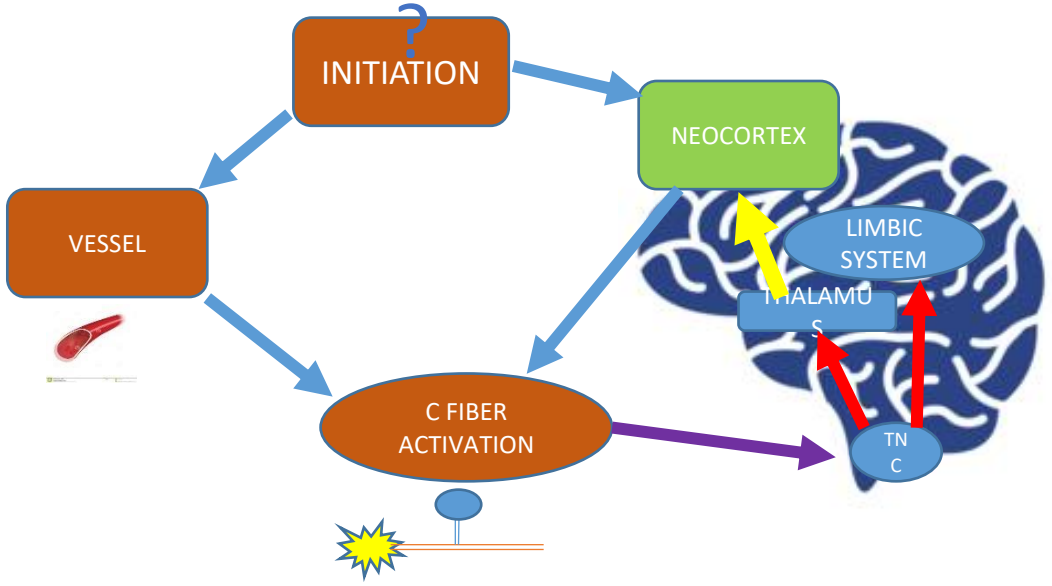
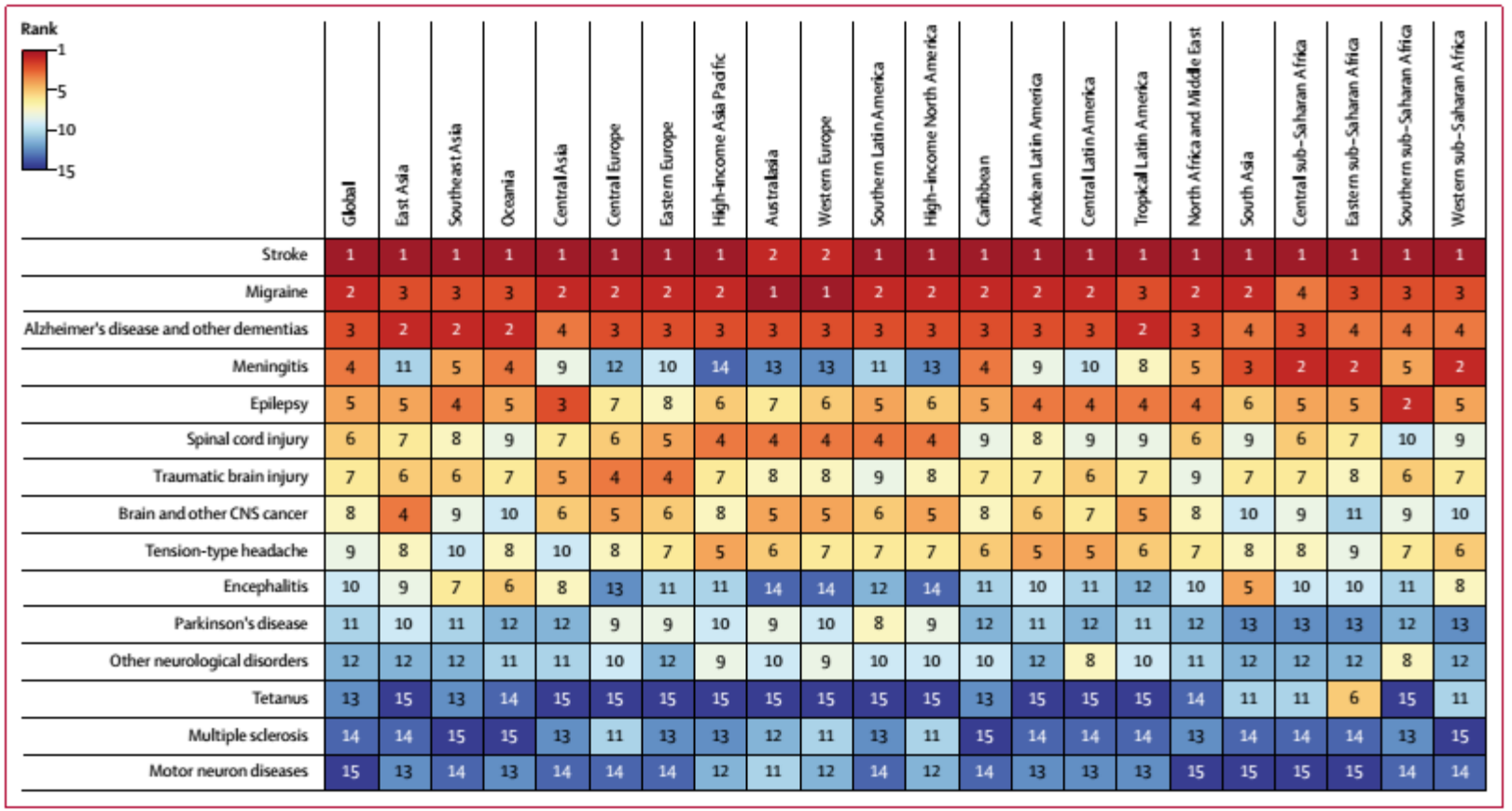
Peripheral interference by CGRP inhibition on basic cortical dysfunction

Marina de Tommaso (Bari)



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

*GBD 2016 Neurology Collaborators**



	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.

TWO MAIN ASPECTS OF MIGRAINE:
1 MECHANISMS PREDISPOSING TO CORTICAL SPREADING DEPRESSION
2 MECHANISMS PREDISPOSING TO CHRONIC EVOLUTION

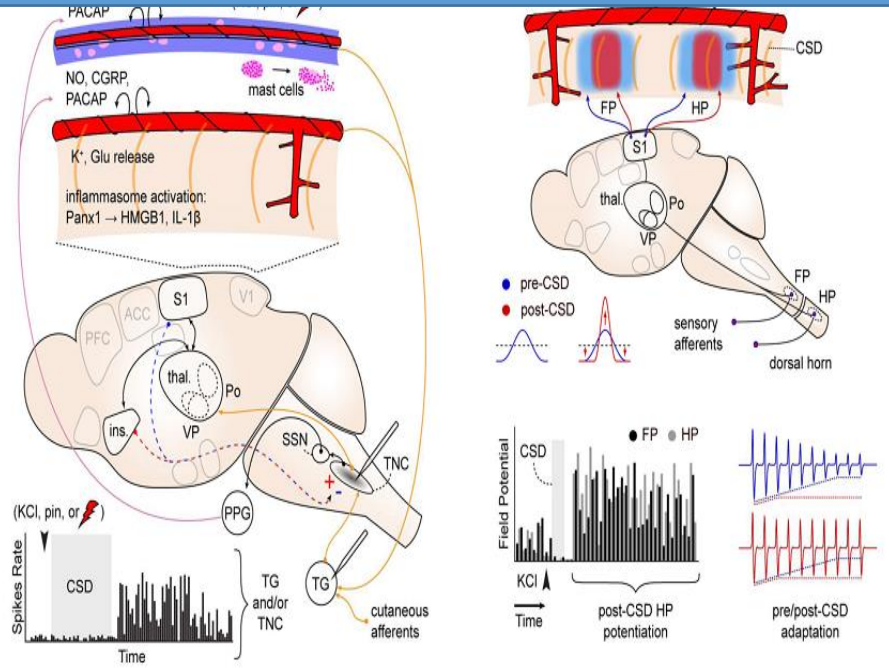
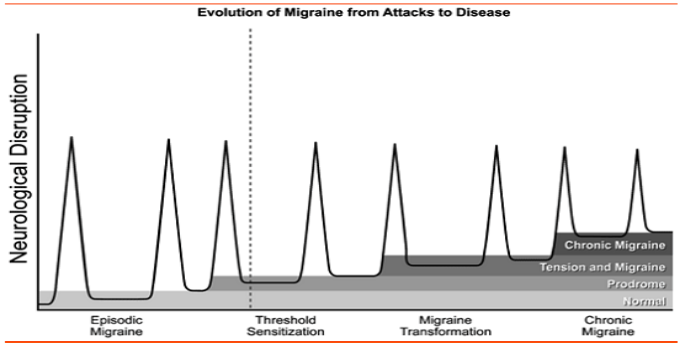
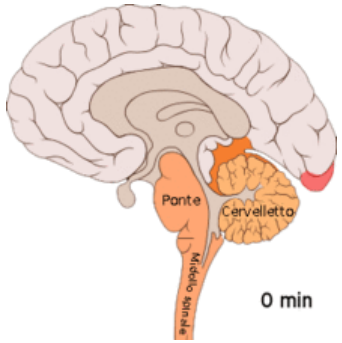


Figure 3. Effects of CSD on network activity

A. Spontaneous firing rate of TG and TNC neurons increases after experimentally-

ecording sites indicated on schematic. c-fos immediate





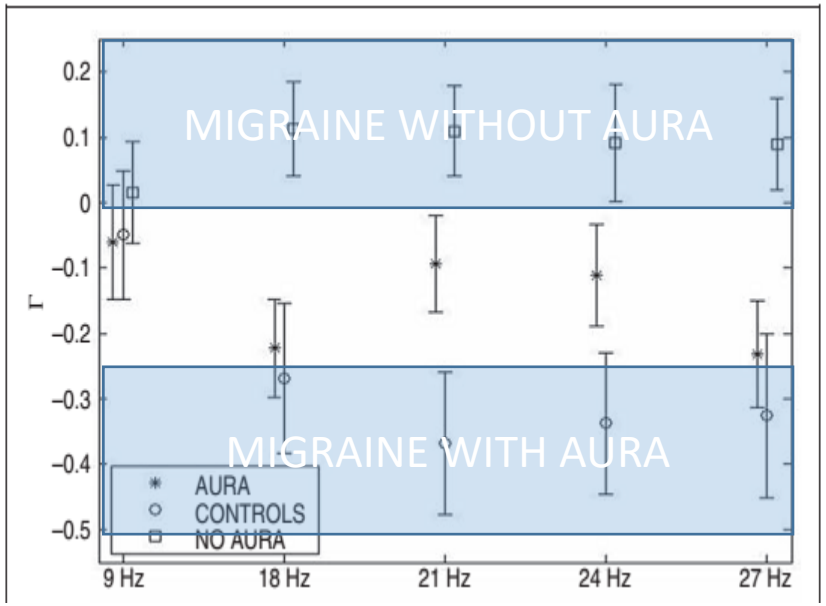
Initiation of spreading depression by synaptic and network hyperactivity: Insights into trigger mechanisms of migraine aura

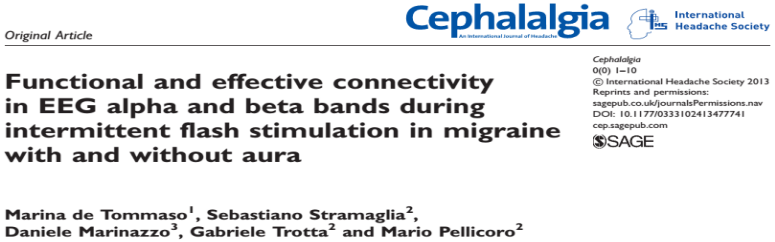
Lyudmila V Vinogradova

MIGRAINE IS AN “OSCILLOPATHY”

Abnormal synchronization of alpha rhythm during intermittent light stimulation.

