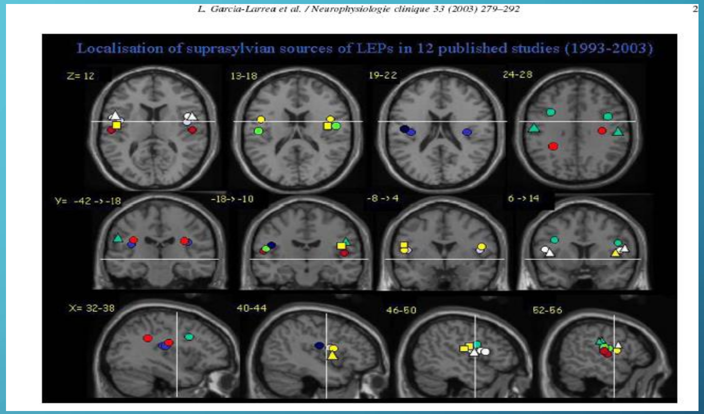
Third International Summer Institute on Network Physiology (ISINP)

Lake Como School of Advanced Studies – 24-29 July 2022

THE CORTICAL NETWORKS REVISED: MOTOR NOCICEPTIVE NETWORK AND NEURO LIMBIC OCCIPITAL NETWORKS IN CHRONIC PAIN AND MIGRAINE, A FNIRS AND EEG STUDY.

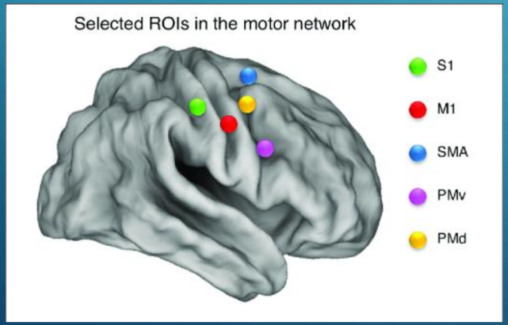
MARINA DE TOMMASO

RELATIONSHIPS BETWEEN MOTOR ACTIVITY AND PAIN: THE MOTOR – NOCICEPTIVE NETWORK



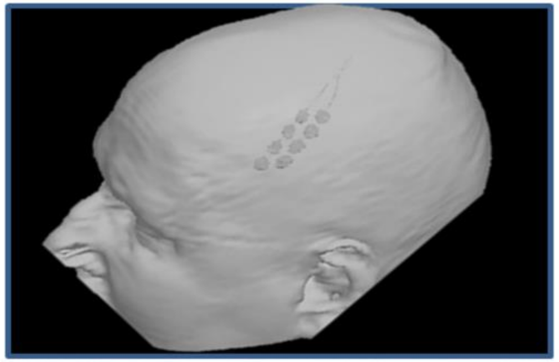
Pain

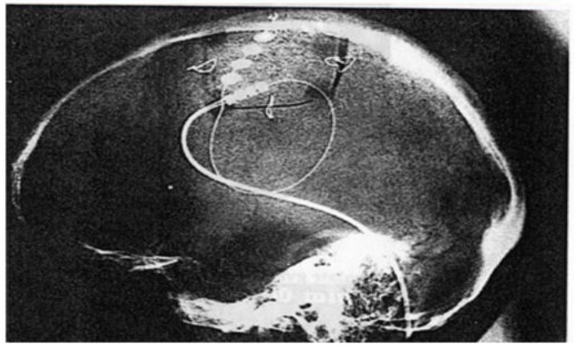
Motor activity



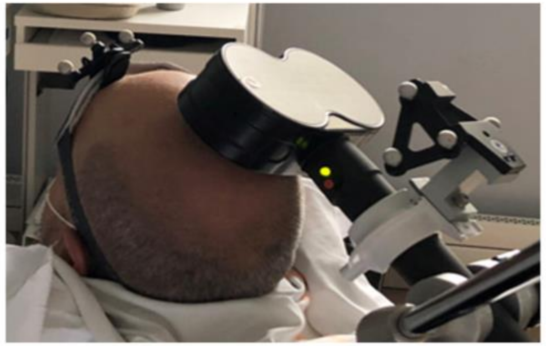
Cortical stimulation for chronic pain: from anecdote to evidence

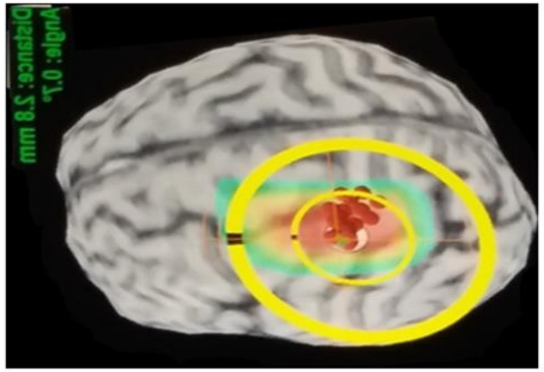
Luis GARCIA-LARREA, Charles QUESADA



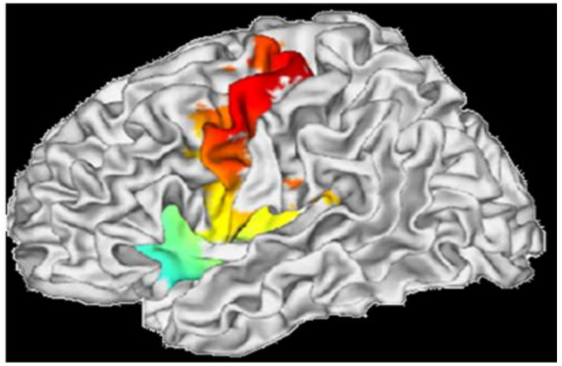


Epidural stimulation
Mode: Invasive, neurosurgical
Target: motor cortex
Stim: 1-4V, 30-80Hz, ~150 us, cyclic mode
Complications: 1-5%, mainly transient (infection, seizures)
Efficacy: Definite in 40-60% cases.
Long-lasting efficacy (years)





Transcranial magnetic stimulation (rTMS)
Mode: Non invasive
Target: motor cortex
Stim: 80-90% SMT, 10-20Hz, 1000-2000 pulses
Contraindication: epilepsy
Efficacy: Probable for motor cortex stim in NP.
Short-lasting efficacy, need repetition of sessions



Transcranial direct current stimulation (tDCS)
Mode: Non invasive
Target : Motor cortex
Stim: DC, 1-2 mA, 20 min
Safety issues: very rare
Contraind.: scalp skin disease
Efficacy: Possible, but inconsistent evidence (2021)
Home-stim available to enhance efficacy?

Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) during capsaicin-induced pain: modulatory effects on motor cortex excitability

Brigida Fierro · Marina De Tommaso ·
Francesca Giglia · Giuseppe Giglia ·
Antonio Palermo · Filippo Brighina

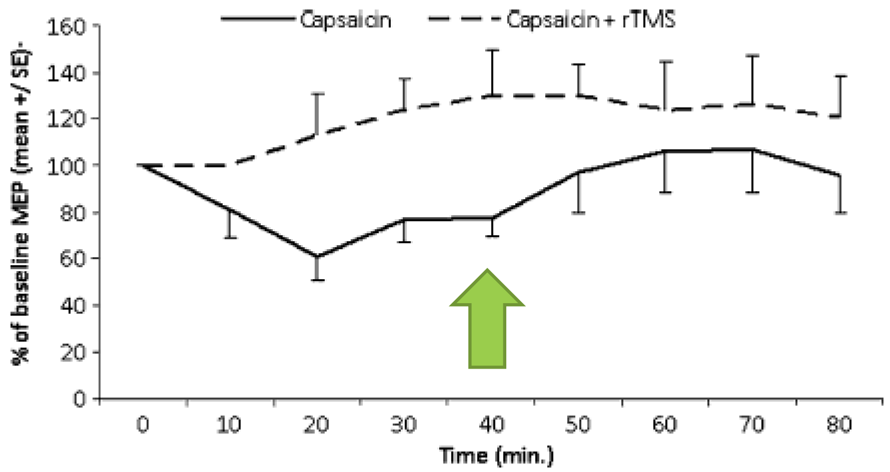


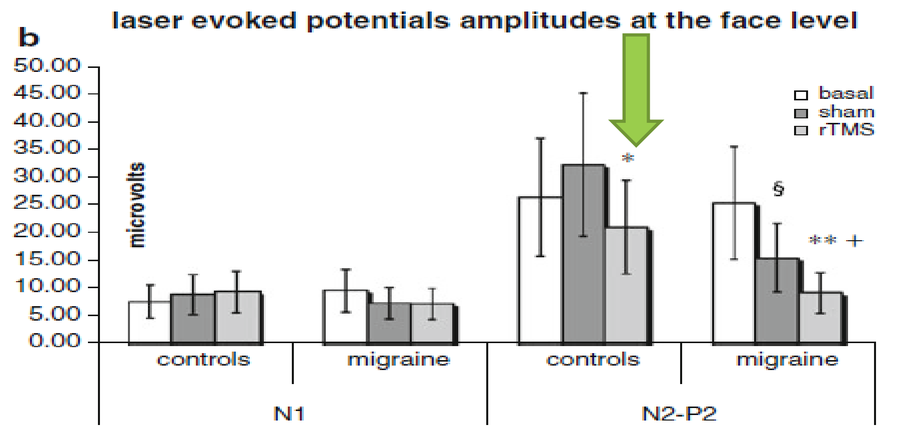
Fig. 1 Changes in MEP values, expressed as percentage of baseline (before capsaicin) MEP, during and after capsaicin application, with and without left DLPFC rTMS, delivered 10 min after capsaicin application

J Headache Pain (2010) 11:505–512
DOI 10.1007/s10194-010-0247-7

ORIGINAL

Effects of high-frequency repetitive transcranial magnetic stimulation of primary motor cortex on laser-evoked potentials in migraine

Marina de Tommaso · Filippo Brighina · Brigida Fierro · Vito Devito Francesco ·
Roberto Santostasi · Vittorio Sciruicchio · Eleonora Vecchio · Claudia Serpino ·
Paolo Lamberti · Paolo Livrea



Motor activity

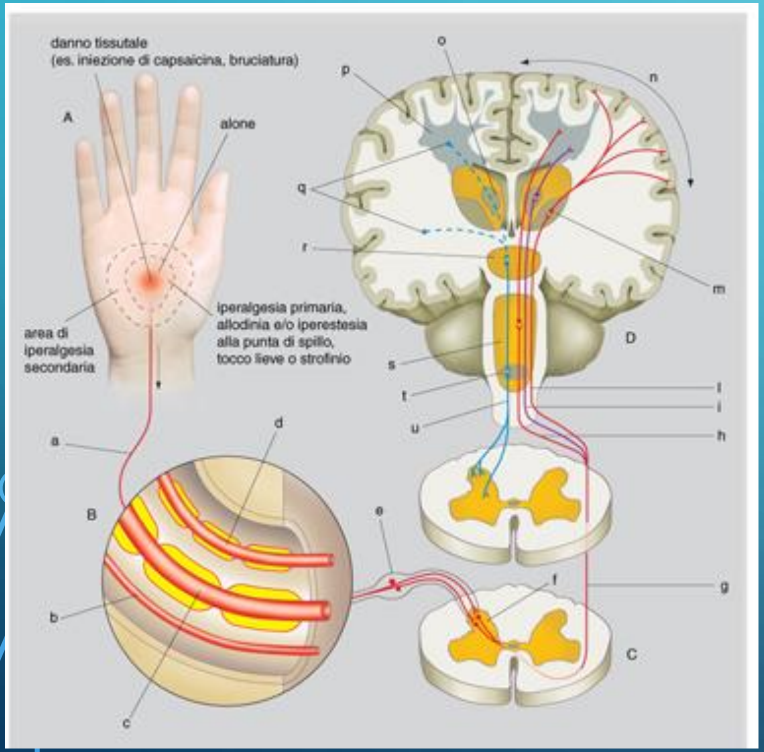
Pain

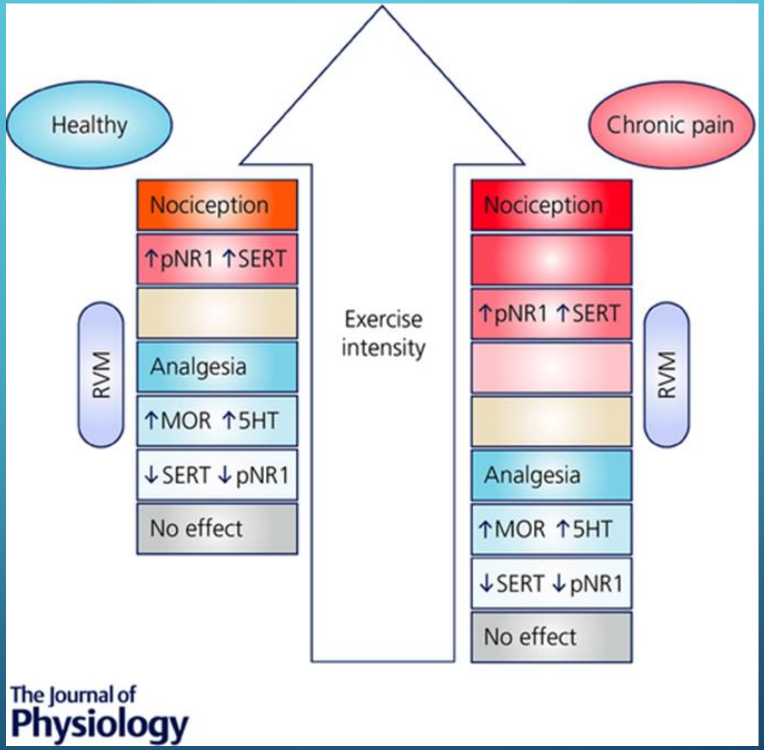
Pain

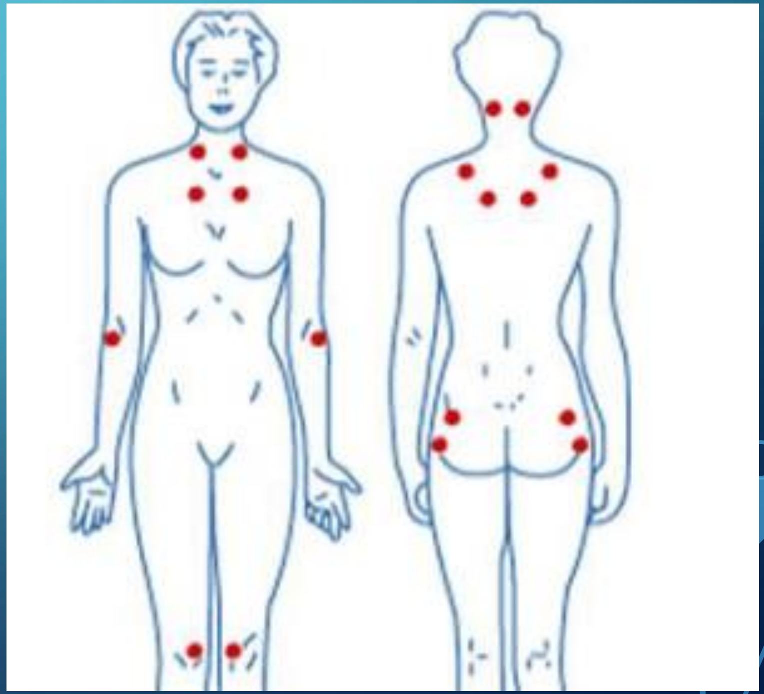
Motor activity

FIBROMYALGIA

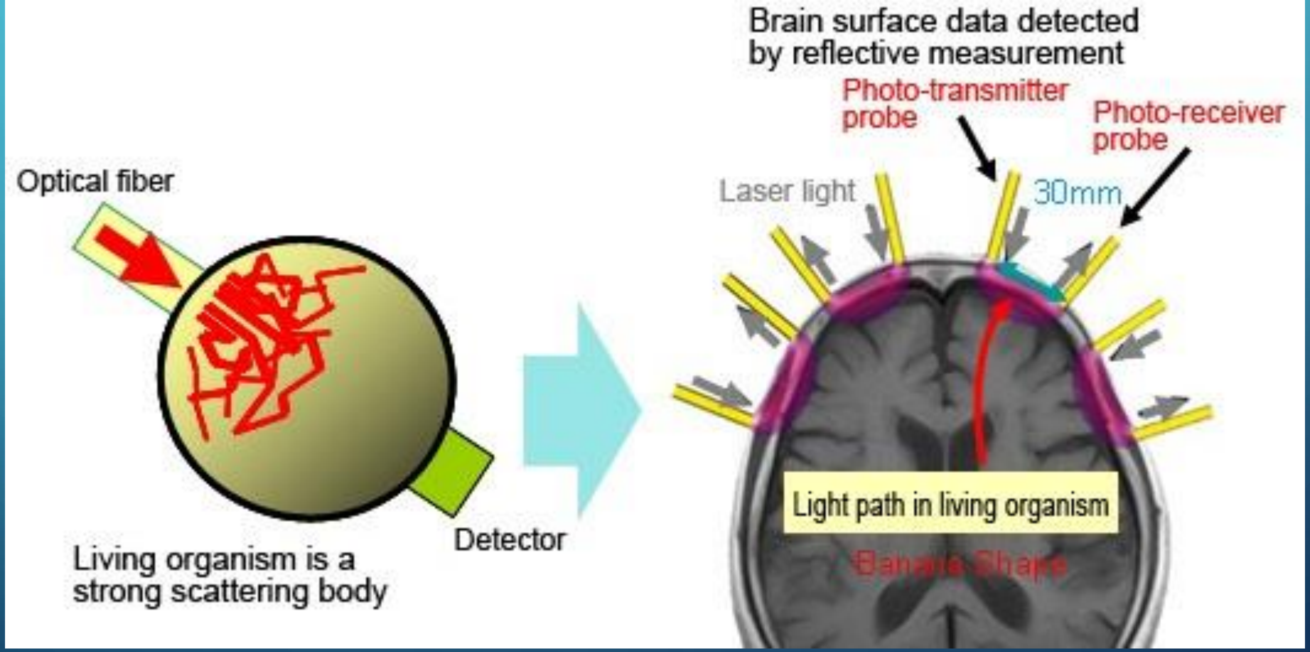
Pain reduces motor activity, inhibiting motor cortex in a self-sustained mechanism of chronic symptoms maintenance.







