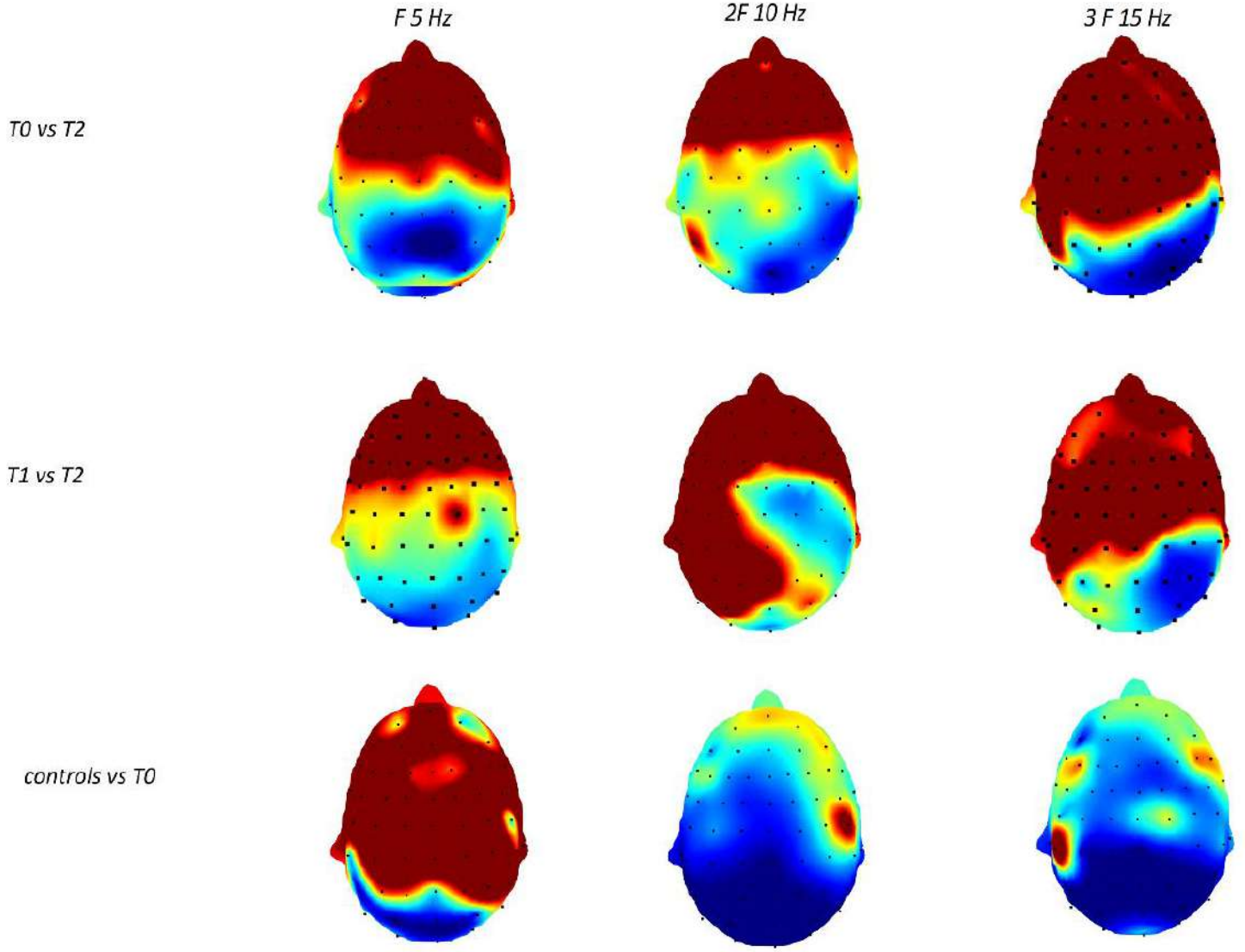
Results

EEG results

Statistical probability maps showing results of Student's t test in the migraine group for T0 vs T2, T1 vs T2, and migraine patients at T0 vs controls.

The comparison between migraine patients in T2 and controls, was not significant.