ALPHA SYNCHRONIZATION PATTERN




Original Article

Cephalalgia

International Headache Society

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

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

Cephalalgia
0(0) 1–10

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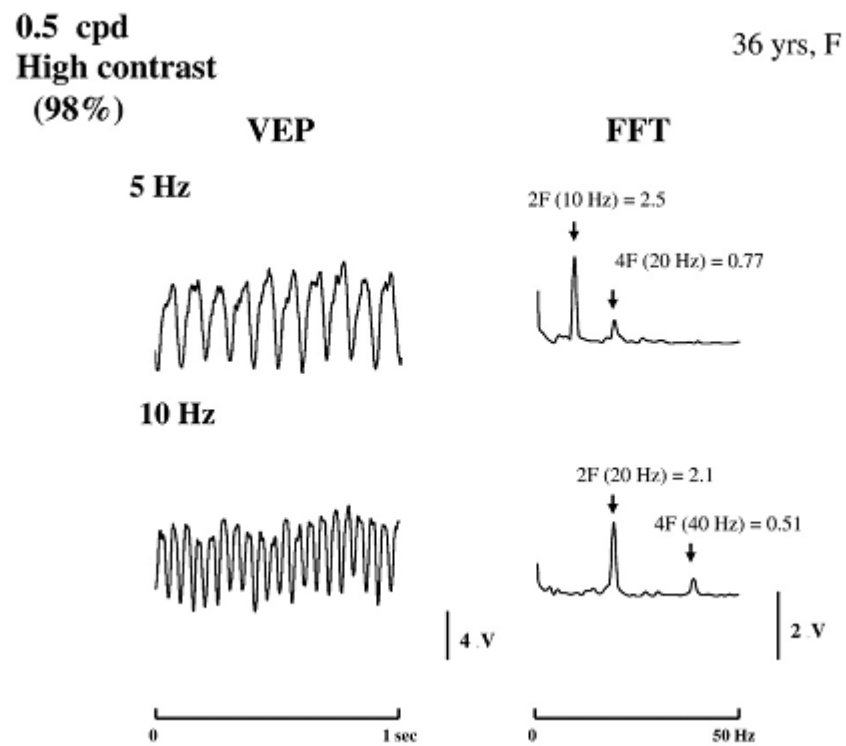
Journal of the Neurological Sciences 271 (2008) 119–126

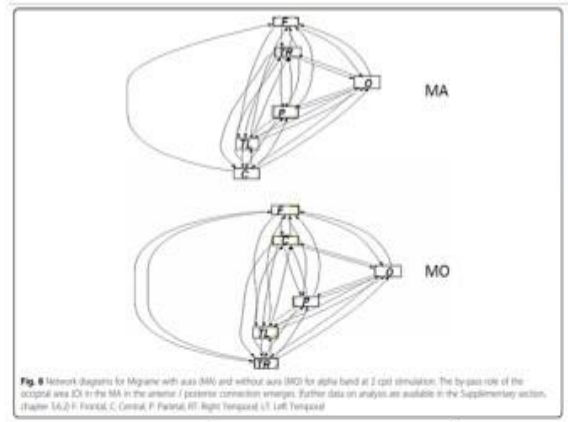
Journal of the Neurological Sciences

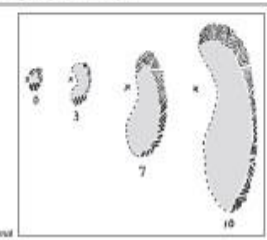
www.elsevier.com/locate/jns

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

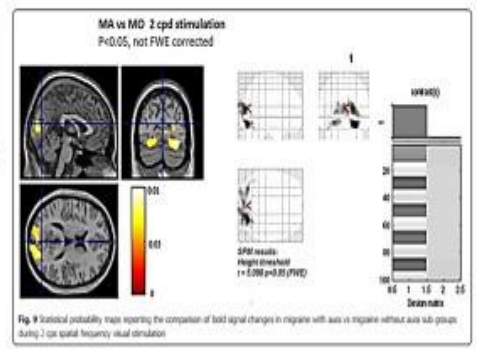
Koichi Shibata [a,*], Kiyomi Yamane [b], Kuniaki Otuka [a], Makoto Iwata [c]



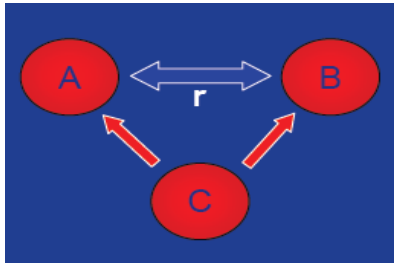




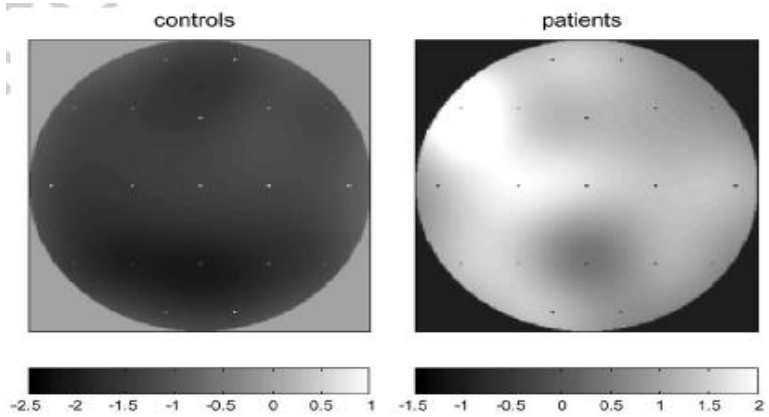
Increased activity of occipital cortex in migraine with aura could be explained in terms of segregated pattern of connections induced by visual stimuli



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

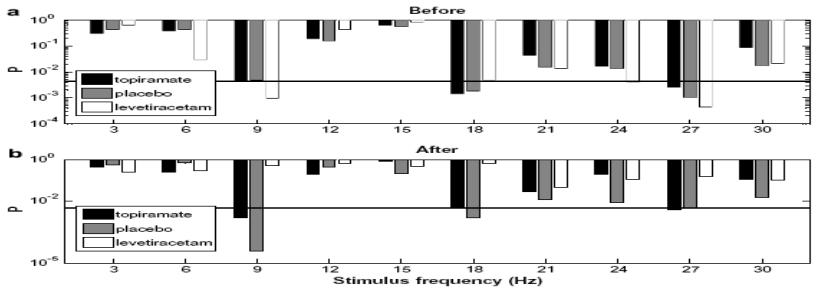


Alpha hypersynchronization under visual stimuli)



(Angelini et al, 2004

Complex modulation by AEDs



(de tommaso et al, 2007)

No effect by LF rTMS cortical inhibition

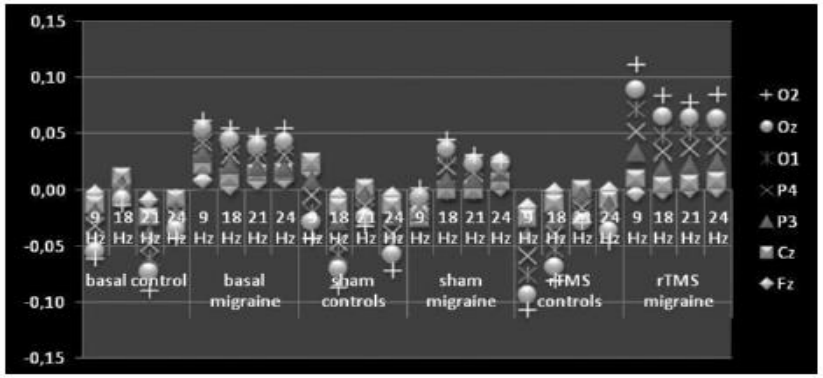
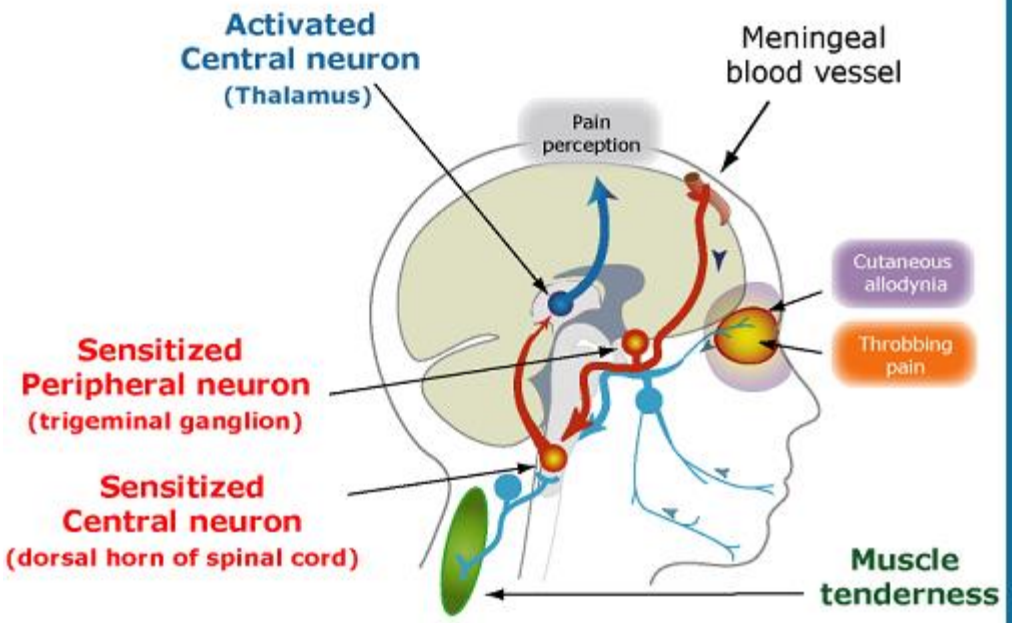
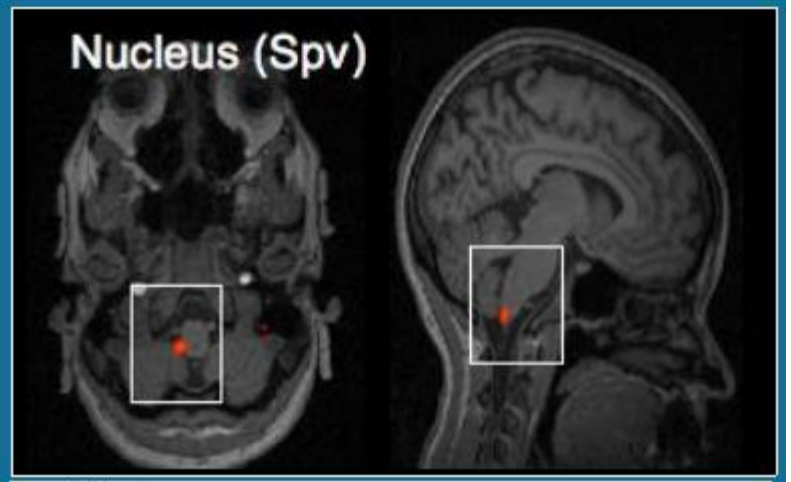


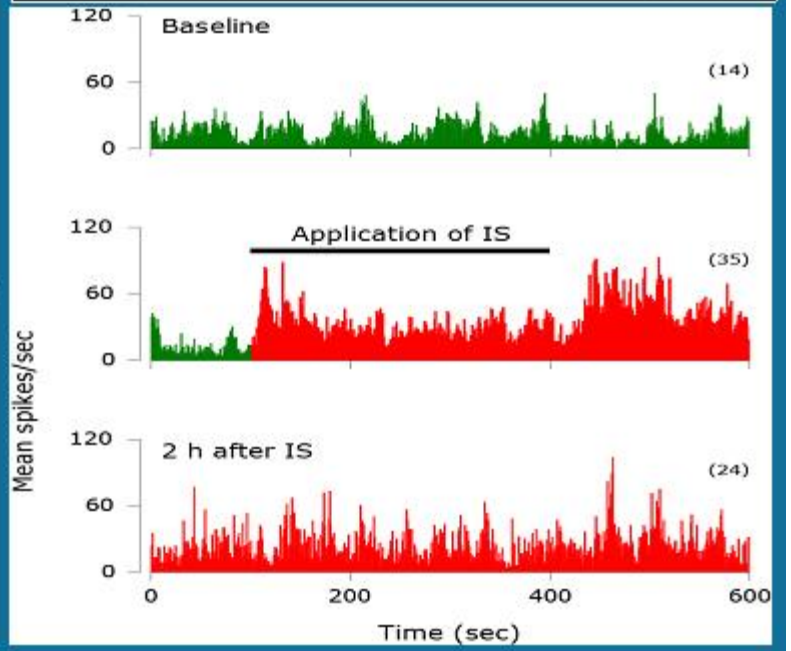
Fig. 1. Mean values of synchronization index Γ computed across migraine patients (no. 15) and controls (no. 10). The standard deviations are detailed in the supplementary table.