THE NEAR-INFRARED LIGHT CAN PENETRATE CEREBRAL TISSUE WITHOUT SIGNIFICANT DEGRADATION OF THE OPTICAL SIGNALS (TAM ET ZOURIDAKIS, 2013). THIS METHOD ALLOWS REAL TIME MONITORING OF THE HEMODYNAMIC SIGNALS IN BRAIN TISSUES, THUS WE CAN SEE THE BRAIN ACTIVATION AND THE OXYGEN CONSUMPTION DURING MOTOR TASK.

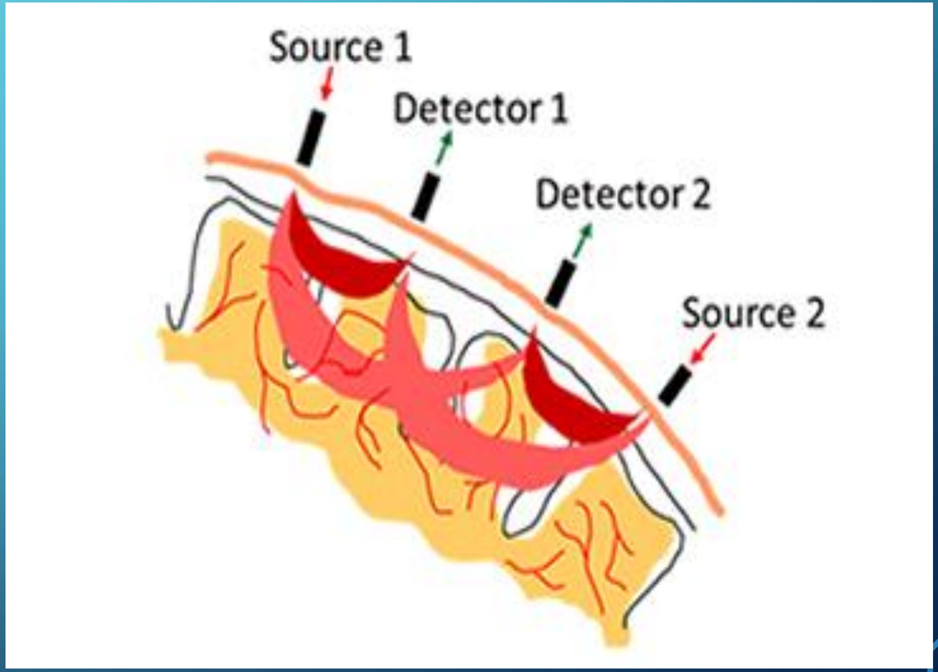


HOW DOES THE NIRS WORK?

- The sources emit NIR photons that penetrate into the biological tissue and then they are absorbed by detectors. The NIR photons follow a banana-shape path. Along the path the NIR photons undergo two processes: scattering and absorption.

- The skin, skull and tissues are trasparent to NIR wavelenghts, while O2Hb and HHb absorb these spectra.

- Absorption of NIR photon is mainly due to hemoglobin. When there is a brain activation we can see the changes in hemoglobin concentration.



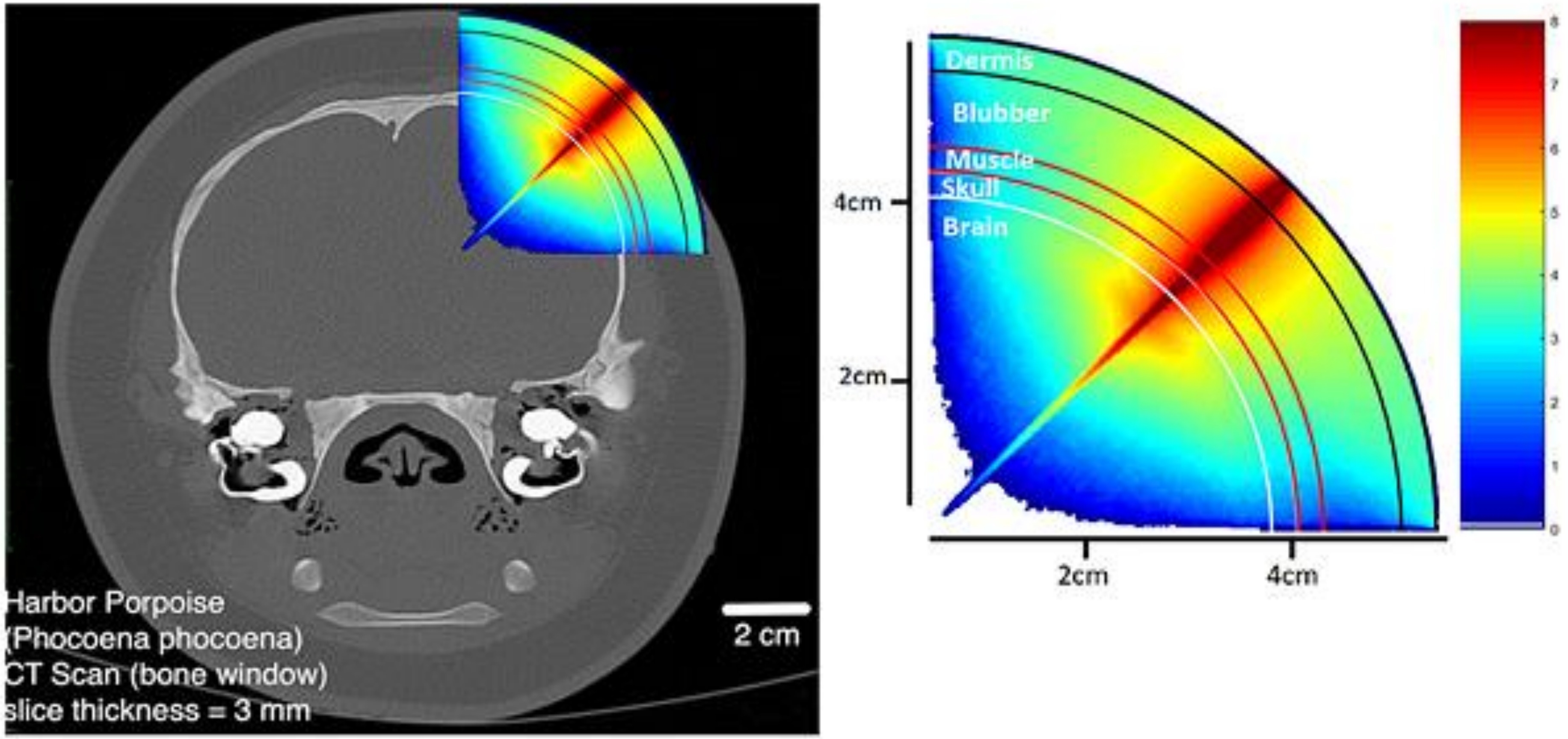


FIGURE 1 | Monte Carlo photon propagation simulation using a point LED source incident at an angle normal to the scalp. Anatomy modeled on the harbor porpoise.

Neuroscience and Biobehavioral Reviews 120 (2021) 335–353

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NIRS measures in pain and analgesia: Fundamentals, features, and function

Keerthana Deepti Karunakaran [a,1], Ke Peng [a,b], Delany Berry [a], Stephen Green [a], Robert Labadie [a], Barry Kussman [c], David Borsook [a,1,*]

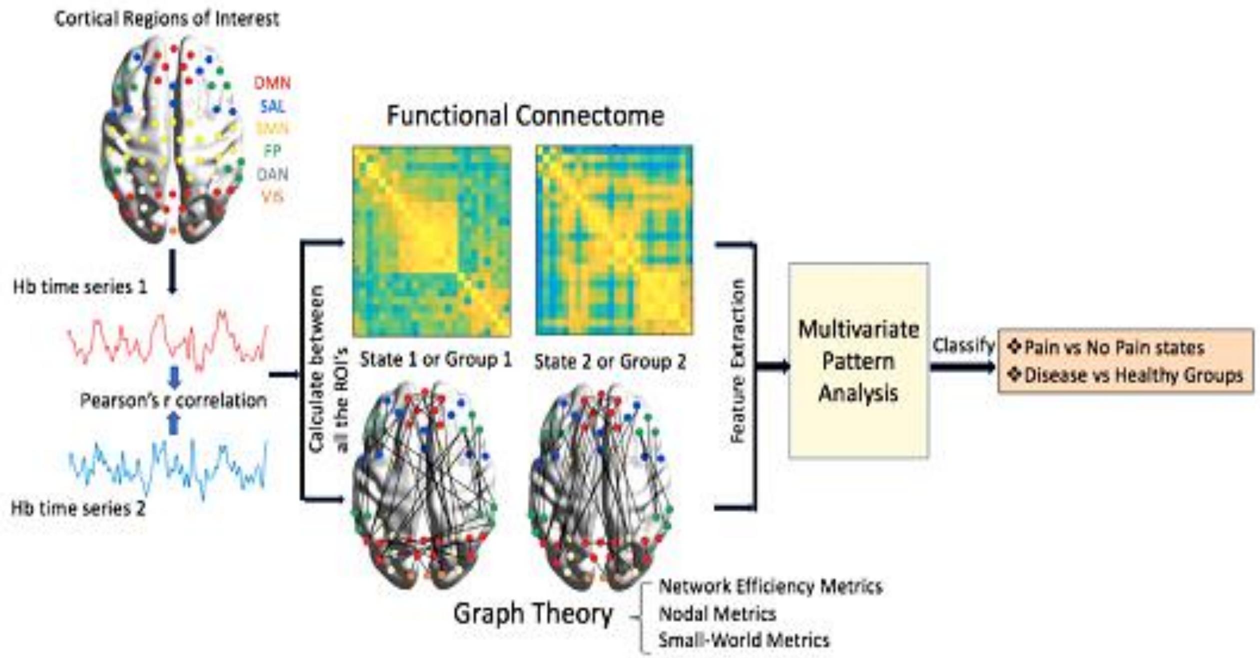
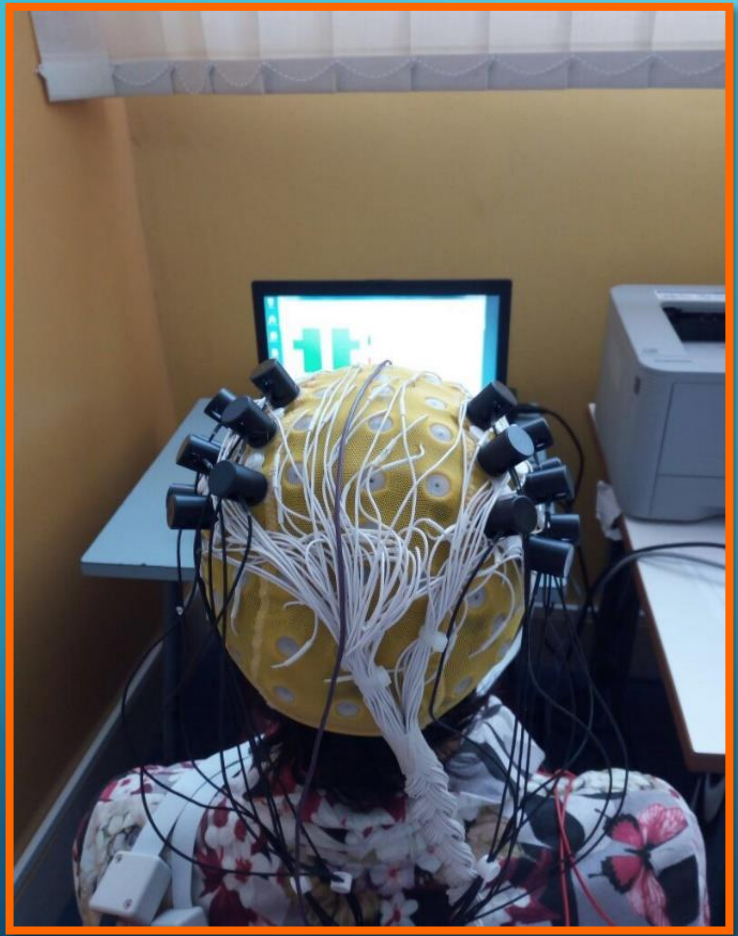
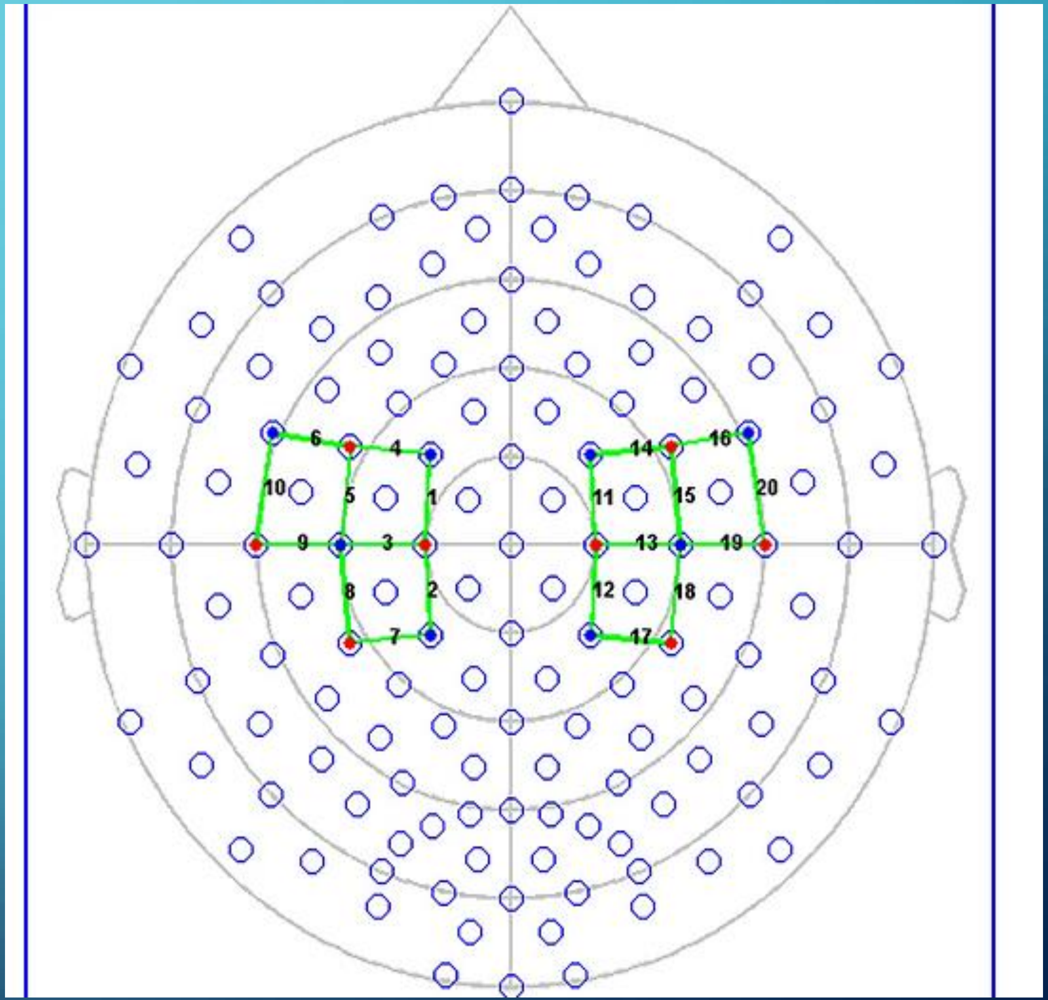