The comparison of episodic migraine vs chronic migraine did not show significant differences

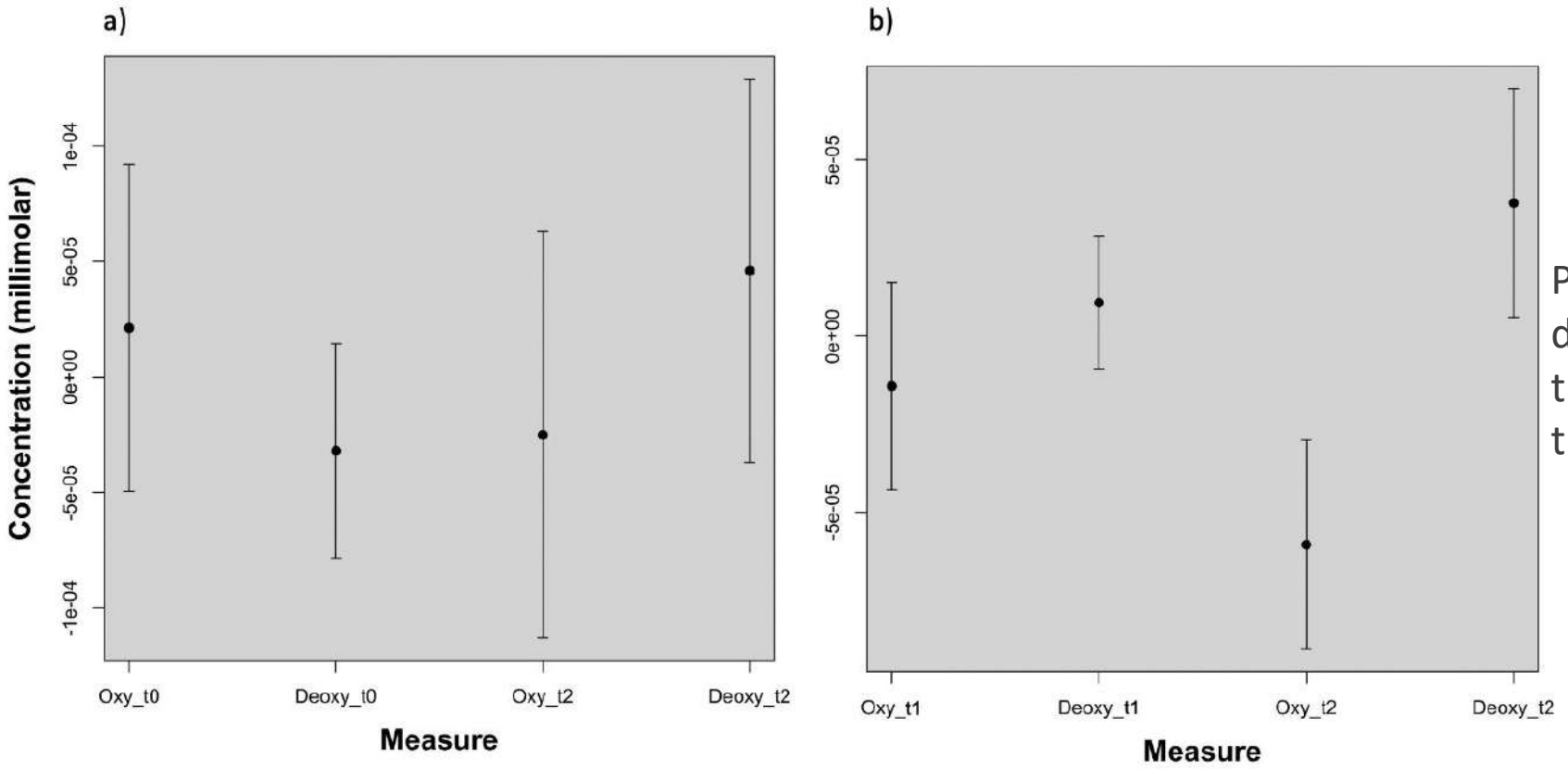


Blue colors express p-values lower than 0.05.

(The Journal of Headache and Pain, 2022)

Results

fNIRS results



Plots reporting the values of oxy and deoxyhemoglobin levels averaged over the channels proved to be significant for the comparisons T0 vs T2 and T1 vs T2

For both EEG and fNIRS data, we did not observe significant association between the reduction of headache days and the neurophysiological changes (electrical and metabolic changes).

(The Journal of Headache and Pain, 2022)