(de tommaso et al, 2011)

Central sensitisation in the spinal cord mediates skin hypersensitivity and muscle tenderness

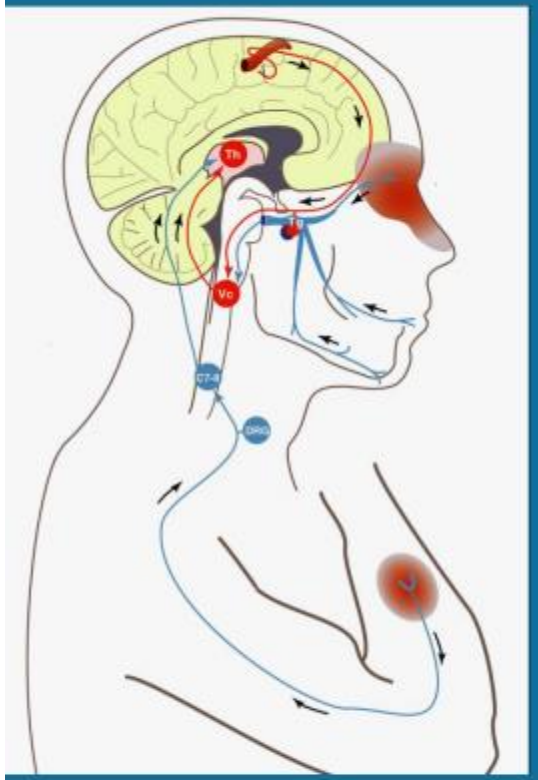


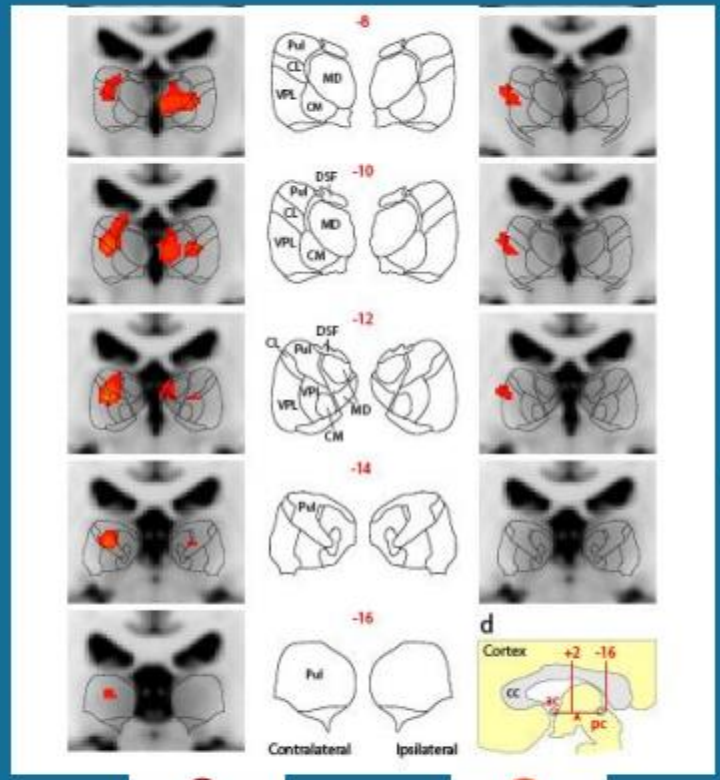


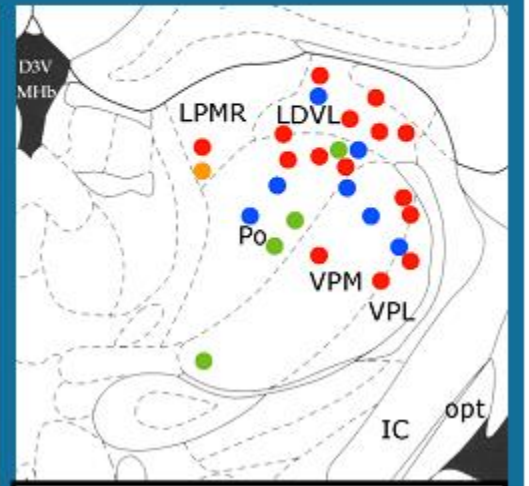


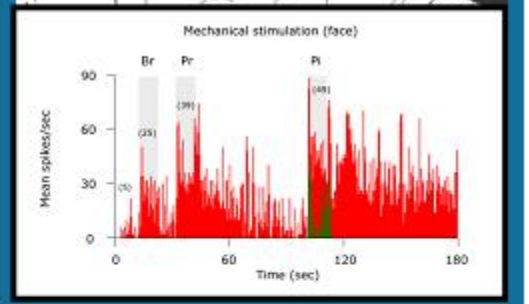
Burstein and Jakubowski (2004) Ann. Neurol. 55:27-36; Burstein et al., (2004) Ann. Neurol. 55:19-26; Noseda et al., (2013) Pain 154:S44-53

Sensitisation of thalamic trigeminovascular neurons mediates whole-body allodynia









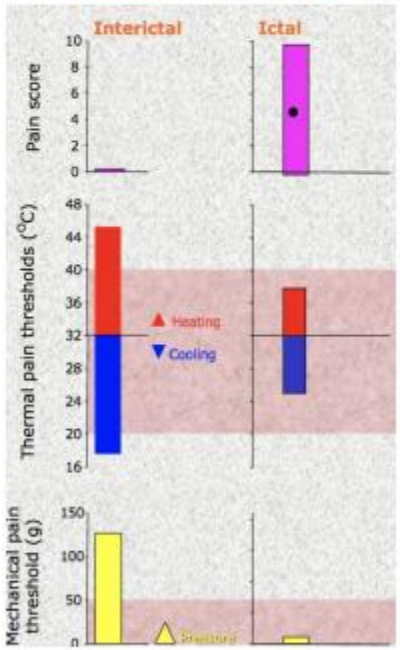
Noseda et al., (2013) Pain 154:S44-53; Burstein et al., (2010) Ann. Neurol. 68:81-91

Progression of disease: chronic state of central sensitisation leads to interictal allodynia and background headache

Episodic migraine

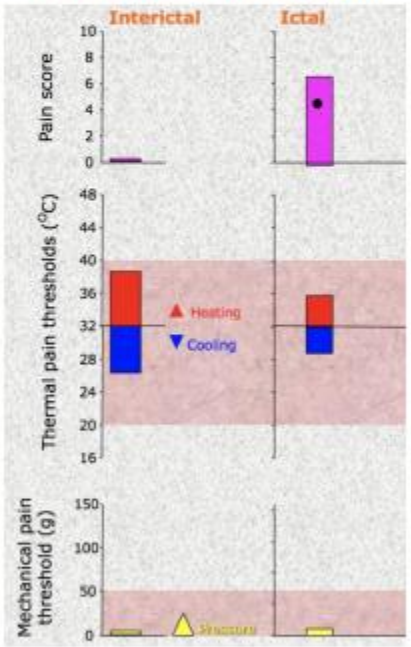
no allodynia

allodynia

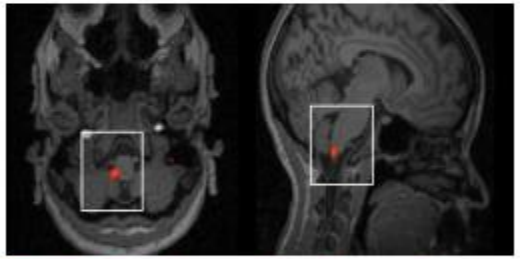


Chronic migraine

allodynia allodynia



Chronically sensitised spinal trigeminal nucleus mediates the ongoing headache and the interictal cephalic allodynia



Spinal trigeminal nucleus

Burstein et al., (2004) Ann. Neurol. 55(1) 19-26; Noseda and Burstein, (2013) Pain 154; S44-S53