Fig. 2. Framework for Pain Detection and Classification using Cortical Functional Connectivity Metrics of fNIRS. Cortical regions of interest may be defined for whole brain or specific anatomic/functional networks. The underlying total or oxyhemoglobin concentration change (time series) can be extracted to perform a connectivity analysis and/or a graph theoretical analysis. Connectivity analysis is performed by correlating the time series of an ROI with the remaining ROIs to form a connectivity matrix per subject or condition. Using these connectivity measures (correlation or covariance matrix), where ROIs are nodes and the connections are edges, the different graph theoretical metrics are calculated. Differences in network properties may be compared using univariate or multivariate analyses to identify and differentiate pain vs. non-pain states and, similarly, disease and healthy conditions. (DMN, Default mode network; SAL, Salient network; SMN, Sensorimotor Network; FP, Fronto-parietal Network; DAN, Dorsal Attention Network; VIS, Visual Network).





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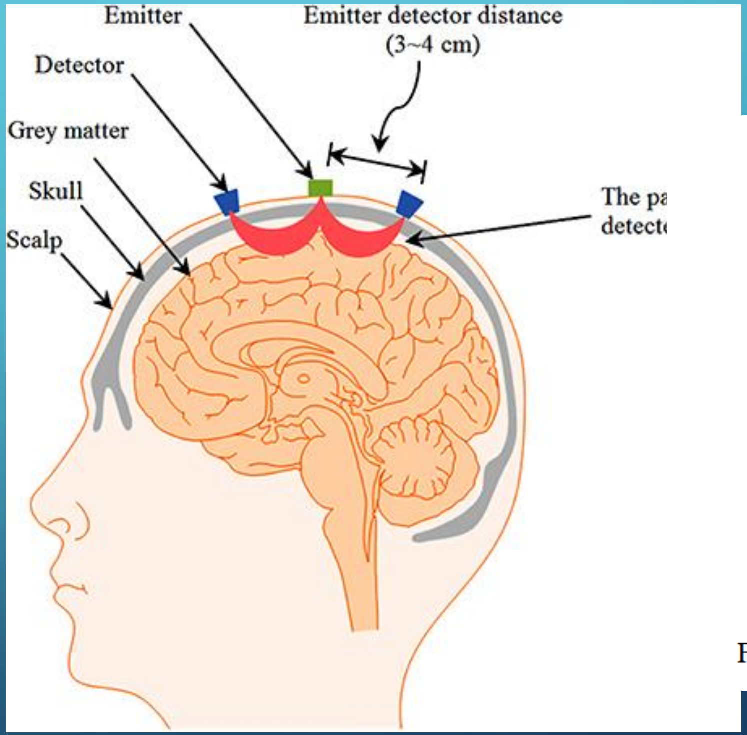
METHOD
NEAR-INFRARED SPECTROSCOPY (FNIRS)

Functional Near-Infrared Spectroscopy (fNIRS) is a non-invasive technique that allows a real time detection of blood flow and metabolism changes in the cerebral cortical tissue.



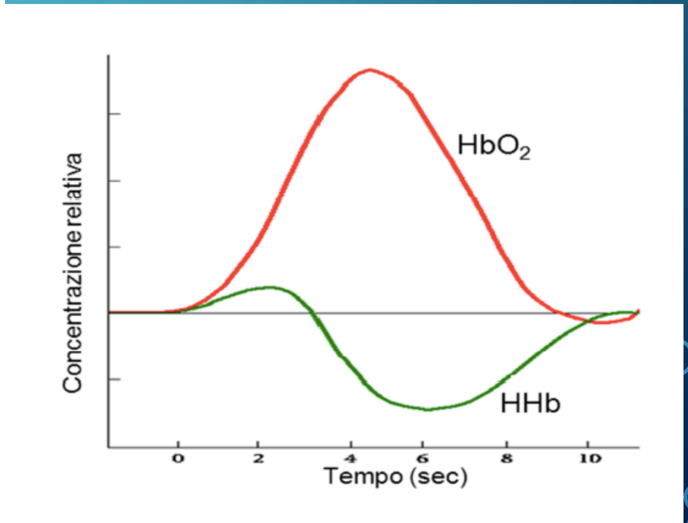
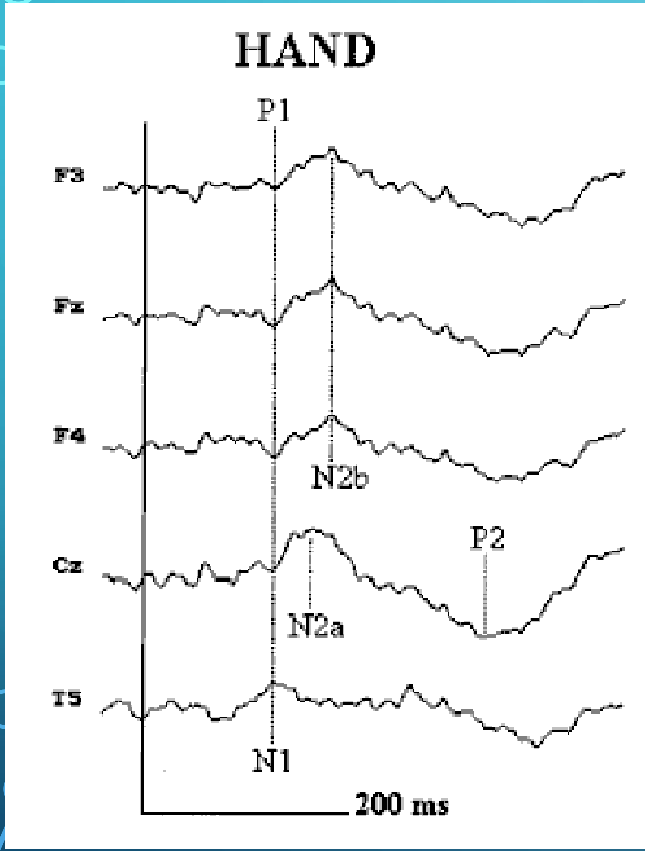


Fig. 2.1.c – Risposta emodinamica attesa per HbO_2 e HHb

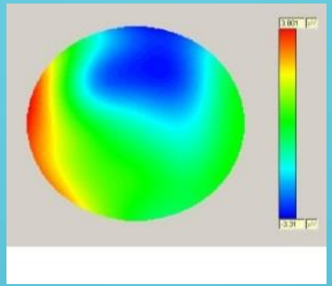
Method

CO_2 Laser Evoked Potentials(LEPs)

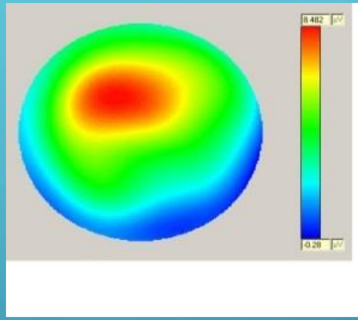


Valeriani et al., Clin Neurophysiol 2000

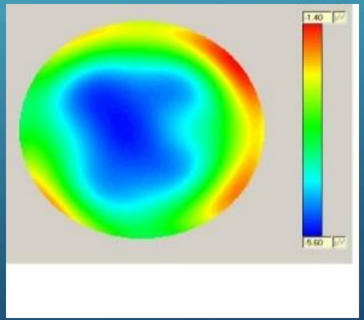
Aδ e C fiber



N1/P1



N2



P2

Sensory-discriminative aspects of pain

Emotional and motivational aspects of pain

METHOD

PARTICIPANTS

- 21 healthy subjects (aged from 19 to 60)
- 38 patients with fibromyalgia

EXPERIMENTAL CONDITIONS RANDOMIZED

2 min Resting state

Laser stimulation on the right hand

1 min rest

Laser stimulation on the left hand

1 min rest

Slow finger tapping task (SFT)

1 min rest

Fast finger tapping task (FFT)

1 min rest

SFT + Laser on the right hand

1 min rest

SFT + Laser on the left hand

1 min rest

FFT + Laser on the right hand

1 min rest

FFT + Laser on the left hand

1 min rest

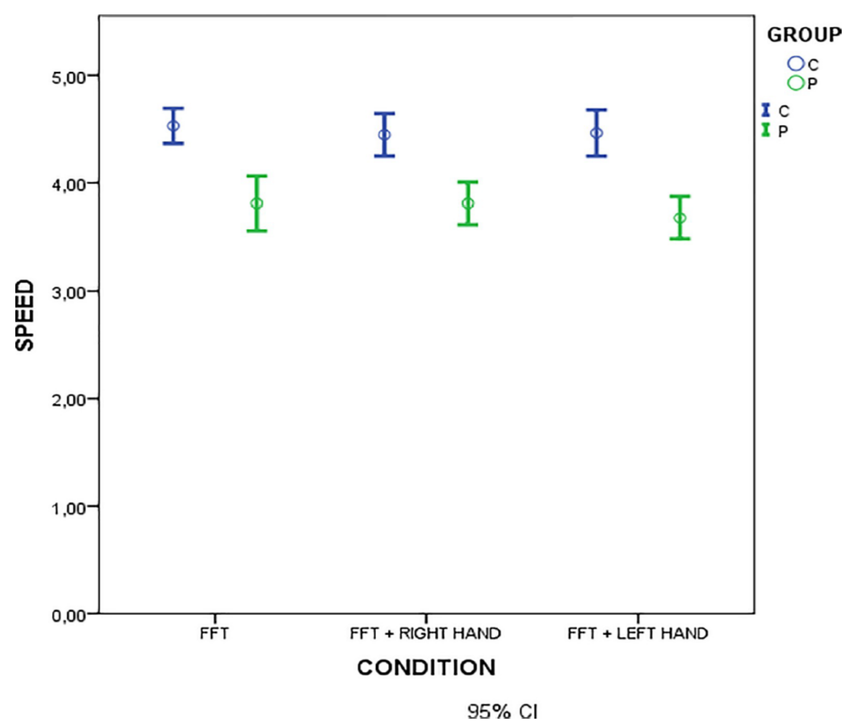
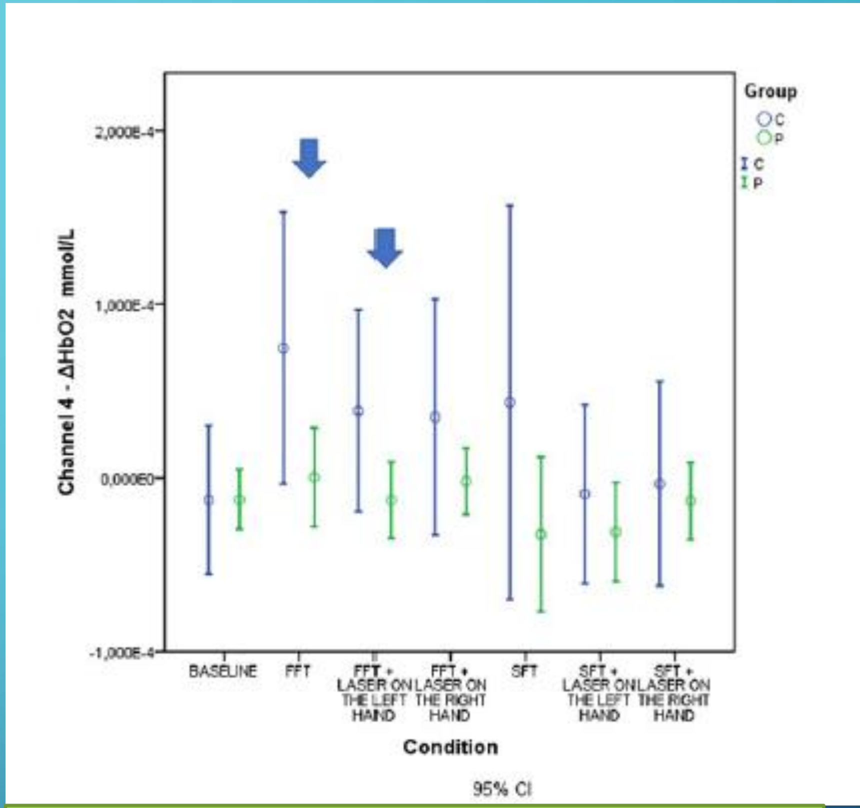


Fig 3. Mean values of finger tapping speed in motor task conditions in patients (green) and controls (blue). Statistical comparison is reported in Table 2.

Finger tapping speed<in FM



Oxyhemoglobin levels< in FM

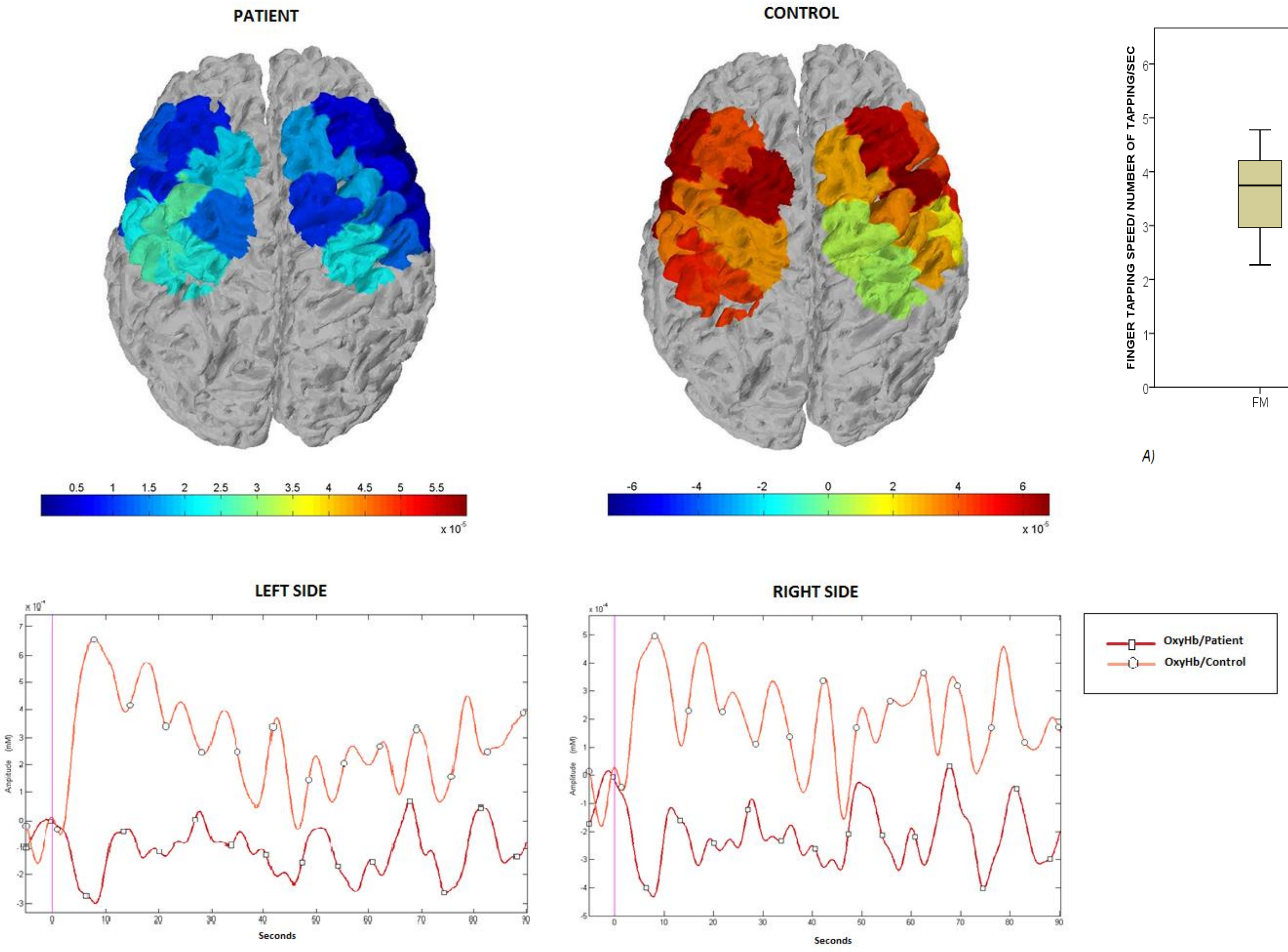
PLOS | ONE

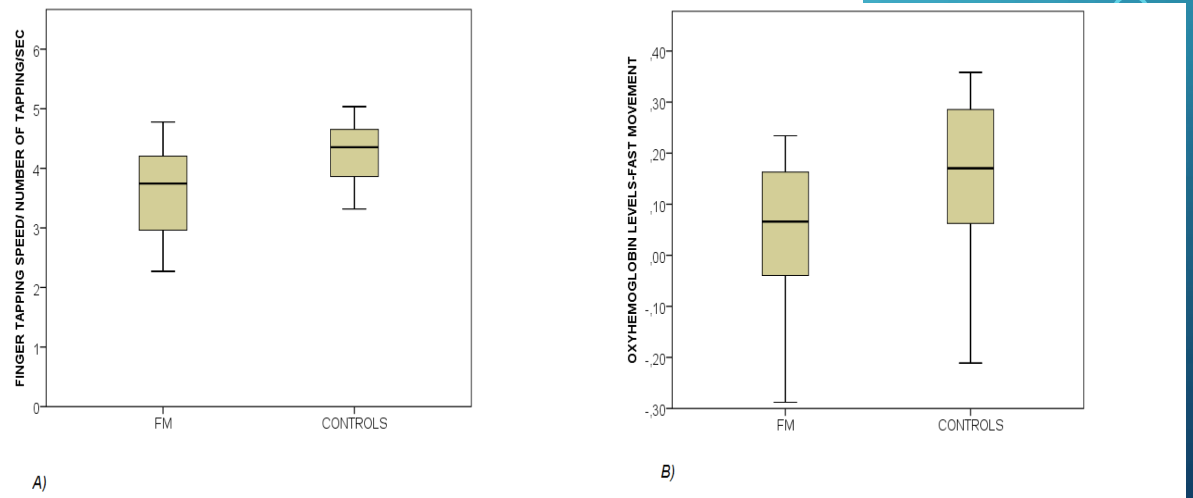
RESEARCH ARTICLE

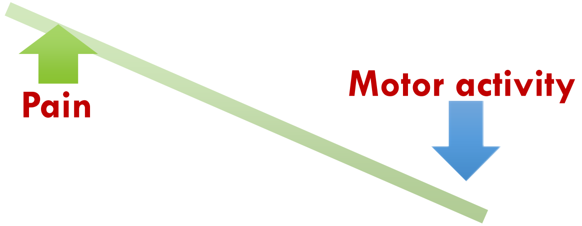
Mutual interaction between motor cortex activation and pain in fibromyalgia: EEG-fNIRS study

Eleonora Gentile[1]*, Antonio Brunetti[2], Katia Ricci[1], Marianna Delussi[1], Vitoantonio Bevilacqua[2], Marina de Tommaso[1]

Oxyhemoglobin levels< in FM







WHAT ABOUT PAIN?

brain sciences

MDPI

Article

A Simple Pattern of Movement Is Not Able to Inhibit Experimental Pain in FM Patients and Controls: An sLORETA Study

Eleonora Gentile [1,*], Katia Ricci [1], Eleonora Vecchio [1], Giuseppe Libro [1], Marianna Delussi [1], Antonio Casas-Barragàn [2] and Marina de Tommaso [1]

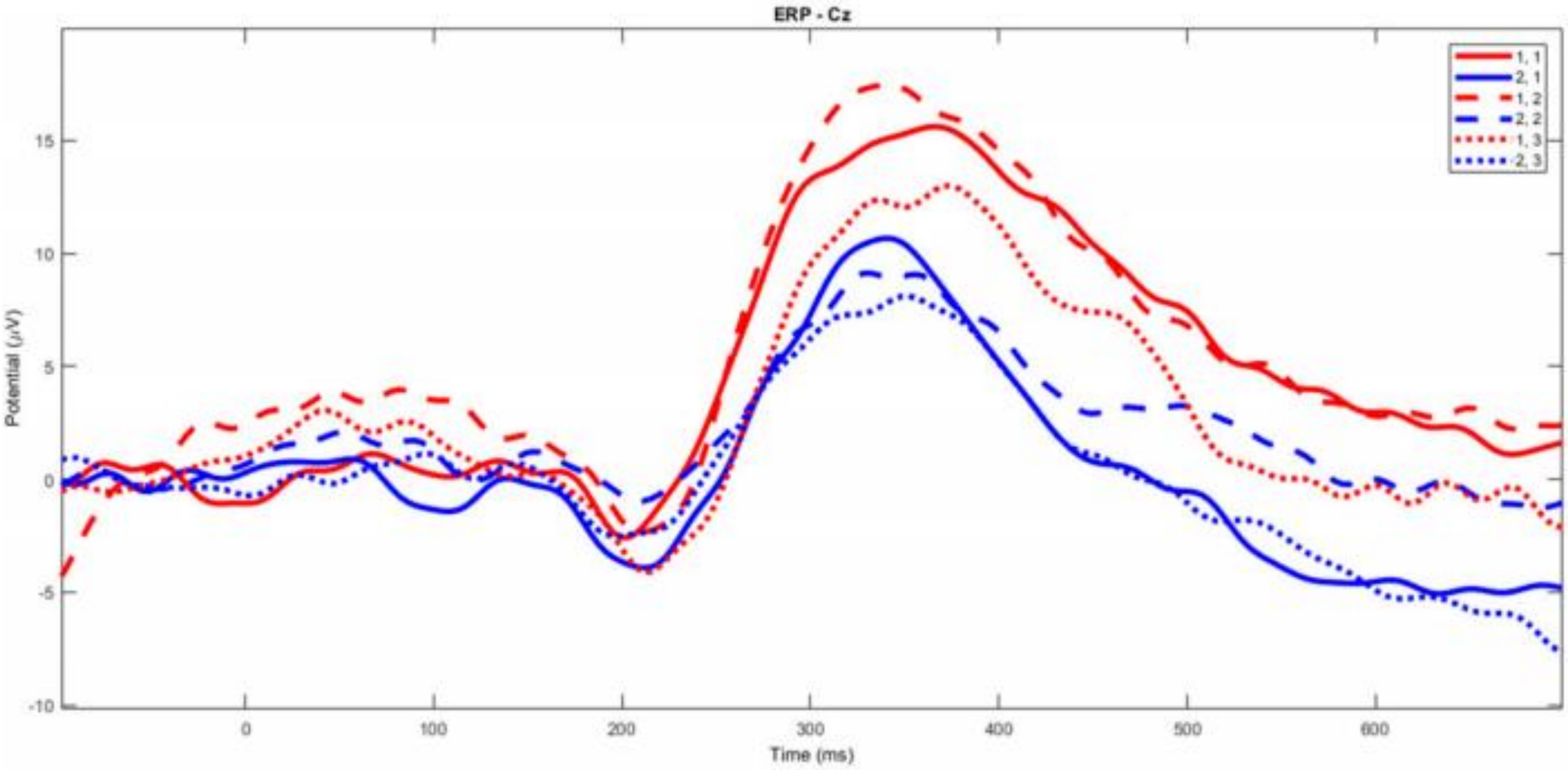


Figure 2. The grand average of the laser–evoked potentials on the right hand stimulation. The control group's basal condition (1,1), slow finger tapping (1,2) and fast finger tapping (1,3); the fibromyalgia (FM) group's basal condition (2,1), slow finger tapping (2,2) and fast finger tapping (2,3) (see also Figure 1).

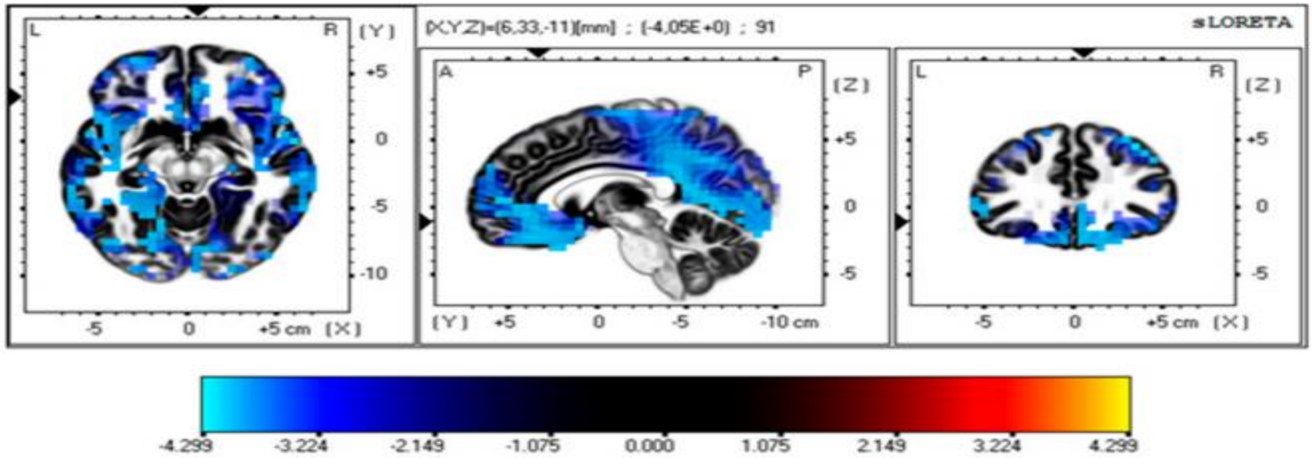


Figure 6. The sLORETA voxels expressing statistical analysis results in the control group between LEPs in the basal condition and during fast finger tapping. The maps express the maximal difference in light blue, corresponding to frontal and limbic regions. For details of the analysis, see Table S1.

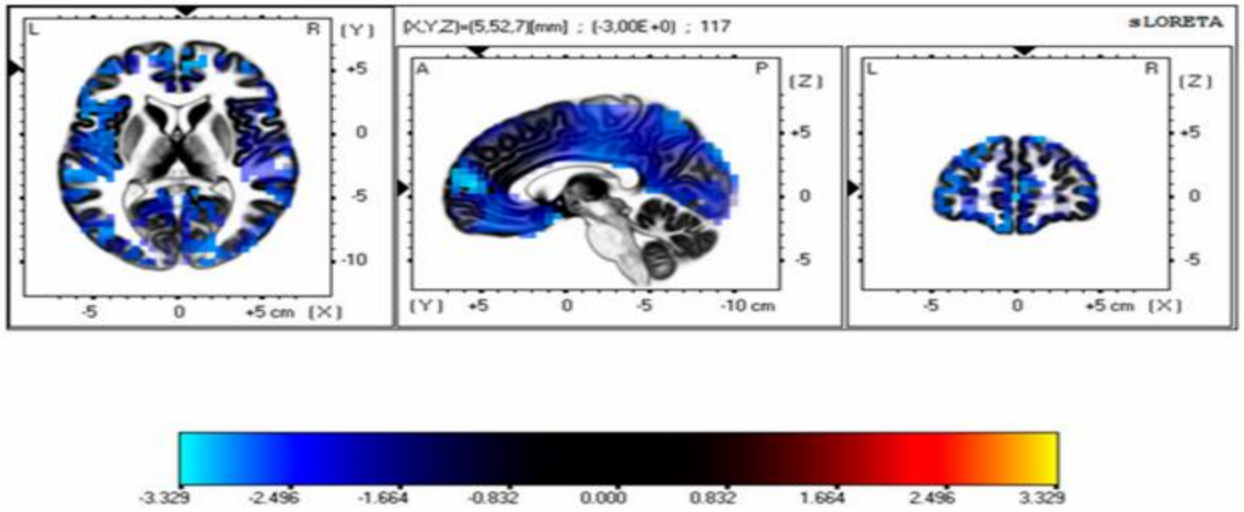
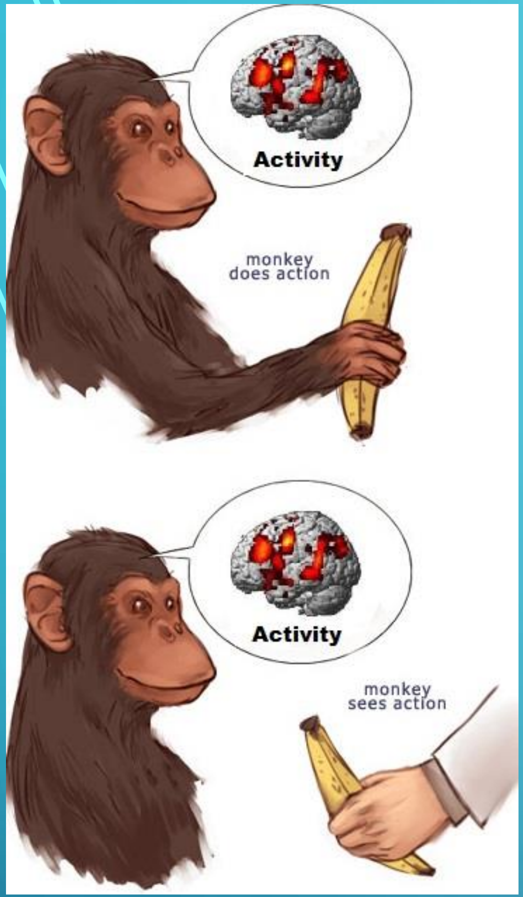


Figure 7. The sLORETA voxels expressing statistical analysis results of the comparison of changes of laser evoked potential (LEP) sources in the basal condition and during fast finger tapping between the controls and the fibromyalgia (FM) patients. The maps express the maximal difference in light blue, corresponding to frontal and limbic regions. For details of the analysis, see Table S2.

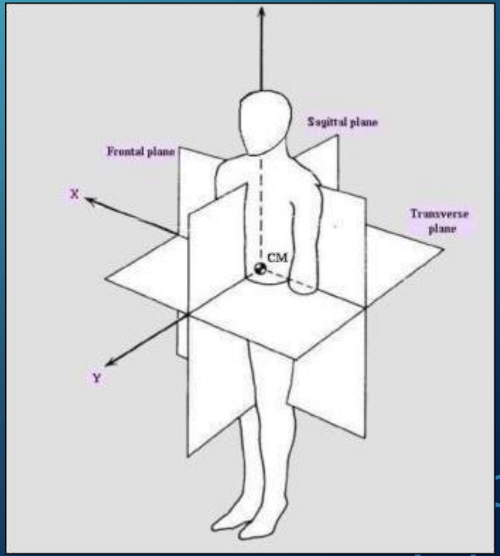


MOTOR EXECUTION AND MOTOR OBSERVATION

When we observe the actions of other people, we activate the same neural circuit responsible for the planning and execution of our actions (Rizzolatti et al., 1996).