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

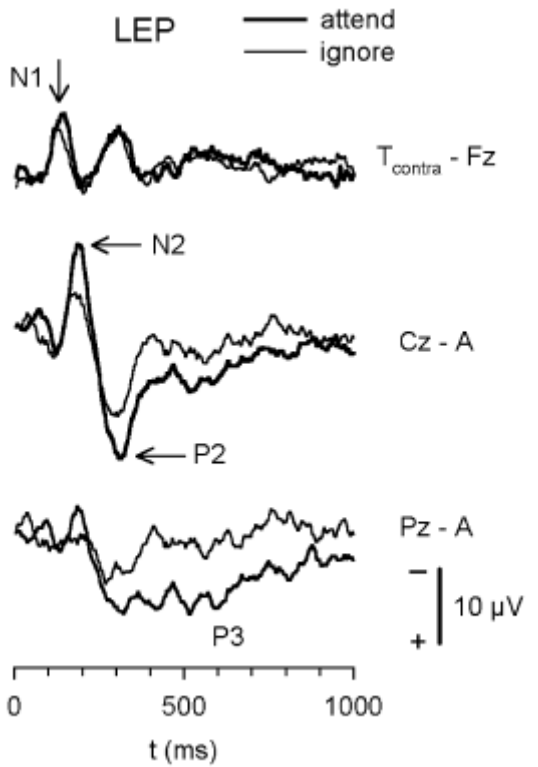
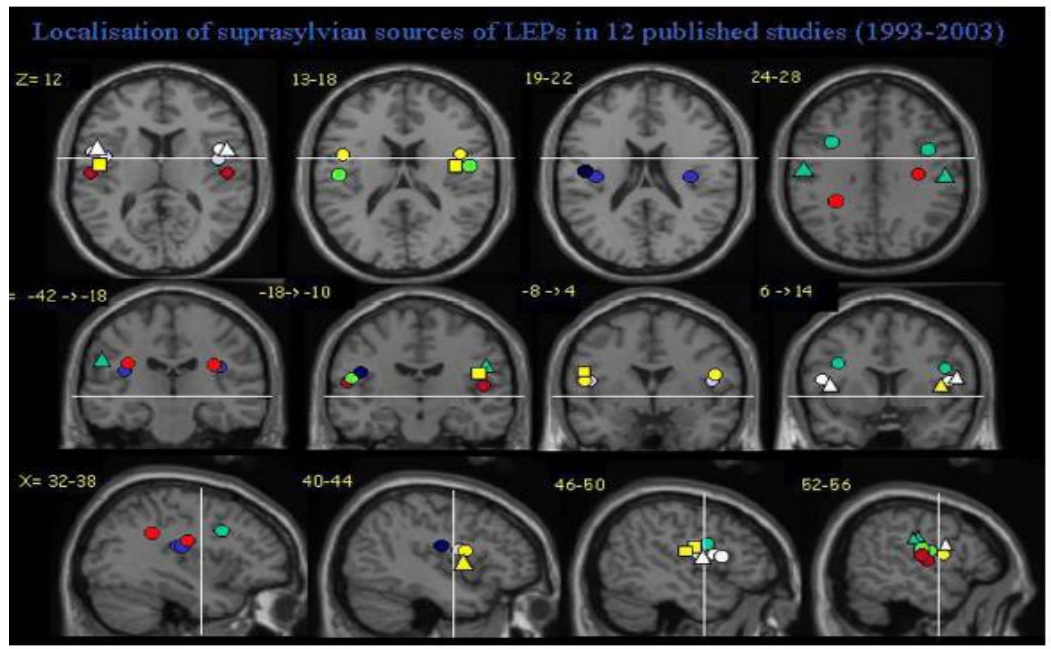
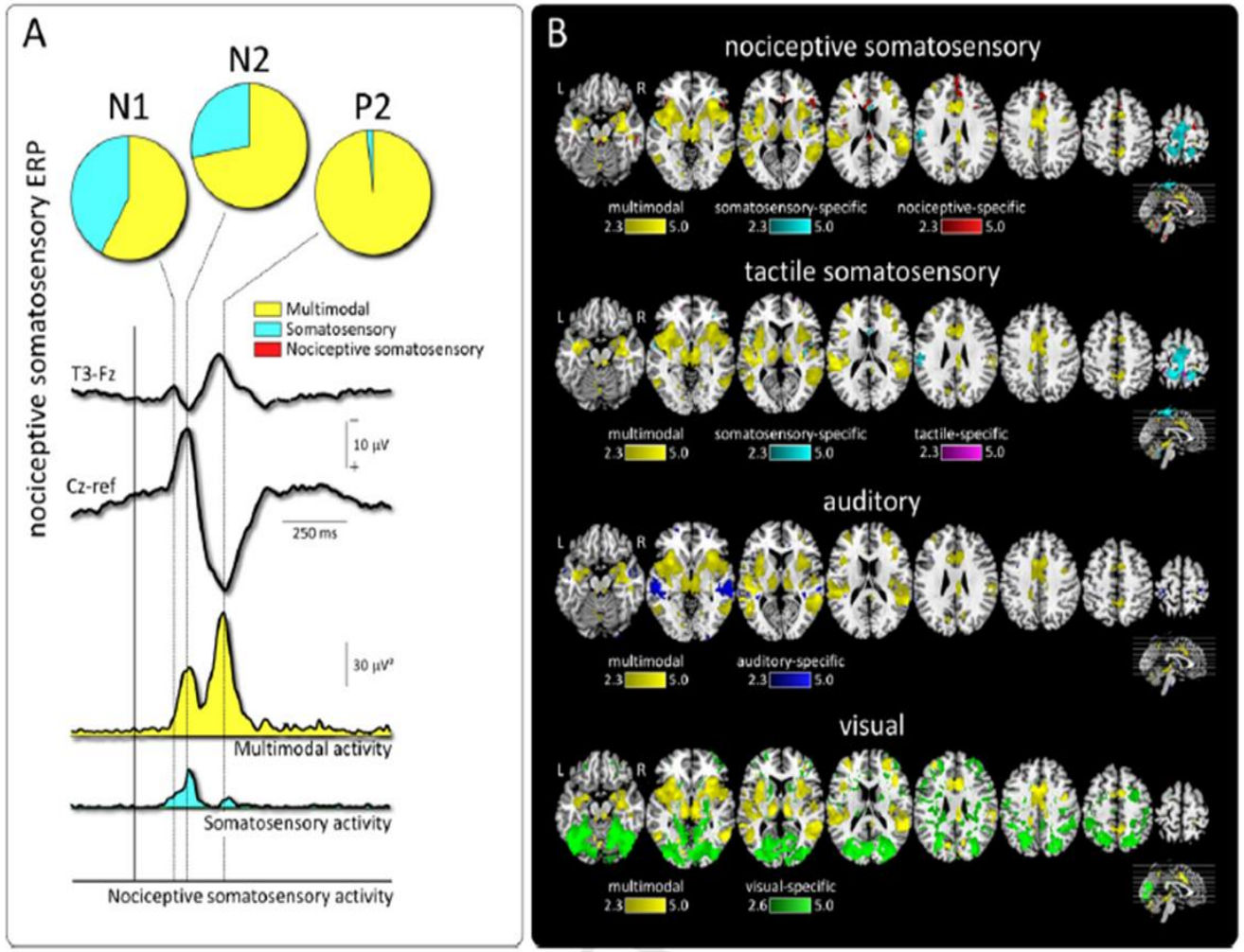
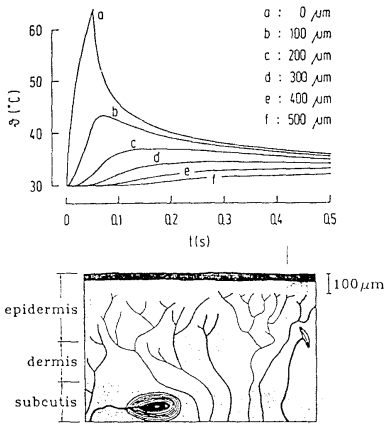


Fig. 2. LEP components and attention effects. Early component N1, late



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





….but they could reflect a modality of pain processing

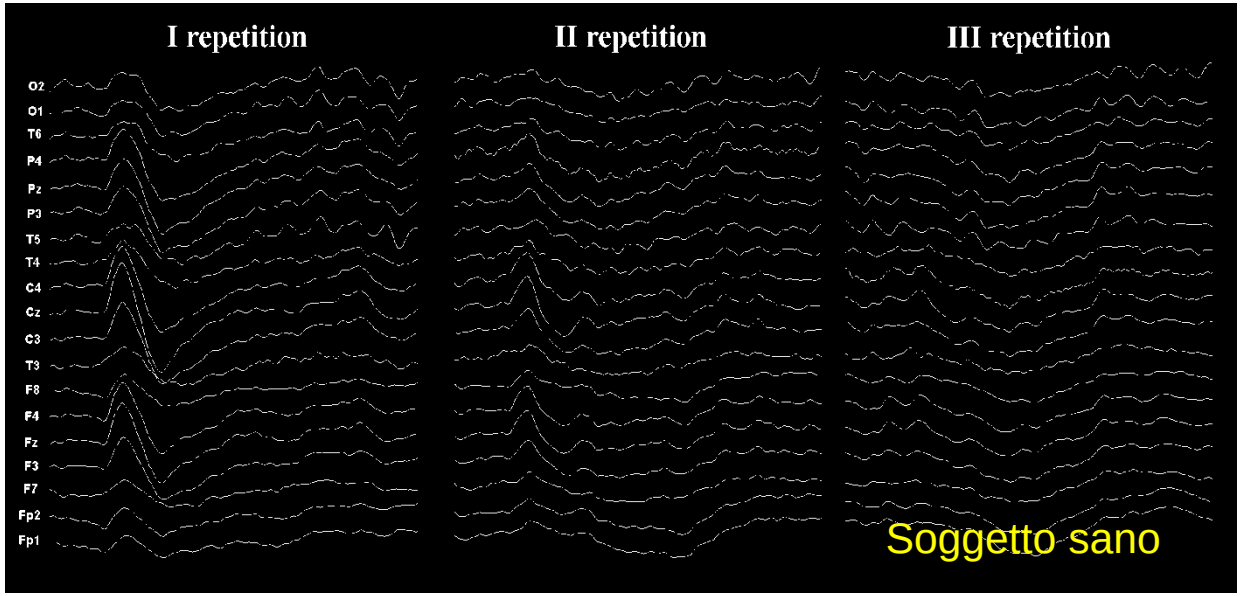
REDUCED HABITUATION TO REPETITIVE LASER STIMULATION: A SIGNATURE OF MIGRAINE AND CENTRAL SENSITIZATION PHENOMENA PREDISPOSITION

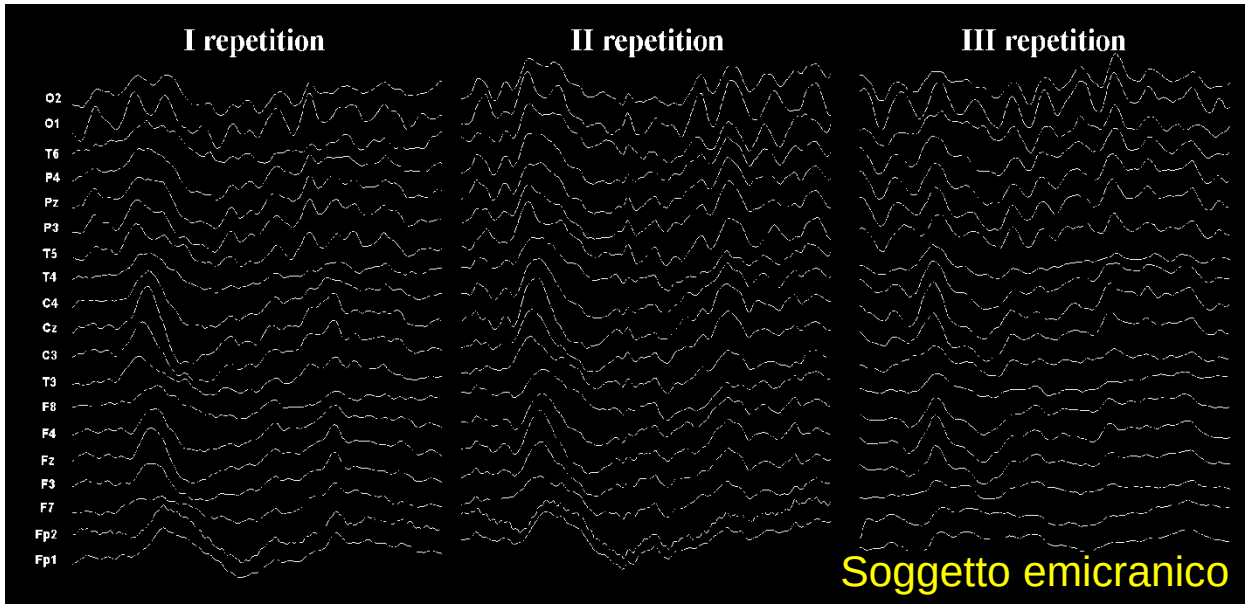
Valeriani et al., 2003

PAIN

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

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





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

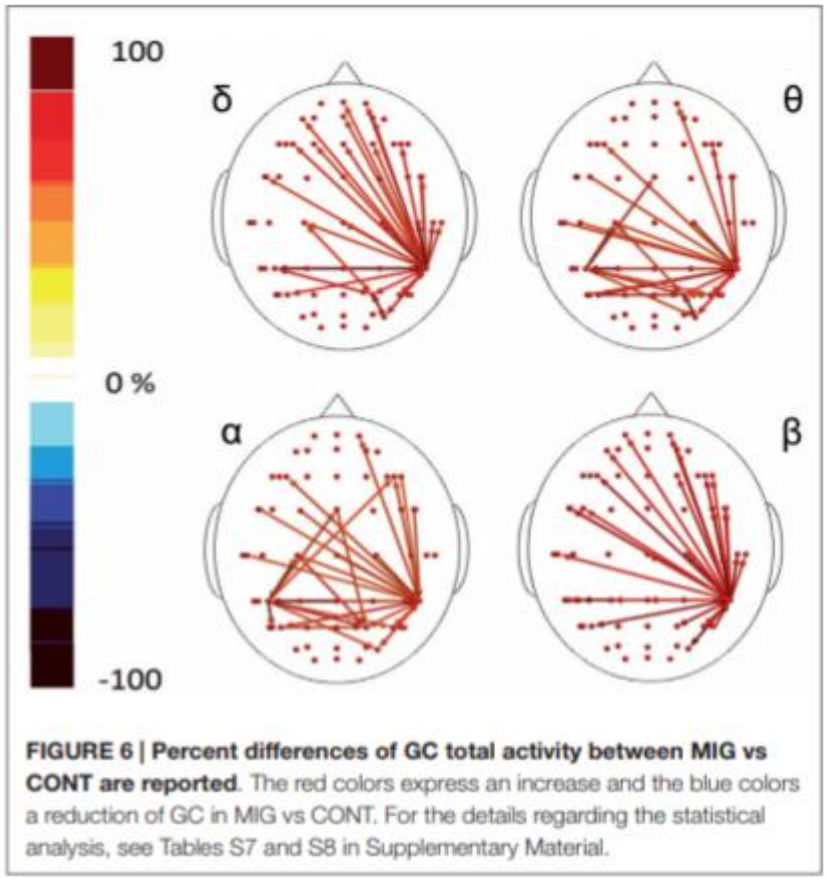


FIGURE 6 | Percent differences of GC total activity between MIG vs CONT are reported. The red colors express an increase and the blue colors a reduction of GC in MIG vs CONT. For the details regarding the statistical analysis, see Tables S7 and S8 in Supplementary Material.