Bodily Self-Consciousness

- Implicit and pre-reflective knowledge of being the subject of a given experience.
- Integration of exteroceptive and interoceptive multisensory information.



scientific reports

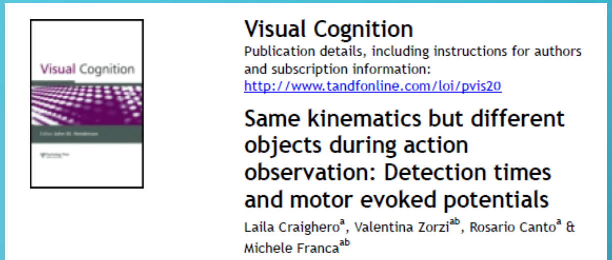
OPEN

Movement observation activates motor cortex in fibromyalgia patients: a fNIRS study

Eleonora Gentile[1✉], Antonio Brunetti[2], Katia Ricci[1], Vitoantonio Bevilacqua[2],
Laila Craighero[3] & Marina de Tommaso[1]

In summary, we expected the control subjects to show faster responses during graspable object videos as compared to ungraspable object videos (i.e., motor facilitation, an index of motor resonance), confirming previous results[28,30]. A similar pattern in the responses of FM patients would indicate the presence of a normal motor resonance. Regarding the fNIRS data, we expected to find a difference in the hemodynamic activity between trials showing graspable and ungraspable object videos but only in those experimental conditions in which the modulation of the detection times indicated the presence of motor resonance. Finally, we decided to subject the participants to an observation session to test the influences on cortical metabolism of a situation as similar as possible to that of AOT. Furthermore, given that previous observation showed reduced metabolism of the motor cortical network during active movement[32], we were interested in whether motor activation was greater when the motor response was required or when it was not, a valuable information for planning a rehabilitation treatment.

STIMULI VIDEOS



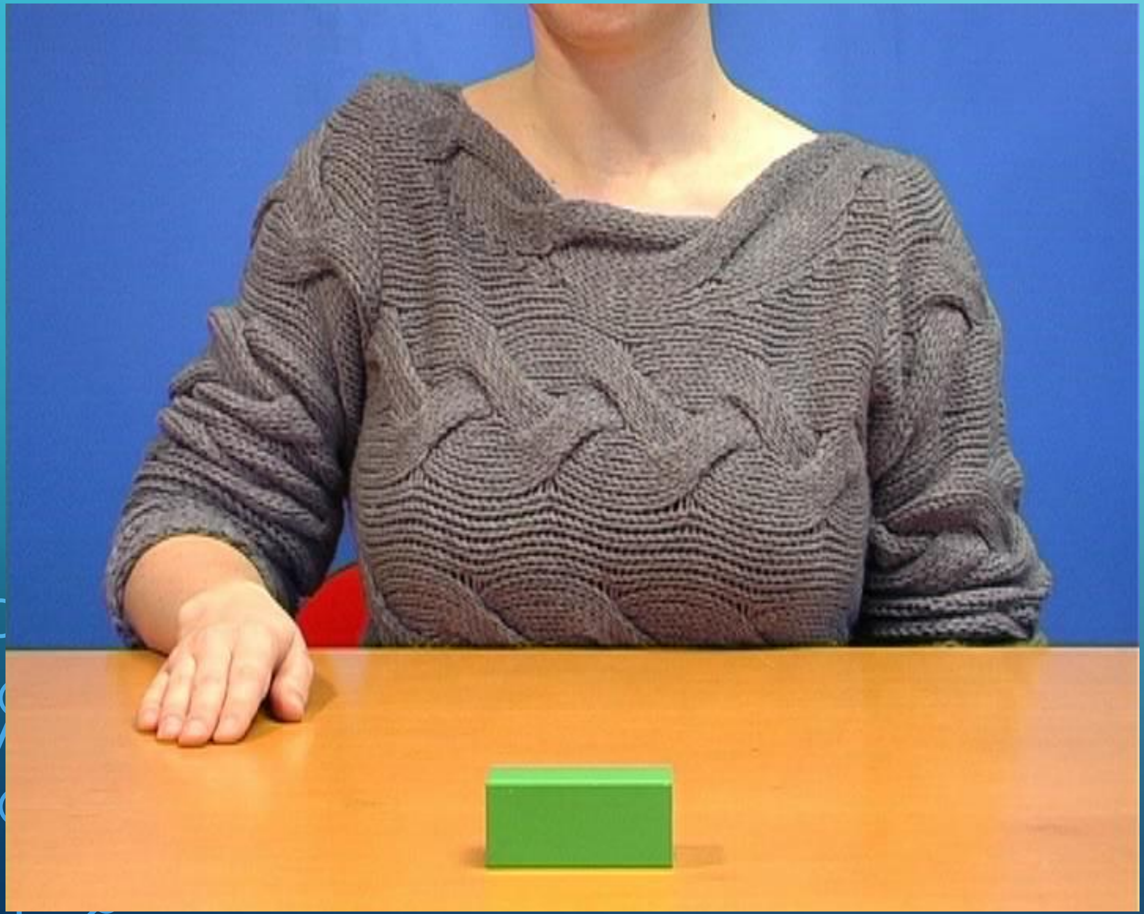
Visual Cognition

Publication details, including instructions for authors and subscription information:

http://www.tandfonline.com/loi/pvis20

Same kinematics but different objects during action observation: Detection times and motor evoked potentials

Laila Craighero[a], Valentina Zorzi[ab], Rosario Canto[a] & Michele Franca[ab]



THE OXYHEMOGLOBIN LEVELS WENT UP IN FM PATIENTS DURING CONGRUENT MOVEMENT OBSERVATION IN RESPECT TO CONTROLS

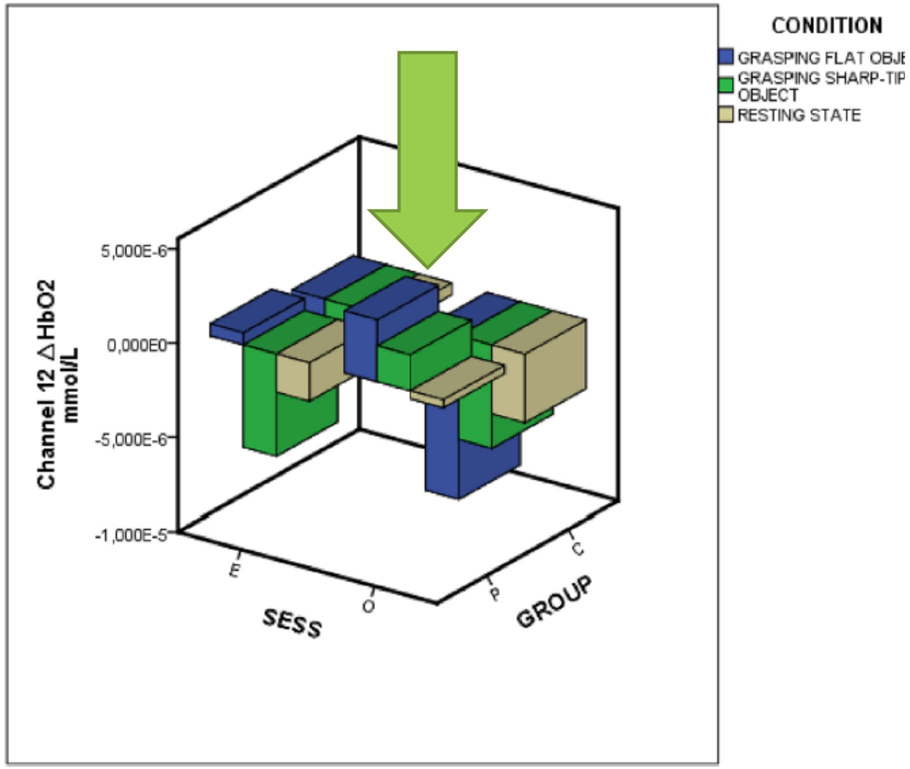


Figure 4. Oxyhemoglobin levels on an exemplificative channel (channel 12). *Sess* session, *O* obser session, *E* time-to-contact detection session, *P* FM patients, *C* controls.

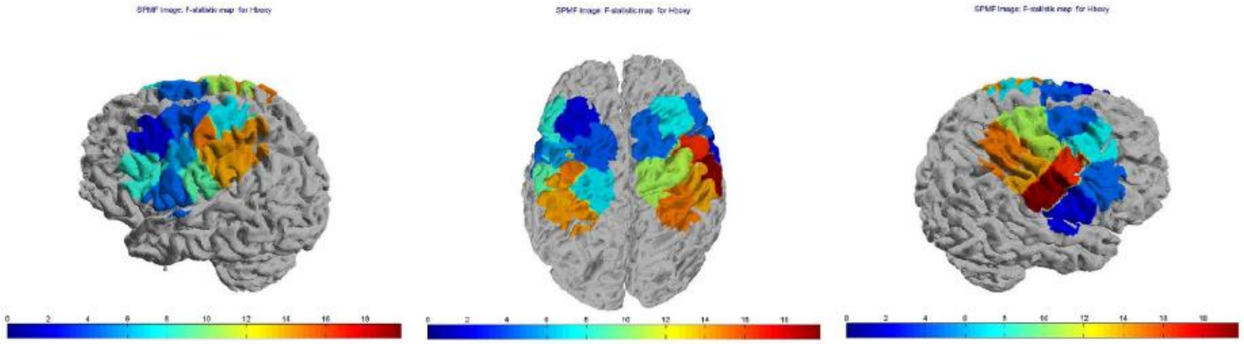


Figure 6. Topographic maps of F-statistic in the comparison among session (Time-to-contact detection vs Observation-only) and groups (FM patients vs controls). Blue areas represent channels with no significant change in hemoglobin levels, red areas represent channels where the variations in hemoglobin levels were significant.

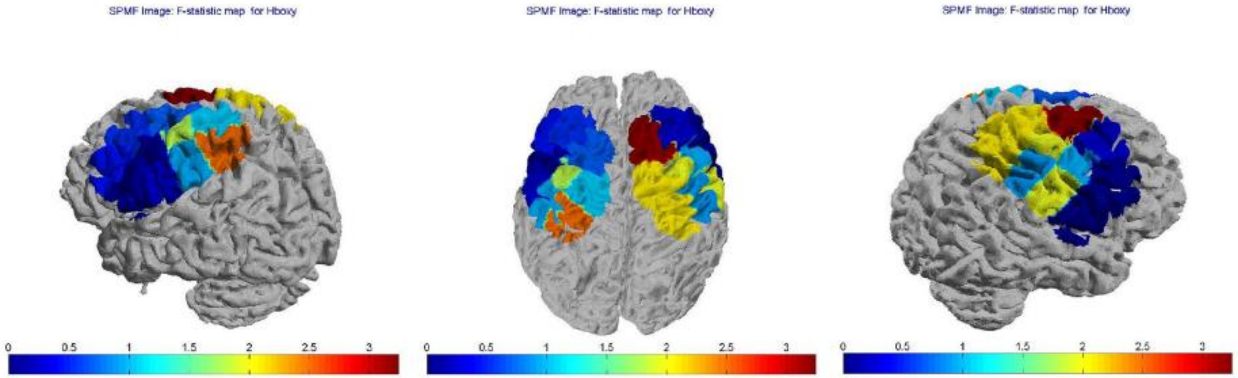
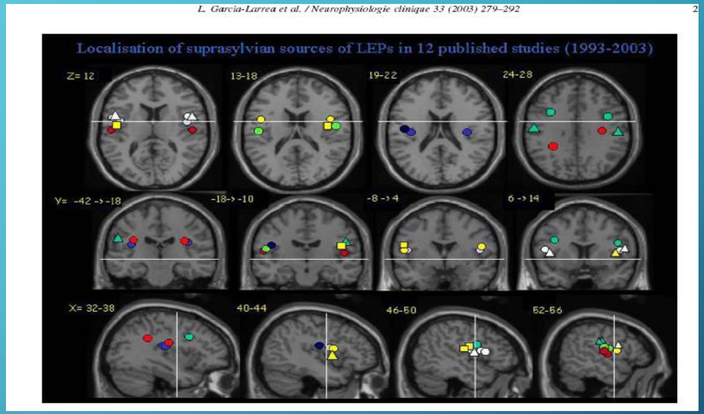


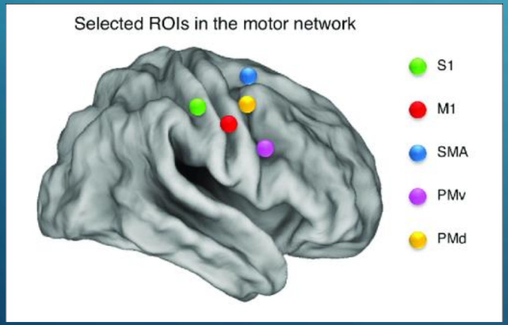
Figure 7. Topographic maps of F-statistic in the comparison among groups (FM patients vs controls) and conditions (Resting State vs Grasping Flat vs Grasping Sharp-tip object). Blue areas represent channels with no significant change in hemoglobin levels, red areas represent channels where the variations in hemoglobin levels were significant.

PAIN CAUSES MOTOR DYSFUNCTION. MOVEMENT OBSERVATION RESTORES MOTOR CORTEX DEFICIT



Pain

Motor activity



THE PARALIMBIC VISUAL NETWORK

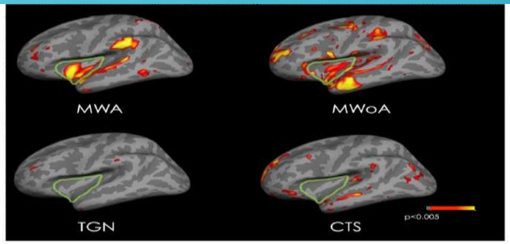
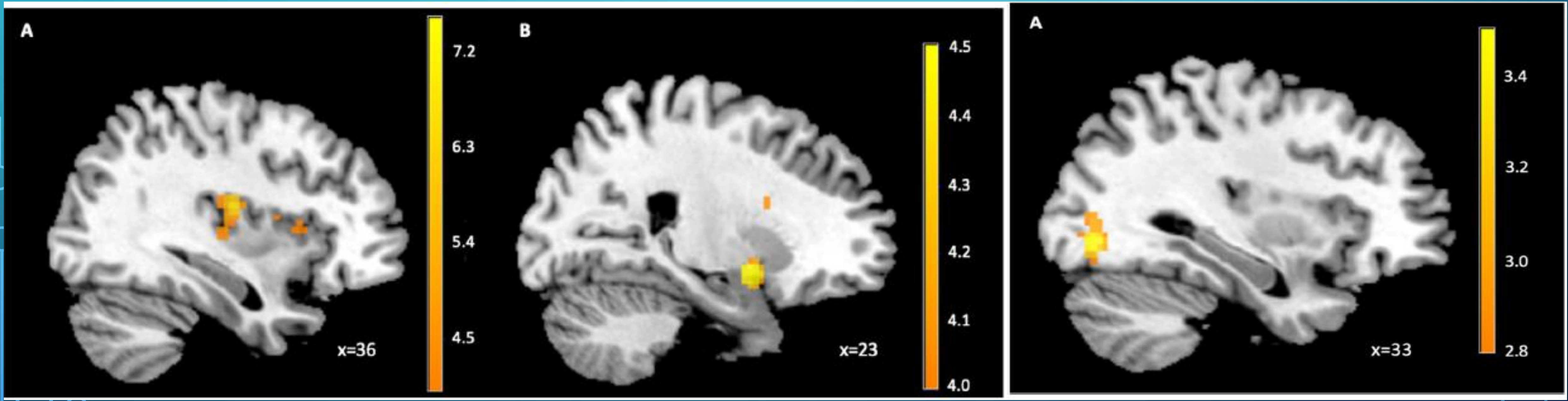


Figure 1.
Top and bottom panels: Statistical maps of connectivity between the amygdala and the rest of the brain ($p<0.005$, uncorrected), in MWA, MWoA, TGN and CTS. Although MWA exhibit the stronger connectivity between the amygdala and the insula, MWoA also present connectivity between these structures, whereas they are absent in TGN and CTS patients. The maps are displayed on the inflated cortical surface of the template FreeSurfer brain (fsaverage) on the lateral surface of the brain

Cephalalgia. 2013 November ; 33(15): 1264–1268.