frontiers in Human Neuroscience

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

..this is the counterpart of reduced habituation

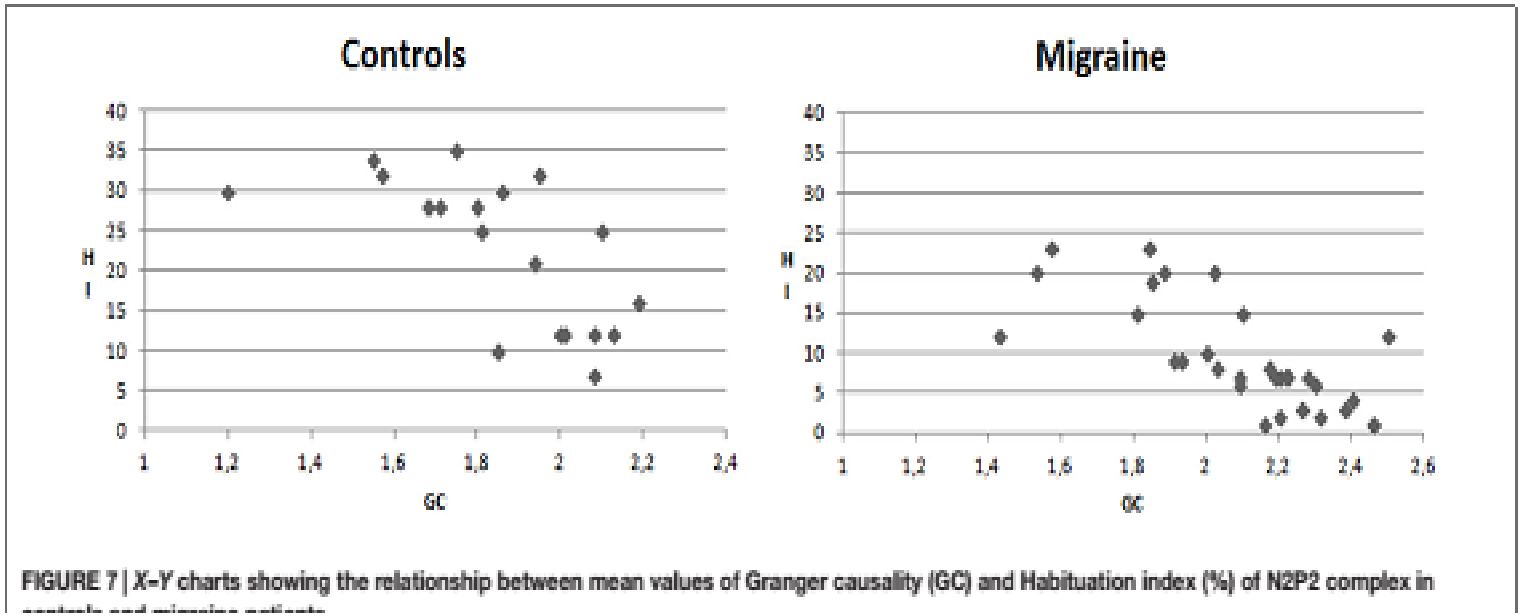
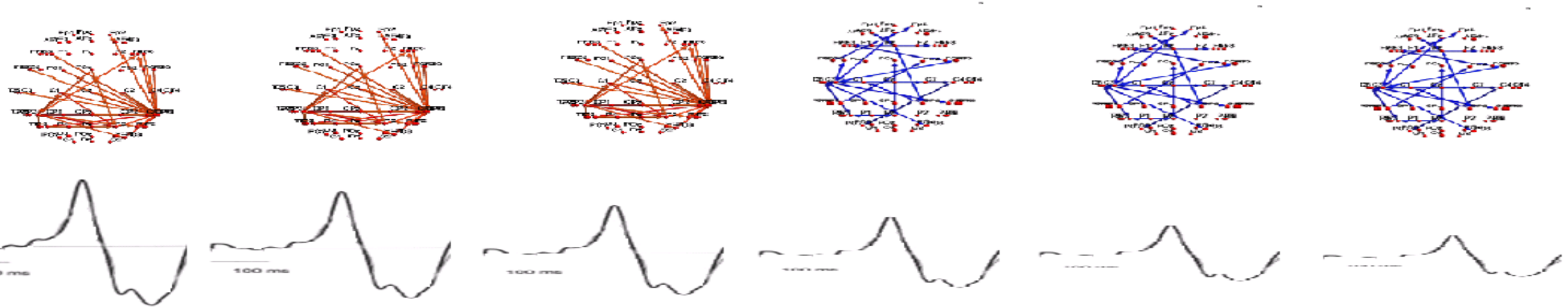


FIGURE 7 | *X–Y* charts showing the relationship between mean values of Granger causality (GC) and Habituation index (%) of N2P2 complex in



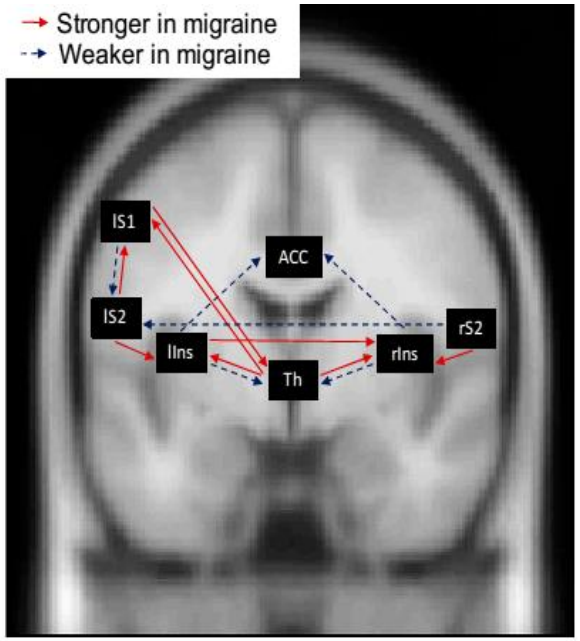
brain sciences

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,*]



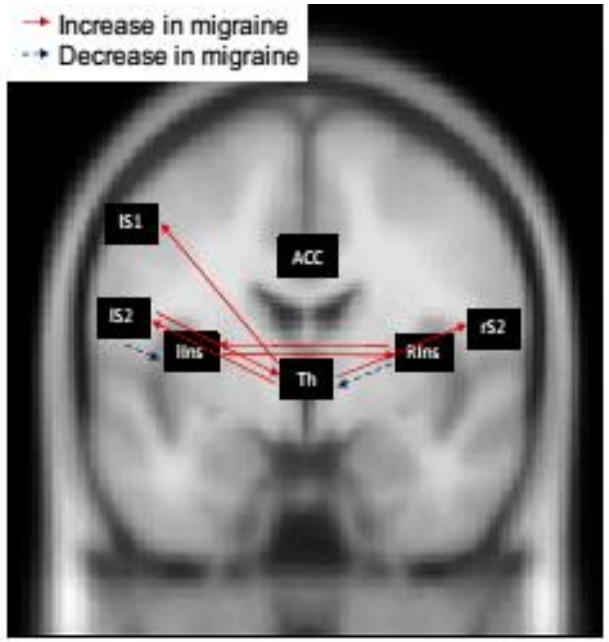


Figure 3. Parametric empirical Bayes results on the connectivity strengths in the first block as estimated with dynamic causal modelling. Only parameters with a posterior probability of being different from zero >0.99 are visualized. Red arrows (solid arrows) indicate that the connectivity strength is 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.

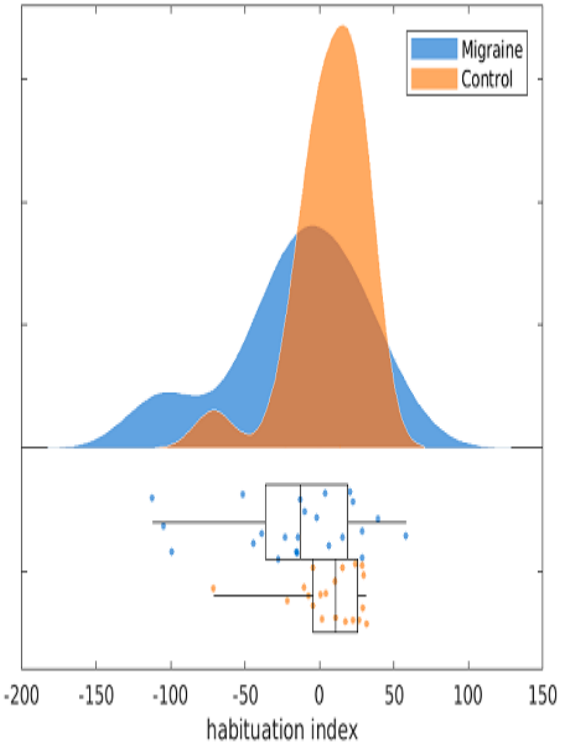
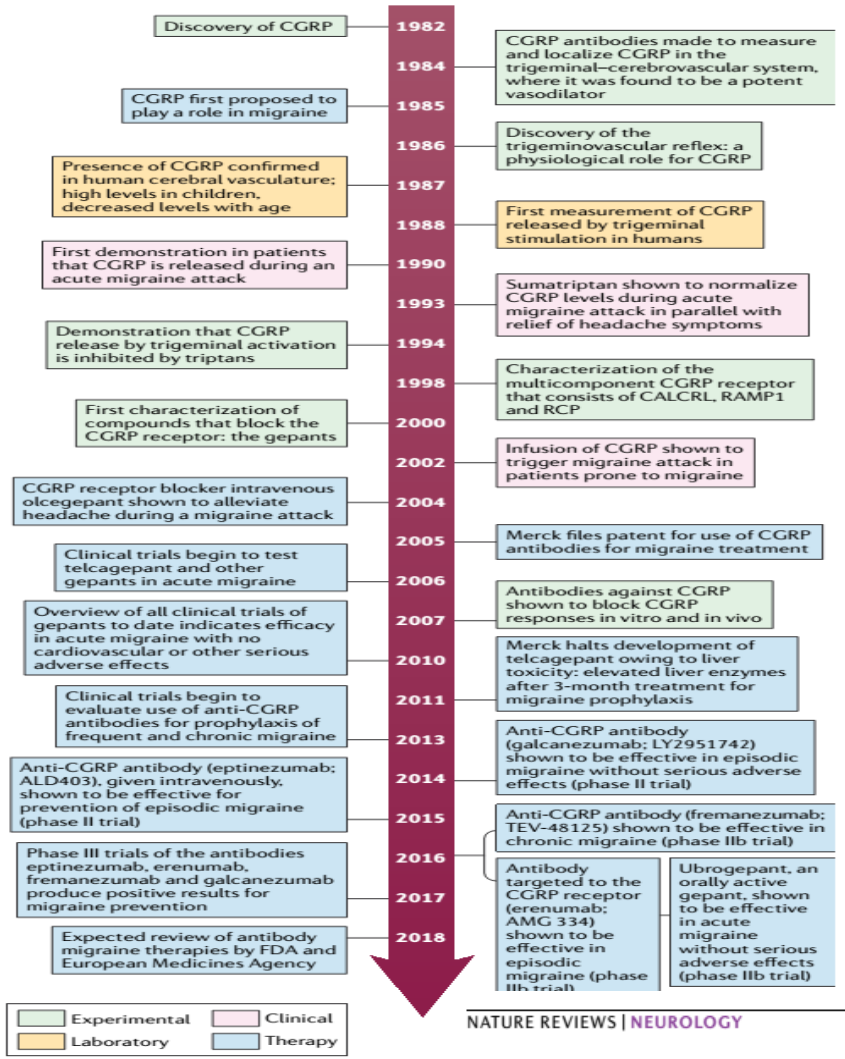


Figure 2. Habituation indices for migraine patients and healthy controls.