NeuroImage 257 (2022) 119333

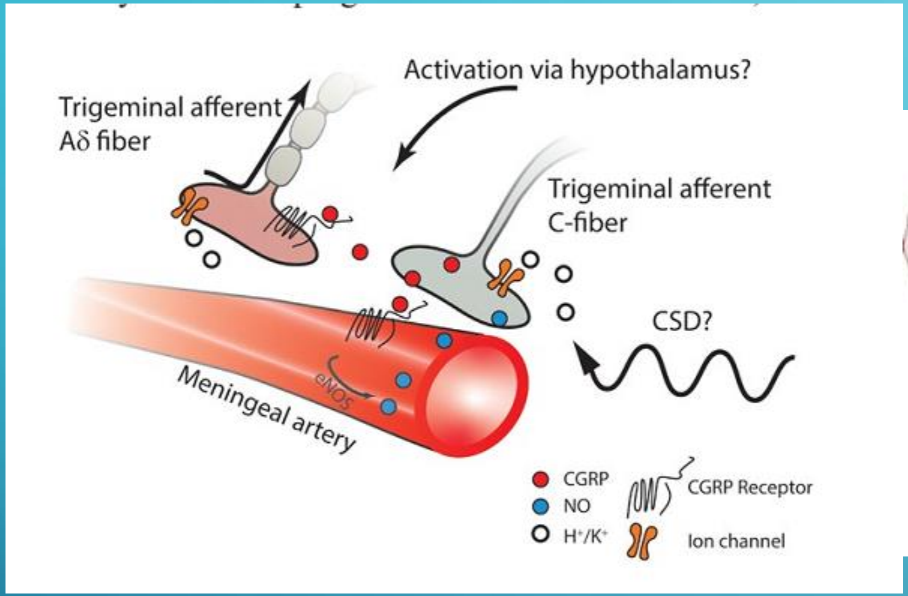
MIGRAINE: NOVEL THERAPIES FOR AN INVALIDATING DISORDER. HOW THEY COULD ACT?

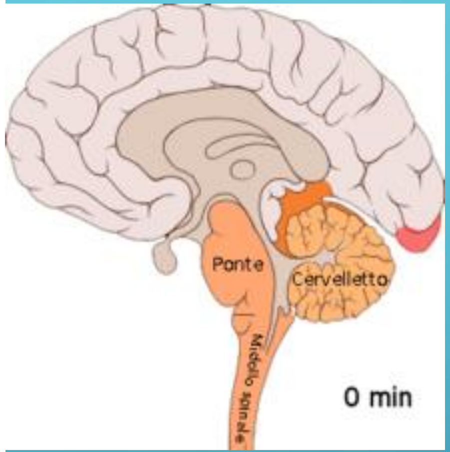
Rank: 1, 5, 10, 15

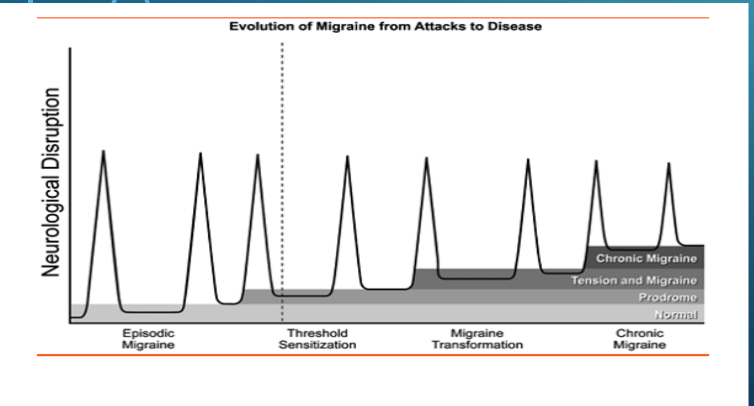
	Global	East Asia	Southeast Asia	Oceania	Central Asia	Central Europe	Eastern Europe	High-income Asia Pacific	Australasia	Western Europe	Southern Latin America	High-income North America	Caribbean	Andean Latin America	Central Latin America	Tropical Latin America	North Africa and Middle East	South Asia	Central 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.

Pathophysiology of migraine and the role of CGRP







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

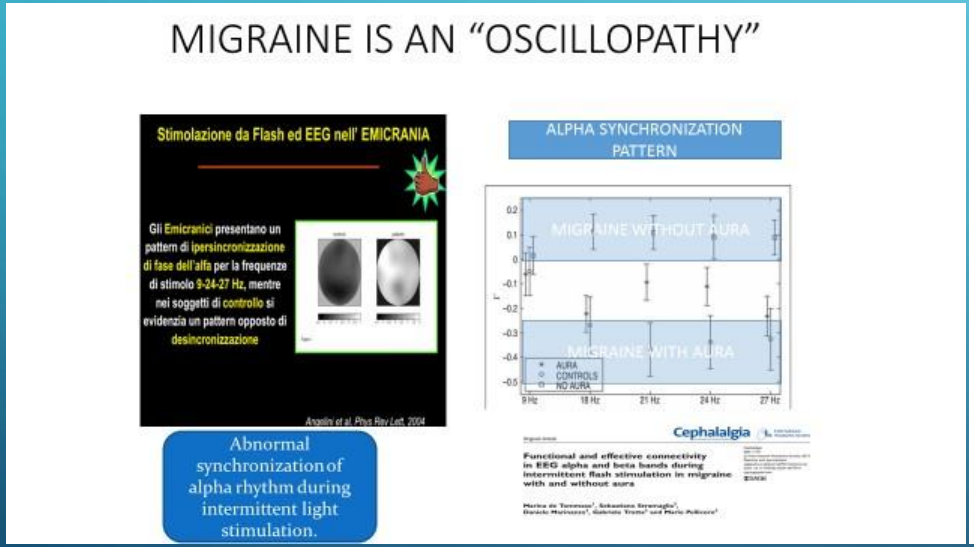
Lyudmila V Vinogradova

brain sciences

Review

Pain-Related Brain Connectivity Changes in Migraine: A Narrative Review and Proof of Concept about Possible Treatments Interference

Marina de Tommaso [1,*], Eleonora Vecchio [1], Silvia Giovanna Quitadamo [1], Gianluca Coppola [2], Antonio Di Renzo [3], Vincenzo Parisi [3], Marcello Silvestro [4], Antonio Russo [4] and Gioacchino Tedeschi [4]



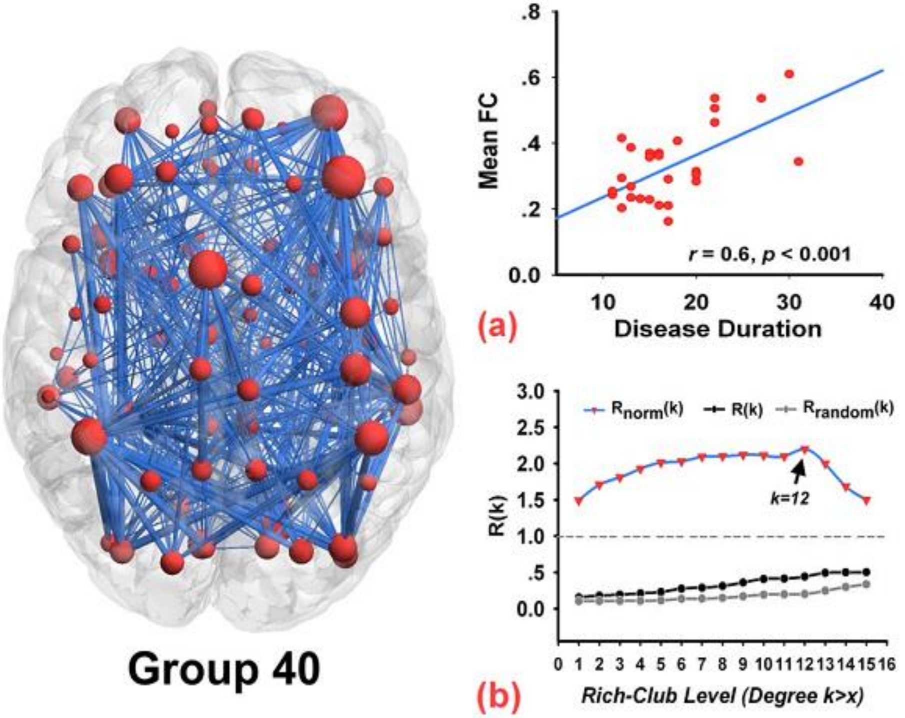


Figure 4.

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 paramet for a random graph $\boldsymbol{R}_{random}(\boldsymbol{k})$ with the same number of no and edges are shown in dark gray. The normalized rich-c coefficient $\boldsymbol{R}_{norm}(\boldsymbol{k})$ is shown by the blue line. [Color figure be viewed in the online issue, which is available at wileyonlin brary.com.]

brain sciences

MDPI

Article

Dynamic Causal Modelling of the Reduced Habituation to Painful Stimuli in Migraine: An EEG Study

Iege Bassez [1,*], Frederik Van de Steen [1], Katia Ricci [2], Eleonora Vecchio [2], Eleonora Gentile [2], Daniele Marinazzo [1] and Marina de Tommaso [2,*]

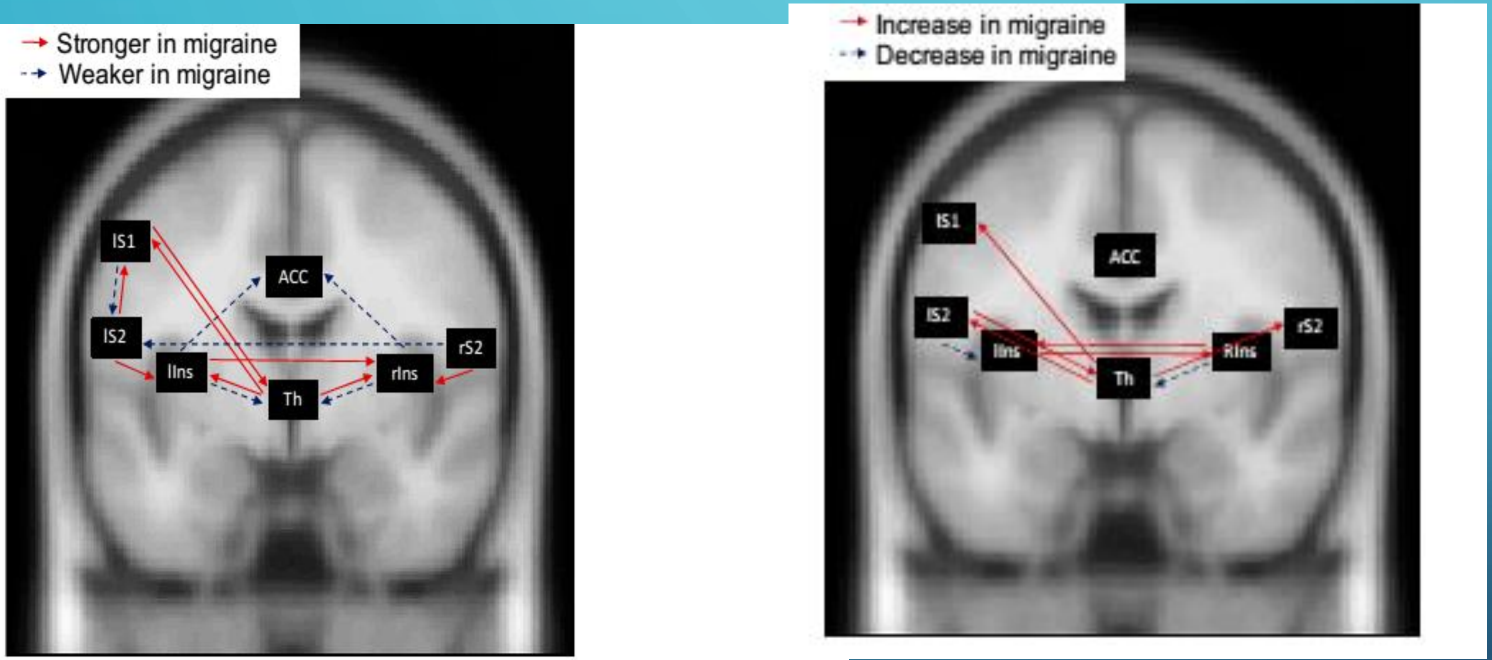


Figure 3. Parametric empirical Bayes results on the connectivity strengths in the first block as estimated with dynamic causal modelling. Only parameters with a posterior probability of being different from zero >0.99 are visualized. Red arrows (solid arrows) indicate that the connectivity strength is stronger in the migraine group, while blue arrows (dashed arrows) indicate that the connectivity strength is weaker in the migraine group. For precise differences between groups, see main text.

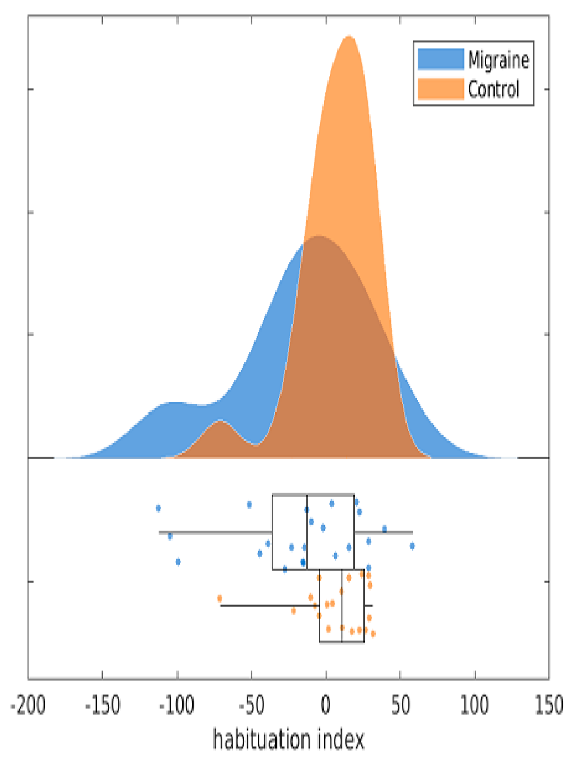


Figure 2. Habituation indices for migraine patients and healthy controls.