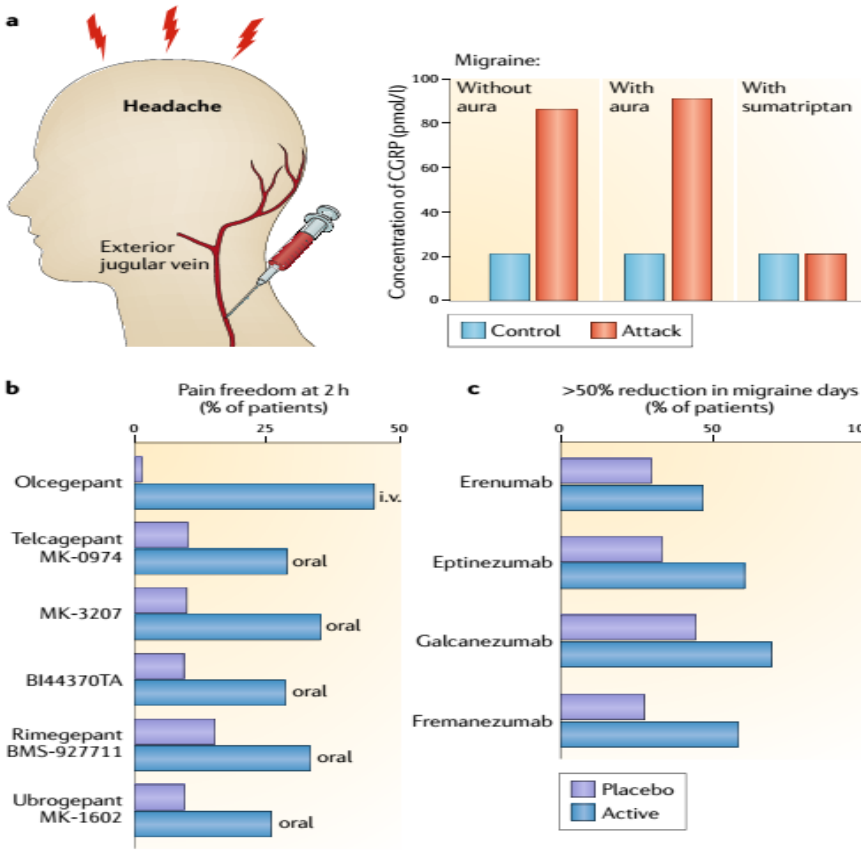


Fig. 1 | **Timeline of the key events in the development of drugs that target CGRP for migraine therapy.** CALCRL, calcitonin receptor-like receptor; CGRP, calcitonin gene-related peptide; RAMP1, receptor activity-modifying protein 1; RCP, receptor coupling protein.

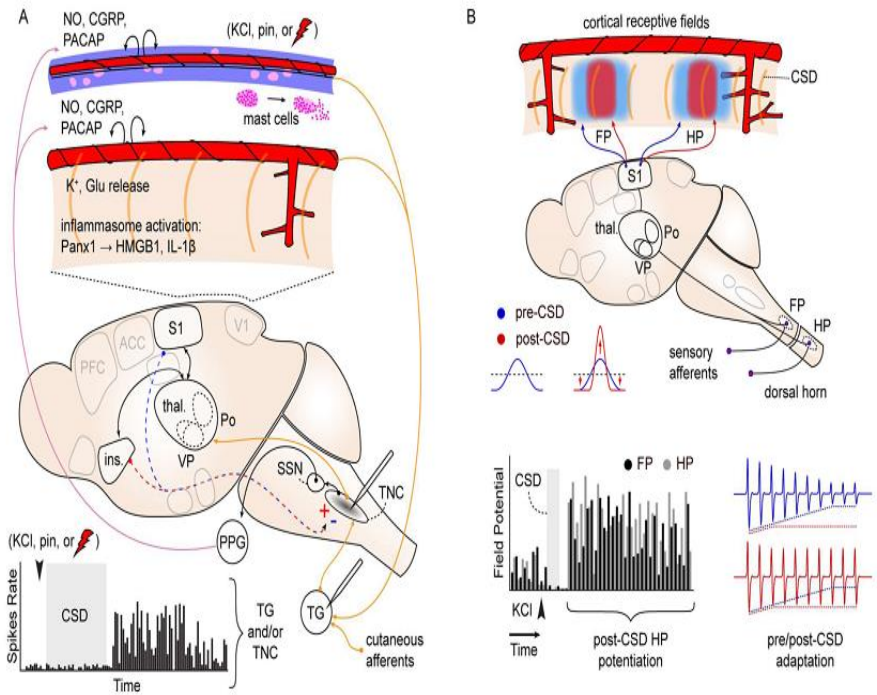
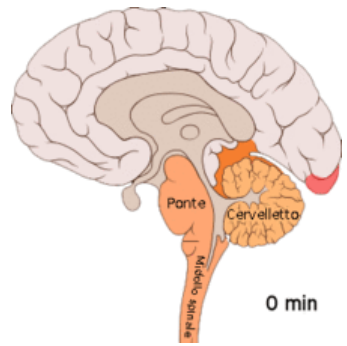


Figure 3. Effects of CSD on network activity

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

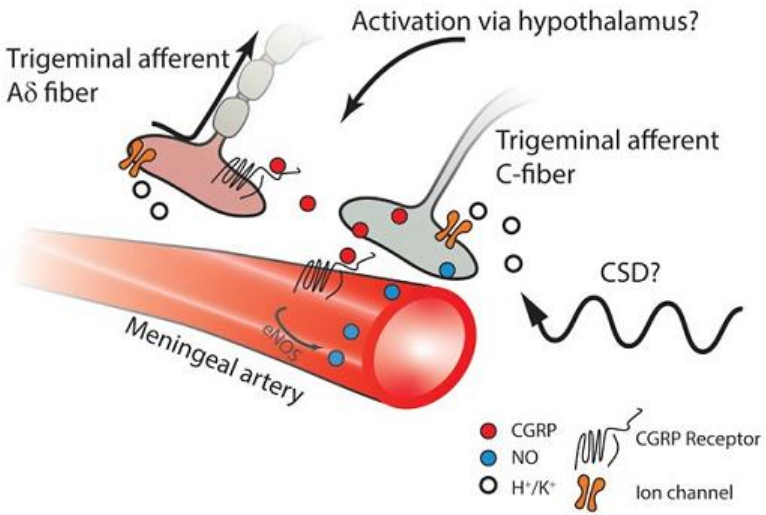


Initiation of spreading depression by synaptic and network hyperactivity: Insights into trigger mechanisms of migraine aura

Lyudmila V Vinogradova

CGRP and the Trigeminal System in Migraine

Smriti Iyengar, PhD; Kirk W. Johnson, PhD; Michael H. Ossipov, PhD; Sheena K. Aurora, MD



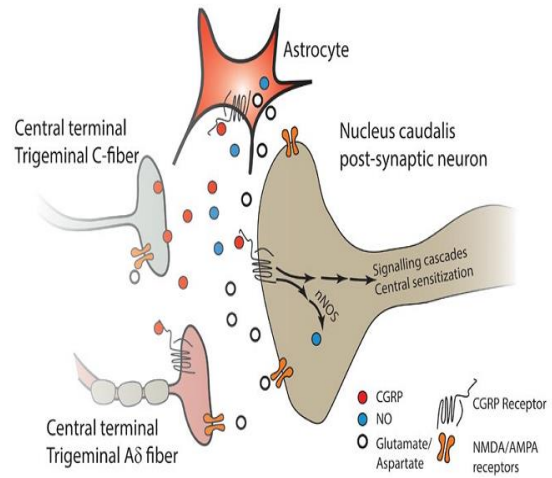


Fig. 3.—CGRP released from the central terminals of unmyelinated nociceptive C-fiber TG neurons can activate the CGRP receptors of the second-order neurons, and elicit production of NO via nNOS. NO acts as a retrograde neuromodulator and

Headache

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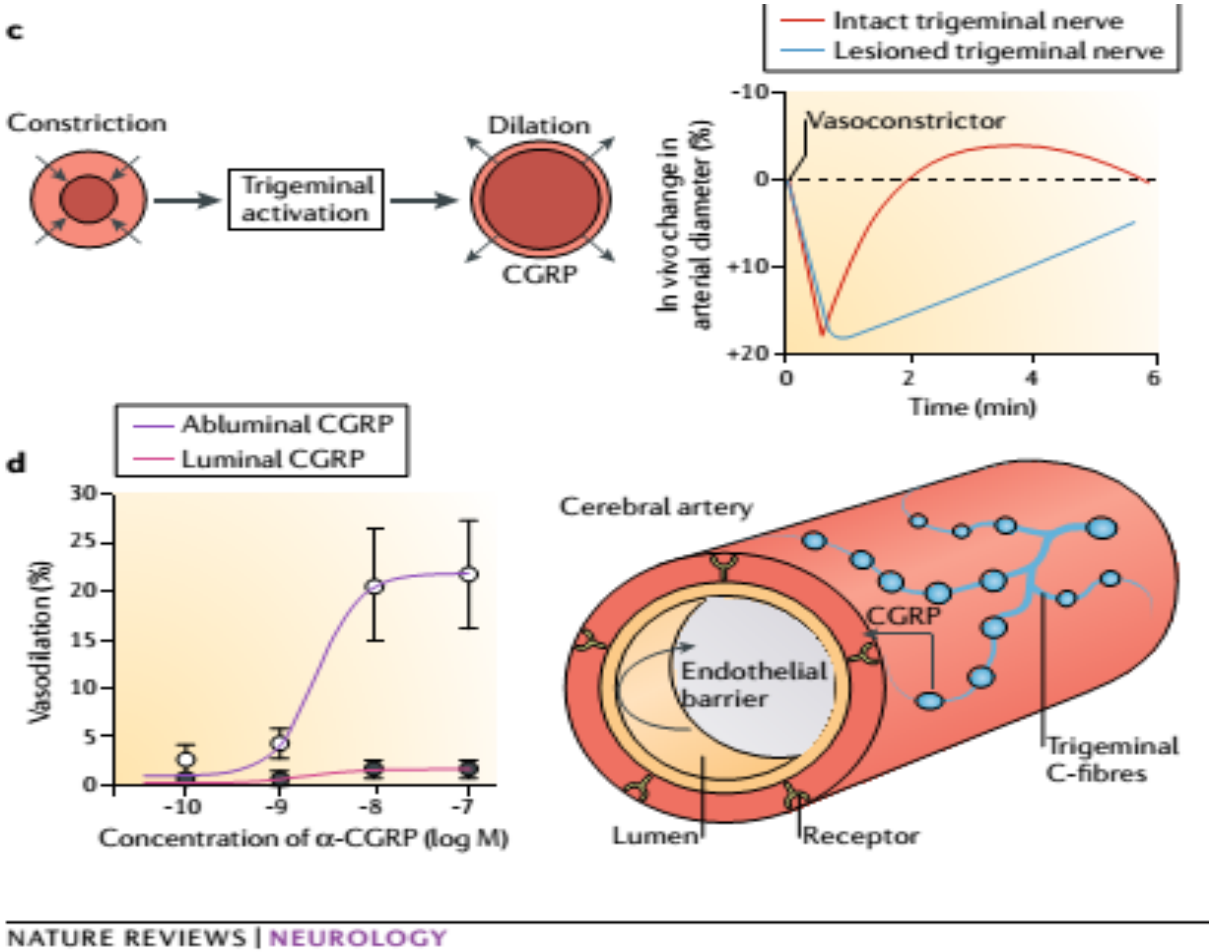
CGRP
regulation of the trigeminovascular reflex in cerebral arteries on the pial surface of the brain. CGRP mediates the reflex that protects the cerebral circulation from excessive vasoconstriction (left). The importance of CGRP is demonstrated by the effect of vasoconstrictors on cerebral arteries in vivo when the trigeminal innervation is either intact or lesioned (right)
1

Access to the vessel wall determines the effect of CGRP. The endothelial barrier in the lumen of the vessel prevents CGRP here from accessing the vessel wall (left), so although CGRP is a potent dilator when applied to the abluminal side of isolated arteries, it has no effect when its application is restricted to the vessel lumen (right)
43,106



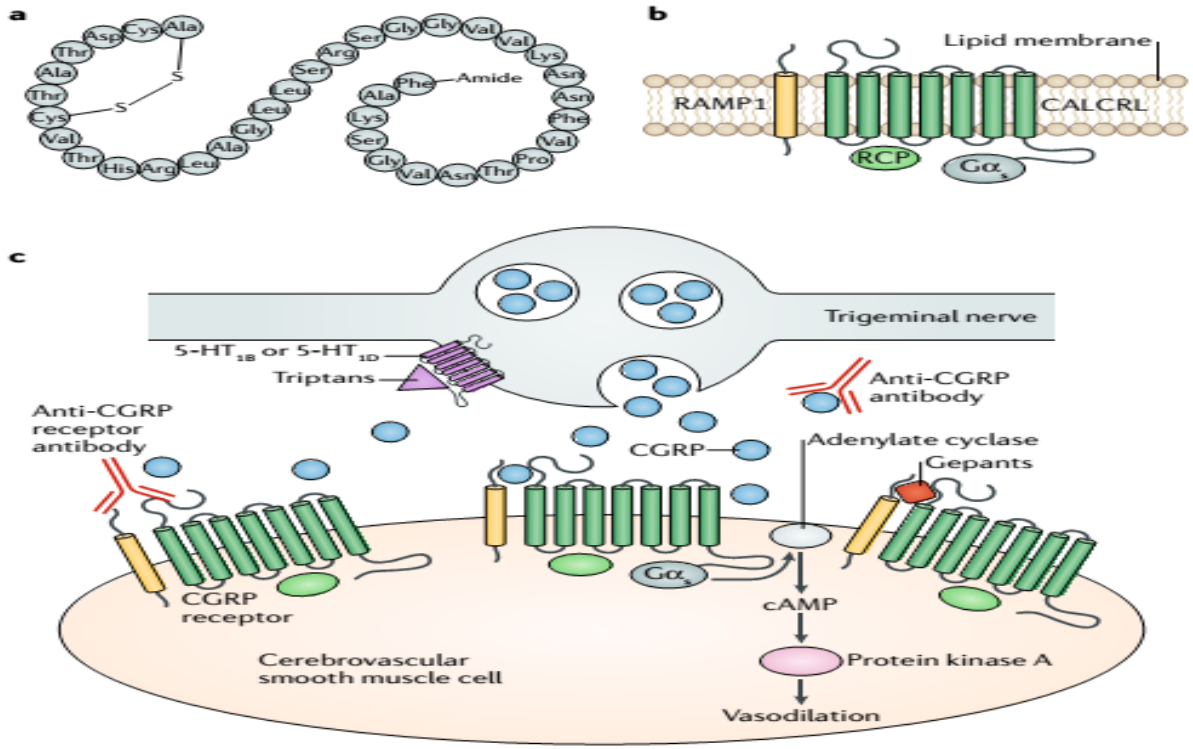
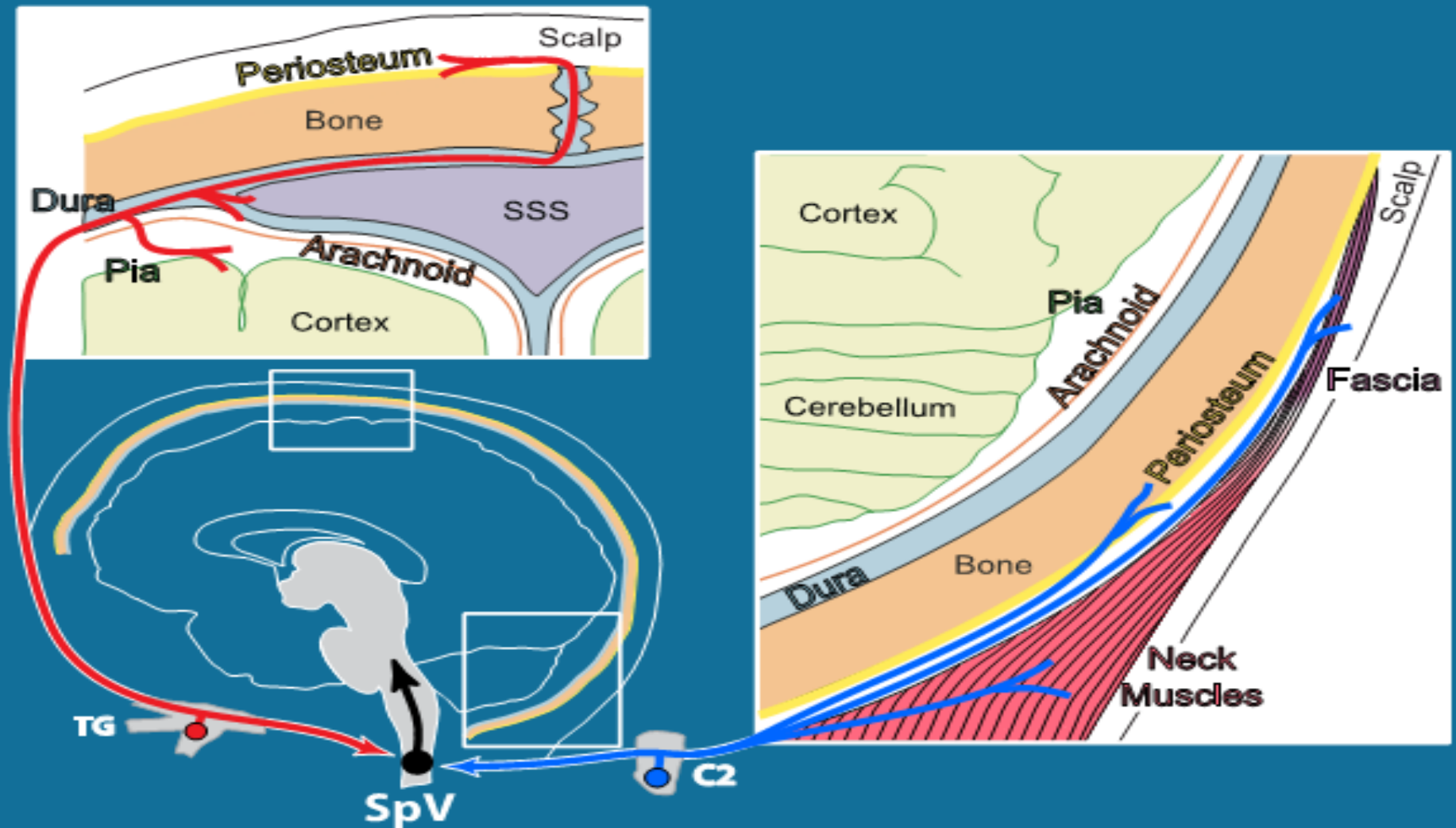


Fig. 2 | **Components of CGRP transmission and sites of action for CGRP-related migraine therapies. a** | Amino acid structure of human α-type calcitonin gene-related peptide (CGRP). **b** | The CGRP receptor complex, which consists of the two integral membrane proteins calcitonin receptor-like receptor (CALCRL) and receptor activity-modifying protein 1 (RAMP1) and two cytoplasmic proteins, receptor coupling protein (RCP) and the α-subunit of the G_S protein ($G\alpha_S$). **c** | The targets for CGRP-related migraine therapies illustrated in a CGRP-containing trigeminal nerve varicosity that innervates a cerebrovascular smooth muscle cell. 5-HT, 5-hydroxytryptamine receptor.

Peripheral action on CGRP receptors is changing migraine scenario

Da Edvinsson

Peripheral Innervation of Cephalic Structures Relevant to Migraine



The content of this slide was provided by Dr Burstein

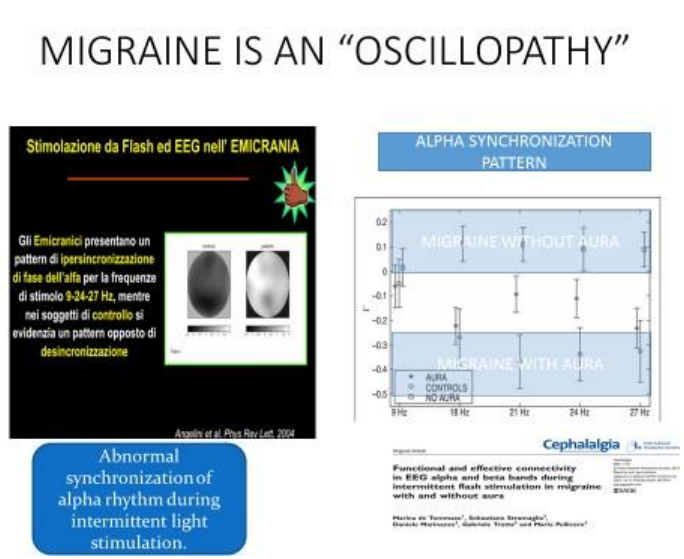
brain sciences

MDPI

Review

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



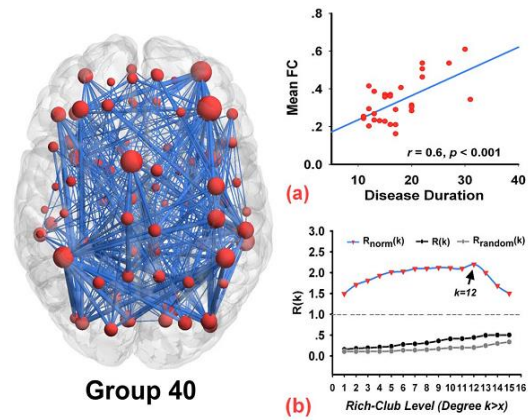


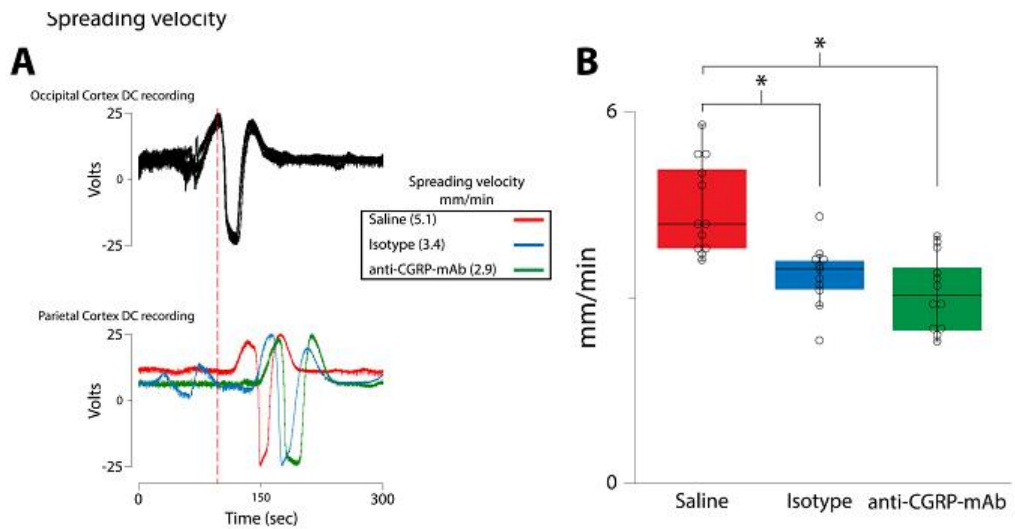
Figure 4.