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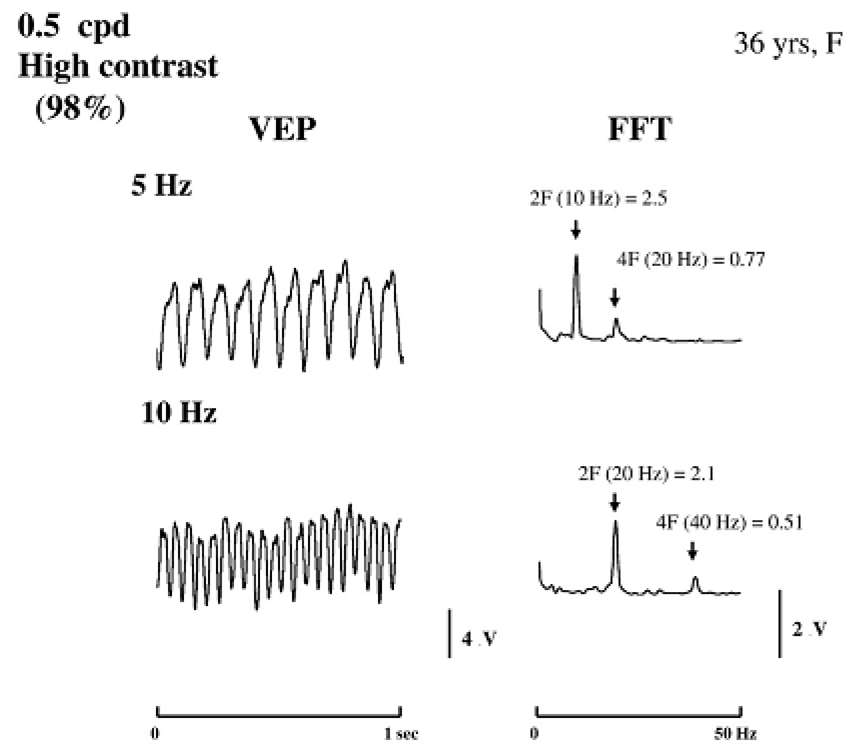
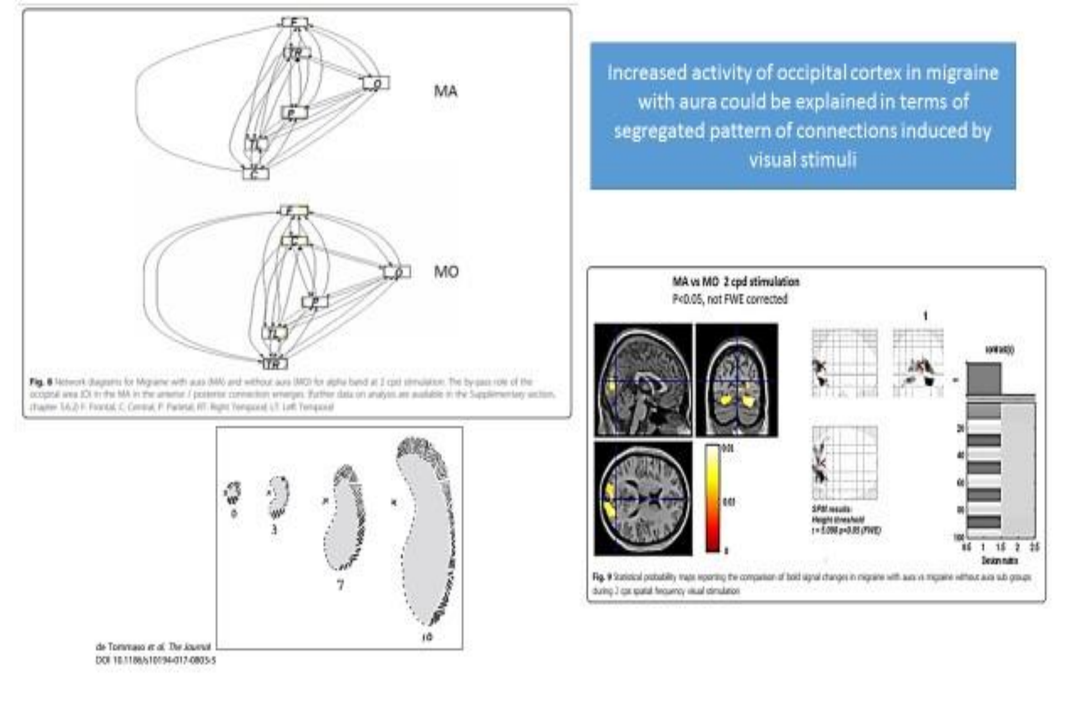
Abnormal visual processing in migraine with aura: A study of steady-state visual evoked potentials

Koichi Shibata [a,*], Kiyomi Yamane [b], Kuniaki Otuka [a], Makoto Iwata [c]

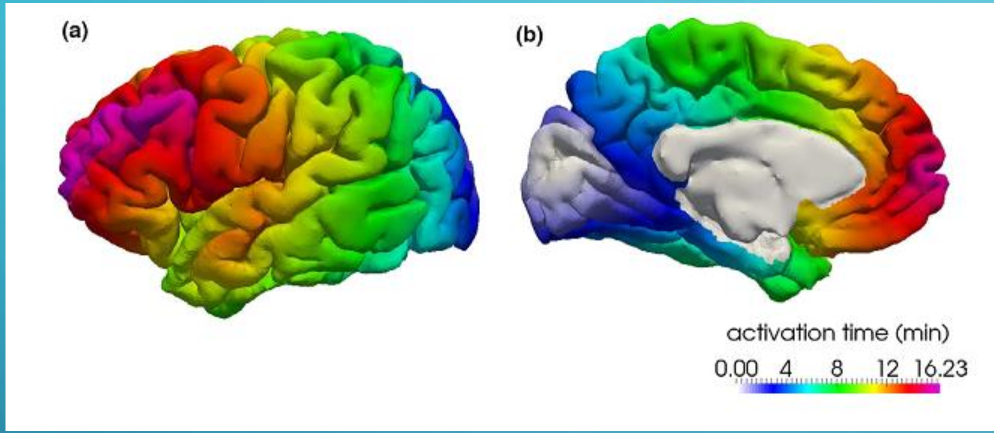
Occipital cortex in migraine

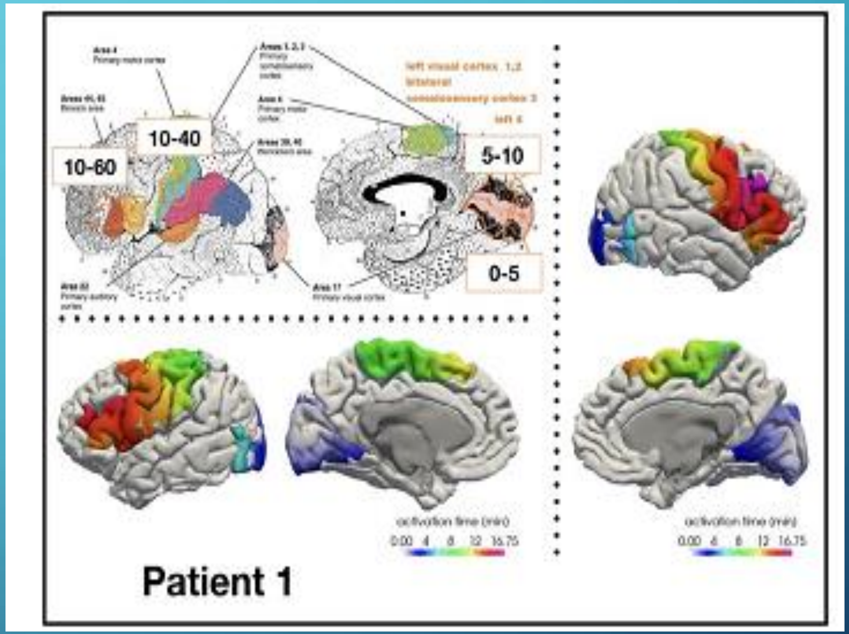
Increased amplitude of steady state visual evoked potentials, increased metabolic response and altered connectivity of occipital cortex





How peripheral modulation of CGRP receptors could prevent migraine?





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DOI: 10.1002/brb3.1387
ORIGINAL RESEARCH
Brain and Behavior WILEY

Clinical correlates of mathematical modeling of cortical spreading depression: Single-cases study

Julia M. Kroos[1] | Marina de Tommaso[2] | Sebastiano Stramaglia[3,4] | Eleonora Vecchio[2] | Nicola Burdi[5] | Luca Gerardo-Giorda[1]

Hypothesis: the inhibition of cortical regions devoted to pain processing, could exert a general modulation of cortical excitability and connectivity, and an interference on CSD progression

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Effect of single dose Erenumab on cortical responses evoked by cutaneous a-delta fibers: A pilot study in migraine patients

Cephalalgia
0(0) 1–11

DOI: 10.1177/0333102421996345
journals.sagepub.com/home/cep
SAGE

Marina de Tommaso, Marianna Delussi, Eleonora Gentile, Katia Ricci, Silvia Giovanna Quitadamo and Giuseppe Libro

Table 1. Demographic and clinical data of migraine subjects under monthly erenumab treatment at Month 0 (M0) and Month 3 (M3).

	Sex	Age (years)	Age of Illness (years)	Diag	HF M0	HF M3	VAS M0	VAS M3	All M0	All M3	Sym M0	Sym M3	Previously used drugs
BM	M	44	30	CM	30	20	10	8	7	3	30	20	Flu, Am, Top, BontA
CG	M	42	25	MO	8	2	10	9	6	4	8	1	Prop, Flu, Am, Top
DN	F	64	30	CM	30	16	10	10	6	4	30	12	Top, Am, BontA
DG	F	22	6	CM	20	9	10	7	8	4	20	3	Flu, Top, BontA
FB	M	35	20	MO+ MA	9	8	10	4	5	3	4	2	Flu, Lam, Top,
FA	F	48	30	CM	20	14	10	10	10	7	20	10	Flun, Top, Am
FD	F	21	4	CM	18	8	9	7	6	3	18	5	Top, Flu, Ami
GI*	F	38	26	CM	20	14	10	8	8	8	20	11	Am, Top, BontA
LV	M	51	43	CM	15	9	8	9	5	1	15	7	Am, Top, BontA
LA	F	42	30	MO+ MA	7	4	8	1	5	0	7	3	Prop, Flu, Top
PV*	F	18	4	CM	30	20	10	5	5	3	20	10	Am, Flu, Top
RM	F	29	10	CM	16	5	8	7	7	4	16	4	Am, Top, BontA
SA	F	60	30	MO	13	3	10	6	9	3	13	3	Am, Flu, Top,
SM	F	37	20	CM	16	4	7	3	4	0	16	3	Am, Top, BontA
SMA	F	35	15	CM	20	10	8	6	7	5	20	10	Am, Top, BontA
VA	F	51	35	CM	20	10	5	2	5	3	20	6	Am, Top, BontA
VM*	F	23	10	CM	30	20	10	8	4	1	30	16	Flu, Top, BontA
						***		***		***		***	

All: Allodynia; Am: Amitriptyline; BontA: Botulin Toxin A; CM: chronic migraine; Flu: Flunarizine; Hf: headache frequency – days with headache/month in the previous 3 months; MA: migraine with aura; MO: migraine without aura Prop: Propanolol; Sym: average number of symptomatic drugs assumed in a month; Top: Topiramate; VAS: headache intensity calculated on 0–100 numerical scale *Erenumab 140 mg.
***Results of Student's t test for paired data $p < 0.001$.

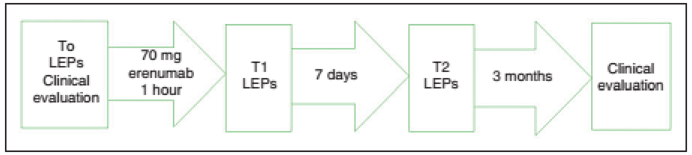

Figure 1. Study design.

How they act on central processing of pain?

de Tommaso M, Delussi M, Gentile E, Ricci K, Quitadamo SG, Libro G. Cephalalgia. 2021 Aug;41(9):1004-1014.

MILD INHIBITION OF EARLY LEP RESPONSES BY TRIGEMINAL STIMULATION. NO EFFECT ON SOMATIC LEPS

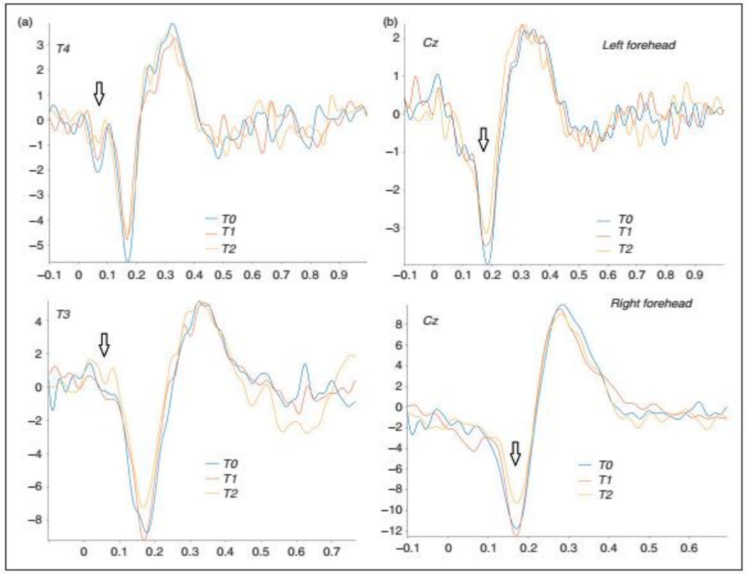

Figure 2. Grand average of laser evoked potentials in 17 migraine patients under Erenumab treatment. (a) N1 responses on temporal electrodes; (b) N2 and P2 responses on central electrodes. Arrows show the relevant amplitude changes.

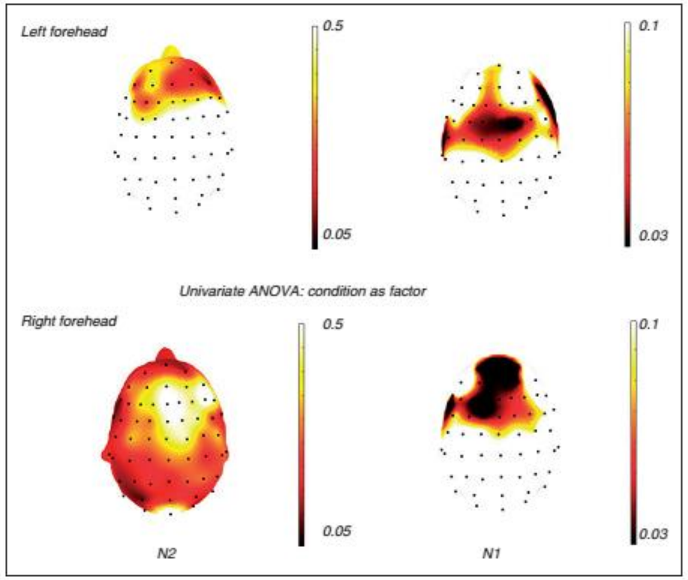

Figure 3. Statistical probability maps (SPMs) reporting p-values obtained from the repeated measures ANOVA between T0, T1 and T2 conditions for the N1 and N2 amplitudes in 17 migraine patients. Black expresses the topographical distribution of statistically significant comparison among the three conditions.

How they act on central processing of pain?

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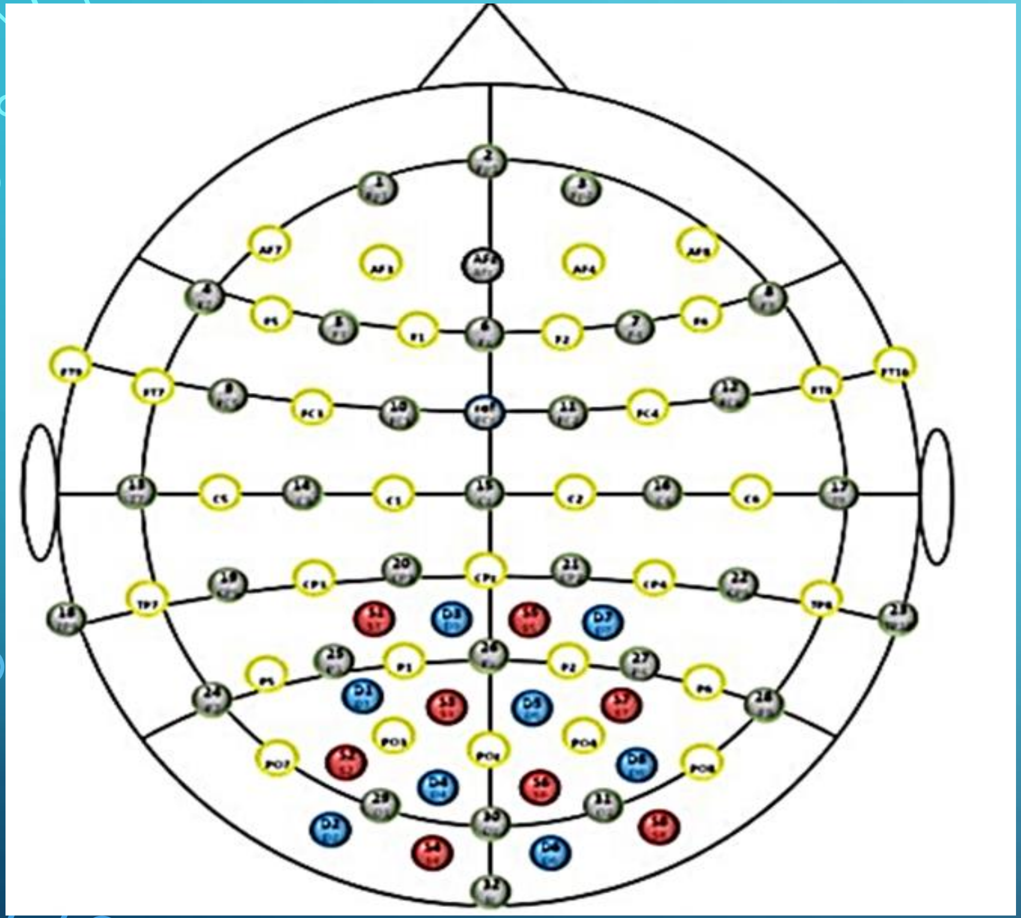
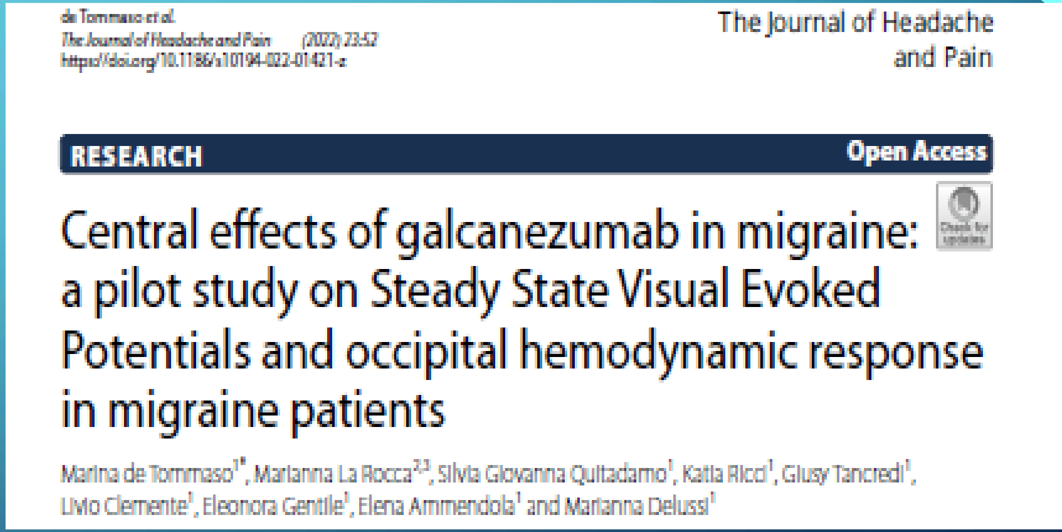
Signal acquisition

How they act on abnormal cortical excitability?

de Tommaso M, La Rocca M, Quitadamo SG, Ricci K, Tancredi G, Clemente L, G entile E, Ammendola E, Delussi M.. J Headache Pain. 2022 Apr 29;23(1):52.





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The Journal of Headache and Pain

RESEARCH Open Access

Central effects of galcanezumab in migraine: a pilot study on Steady State Visual Evoked Potentials and occipital hemodynamic response in migraine patients

Marina de Tommaso[1*], Marianna La Rocca[2,3], Silvia Giovanna Quitadamo[1], Katia Ricci[1], Giusy Tancredi[1], Livio Clemente[1], Eleonora Gentile[1], Elena Ammendola[1] and Marianna Delussi[1]

EEG results

How they act on abnormal cortical excitability?

de Tommaso M, La Rocca M, Quitadamo SG, Ricci K, Tancredi G, Clemente L, G entile E, Ammendola E, Delussi M.. J Headache Pain. 2022 Apr 29;23(1):52.

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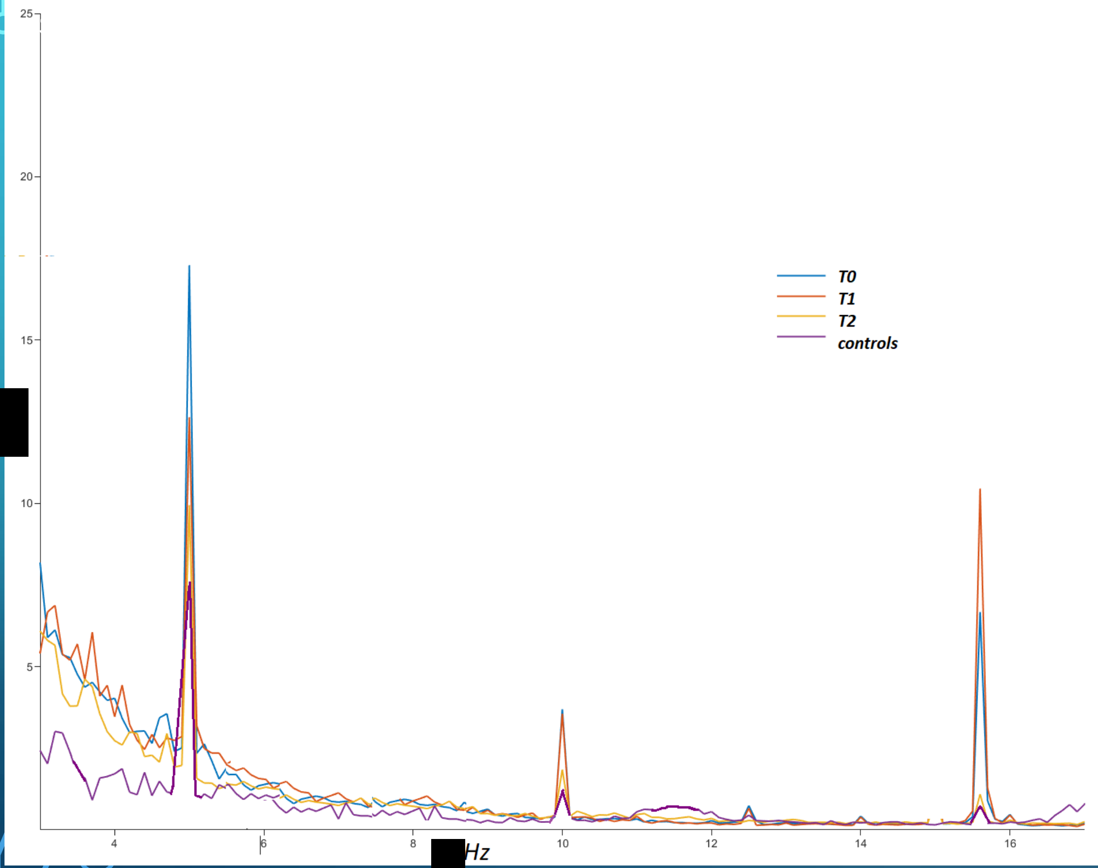
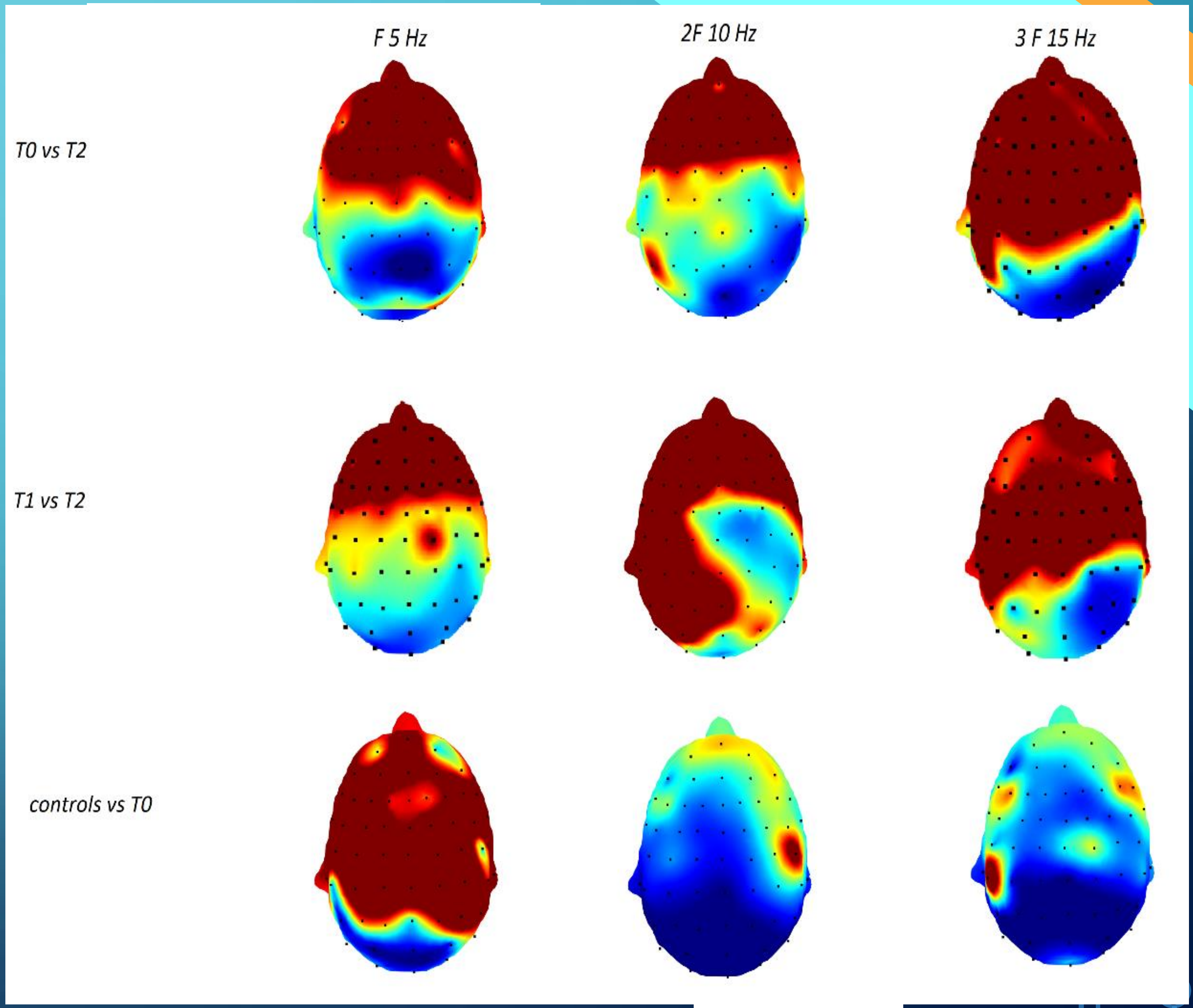


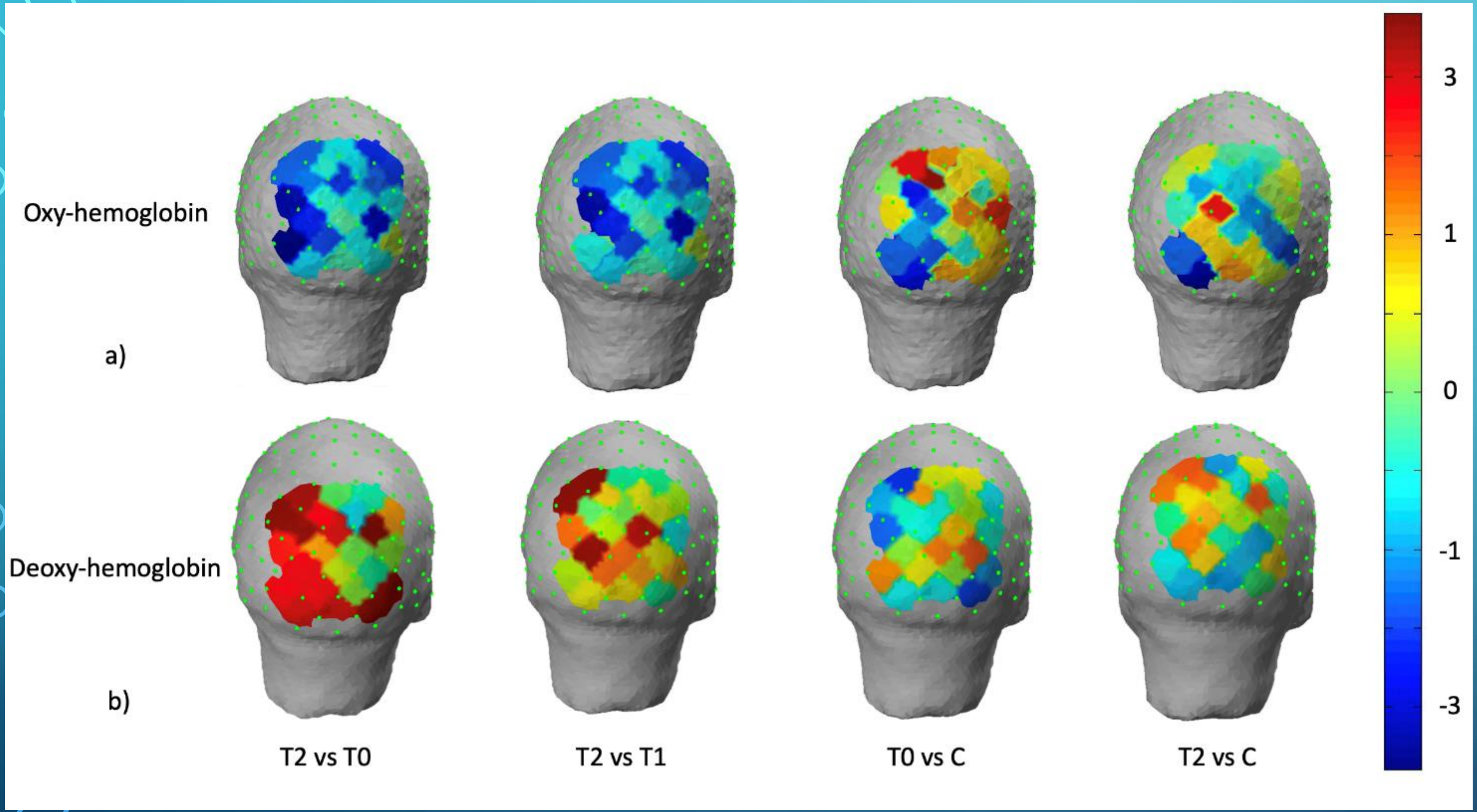
Frequency (Hz)



Results

How they act on abnormal cortical excitability?

de Tommaso M, La Rocca M, Quitadamo SG, Ricci K, Tancredi G, Clemente L, Gentile E, Ammendola E, Delussi M.. J Headache Pain. 2022 Apr 29;23(1):52.

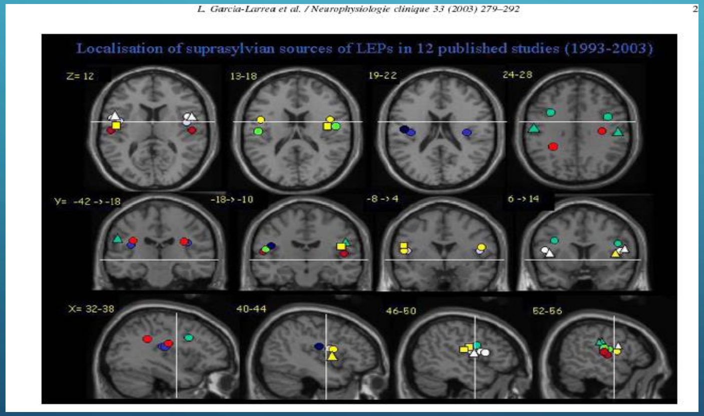


The paired Student's t test showed a general reduction of the oxyhemoglobin concentration at T2 compared with T0 and T1 , with significance ($p<0.05$) on left occipital channels and a general increase in deoxyhemoglobin at T2, with significance on left and right occipital channels for T2 vs T0, and on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

The Journal of Headache and Pain, 2022

PAIN IS A PRIMARY FUNCTION. THE CORTICAL ZONES DEVOTED TO PAIN PROCESSING ARE STRICTLY INTEGRATED TO MOTOR AND MULTIMODAL SENSORY AREAS.

RESOLVING PAIN IN CHRONIC PATIENTS, LEAD TO A GENERAL RESET OF ABNORMAL NEURONAL EXCITABILITY AND CONNECTIVITY CAUSING THE DISEASE ITSELF



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