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 $R(k)$ are indicated with a black line, and corresponding parameters for a random graph $R_{random}(k)$ with the same number of nodes and edges are shown in dark gray. The normalized rich-club coefficient $R_{norm}(k)$ is shown by the blue line. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Pain. 2020 May ; 161(5): 1037–1043. doi:10.1097/j.pain.0000000000001791.

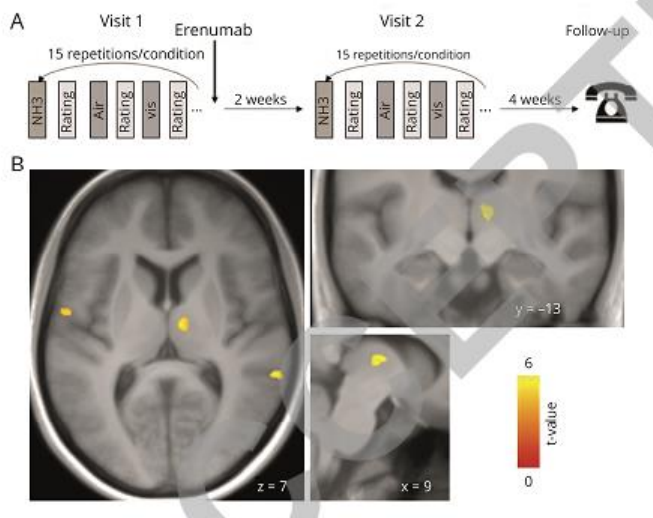
Fremanezumab and its isotype slow propagation rate and shorten cortical recovery period but do not prevent occurrence of cortical spreading depression in rats with compromised blood brain barrier

Agustin Melo-Carrillo[1,2], **Aaron J. Schain**[1,2], **Jennifer Stratton**[3], **Andrew M. Strassman**[1,2], **Rami Burstein**[1,2]

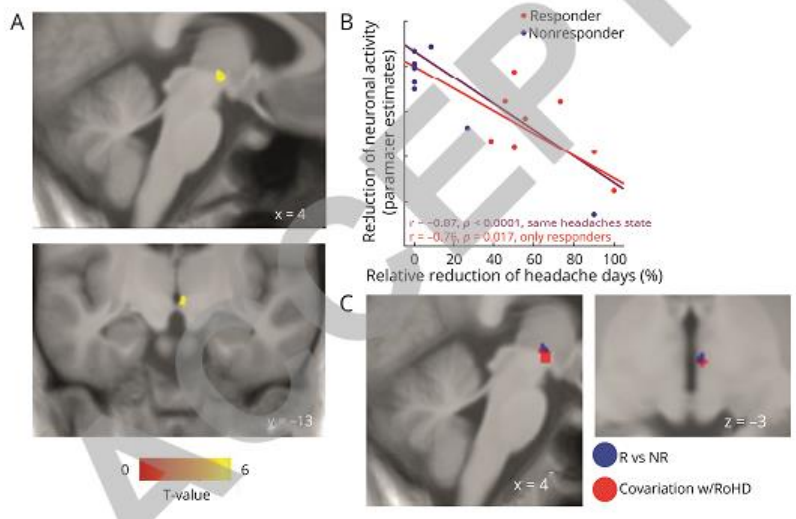


Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000010740

Erenumab (70 mg) inhibits hypothalamic activity in responders



C) Overlap of the activation in the hypothalamus for the covariation with decrease of monthly headache days (red) and the comparison of responders and non-responders.
R = responder, NR = non-responder, RoHD = Reduction of headache days



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
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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 $p < 0.001$.

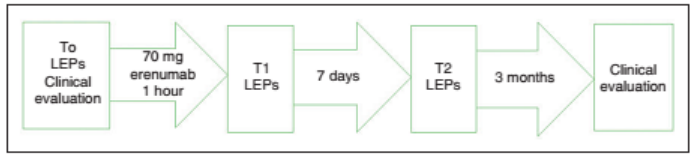


Figure 1. Study design.

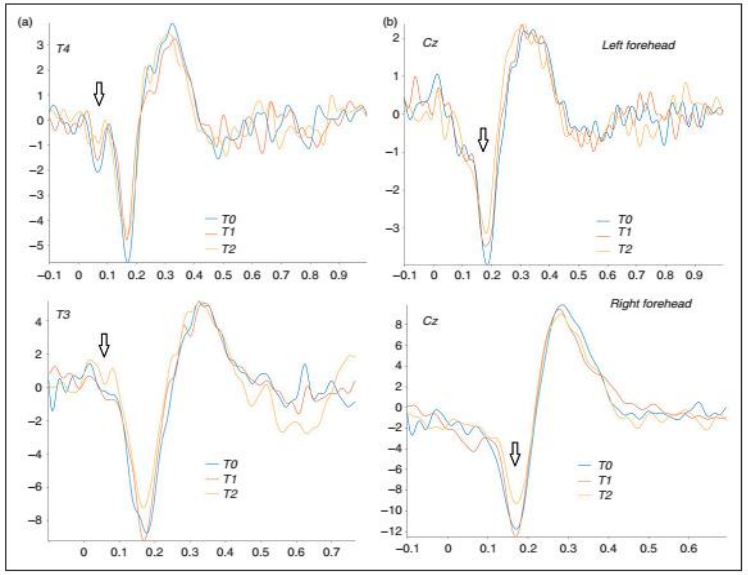


Figure 2. Grand average of laser evoked potentials in 17 migraine patients under Erenumab treatment. (a) N1 responses on temporal electrodes; (b) N2 and P2 responses on central electrodes. Arrows show the relevant amplitude changes.

Mild inhibition of early LEP responses by trigeminal stimulation. No effect on somatic LEPs

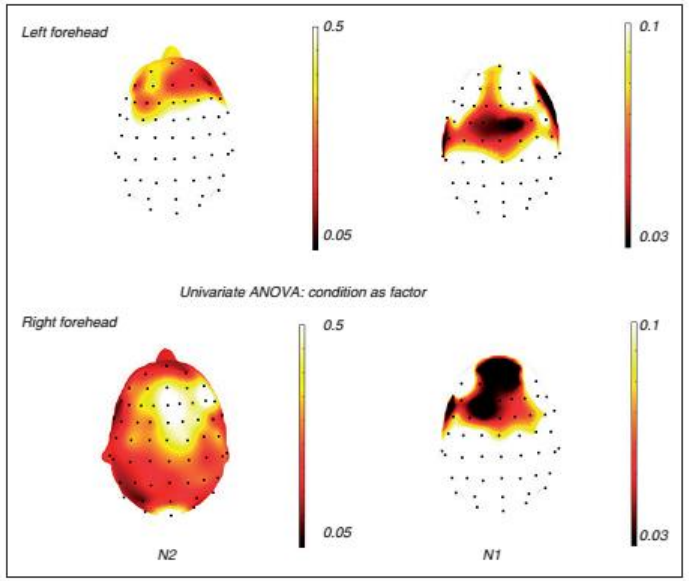


Figure 3. Statistical probability maps (SPMs) reporting *p*-values obtained from the repeated measures ANOVA between T0, T1 and T2 conditions for the N1 and N2 amplitudes in 17 migraine patients. Black expresses the topographical distribution of statistically significant comparison among the three conditions.

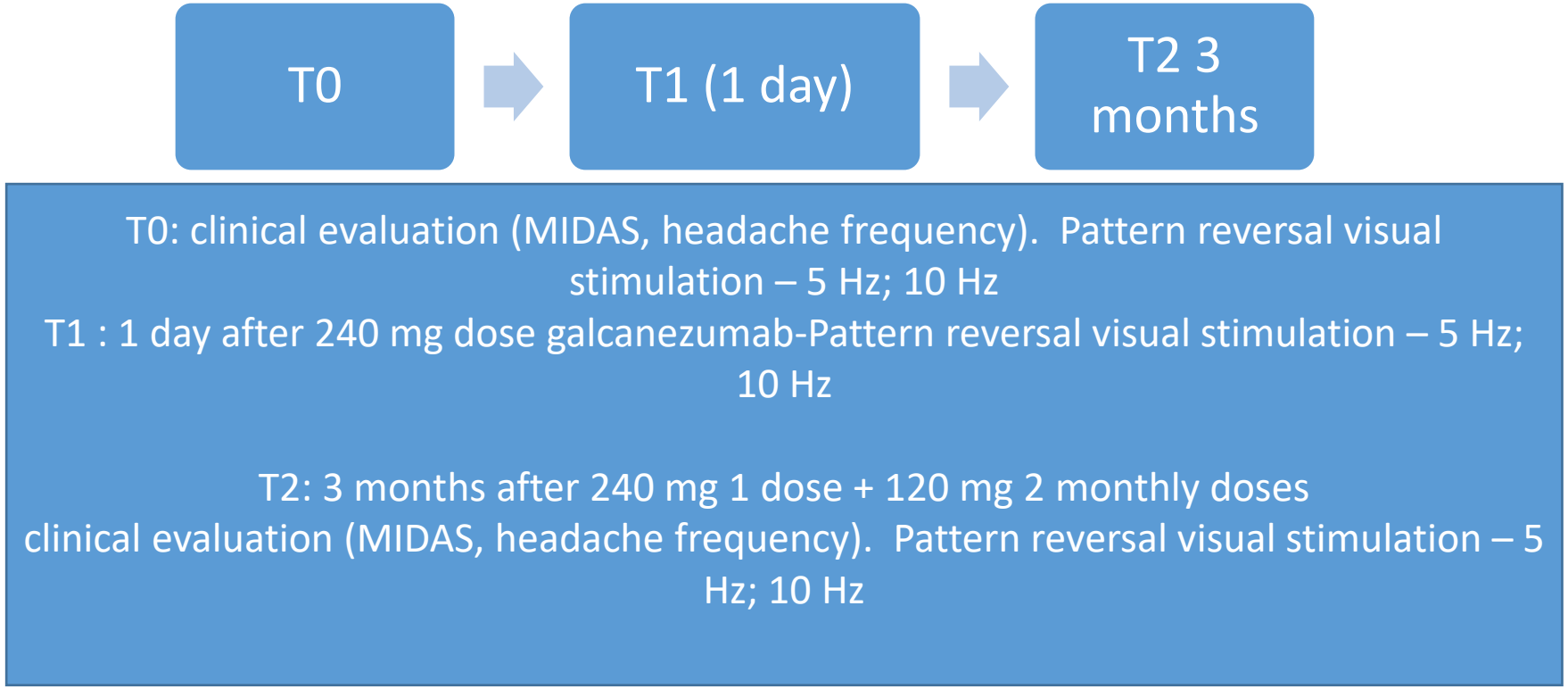
Erenumab restored N2 reduced habituation (trigeminal stimulation)

Table 3. Mean, standard errors (SD) and 95% confidence intervals (CI) of habituation index (the ratio between the average of the first and last series of 10 consecutive responses, 3rd/1st). Higher habituation index corresponded to reduced habituation. Results of repeated measures ANOVA with condition as factor and repetitive contrasts are reported.

	N1				N2				P2			
Left forehead	Mean	DS	95% CI		Mean	Error DS	95% CI		Mean	DS	95% CI	
T0	0.949	0.079	0.782	1.116	1.044	0.197	0.627	1.461	0.644	0.106	0.419	0.87
T1	0.941	0.098	0.733	1.149	1.729	0.571	0.519	2.940	0.889	0.128	0.616	1.163
T2	0.778	0.083	0.602	0.954	0.502	0.125	0.237	0.767	0.581	0.275	−0.005	1.166
	ANOVA F	0.73			ANOVA F	4.32			ANOVA F	1.95		
	DF	2			DF	2			DF	2		
	Error DF	15			Error DF	15			Error DF	15		
	p	0.49			*p*	0.031			*p*	0.17		
	T0 vs. T2	n.s.			T0 vs. T2	*p* 0.037			T0 vs T2	n.s.		
	T2 vs. T1	n.s.			T2 vs. T1	*p* 0.058			T2 vs. T1	n.s.		
	T0 vs. T1	n.s.			T0 vs. T1	*p* 0.058			T0 vs. T1	n.s.		

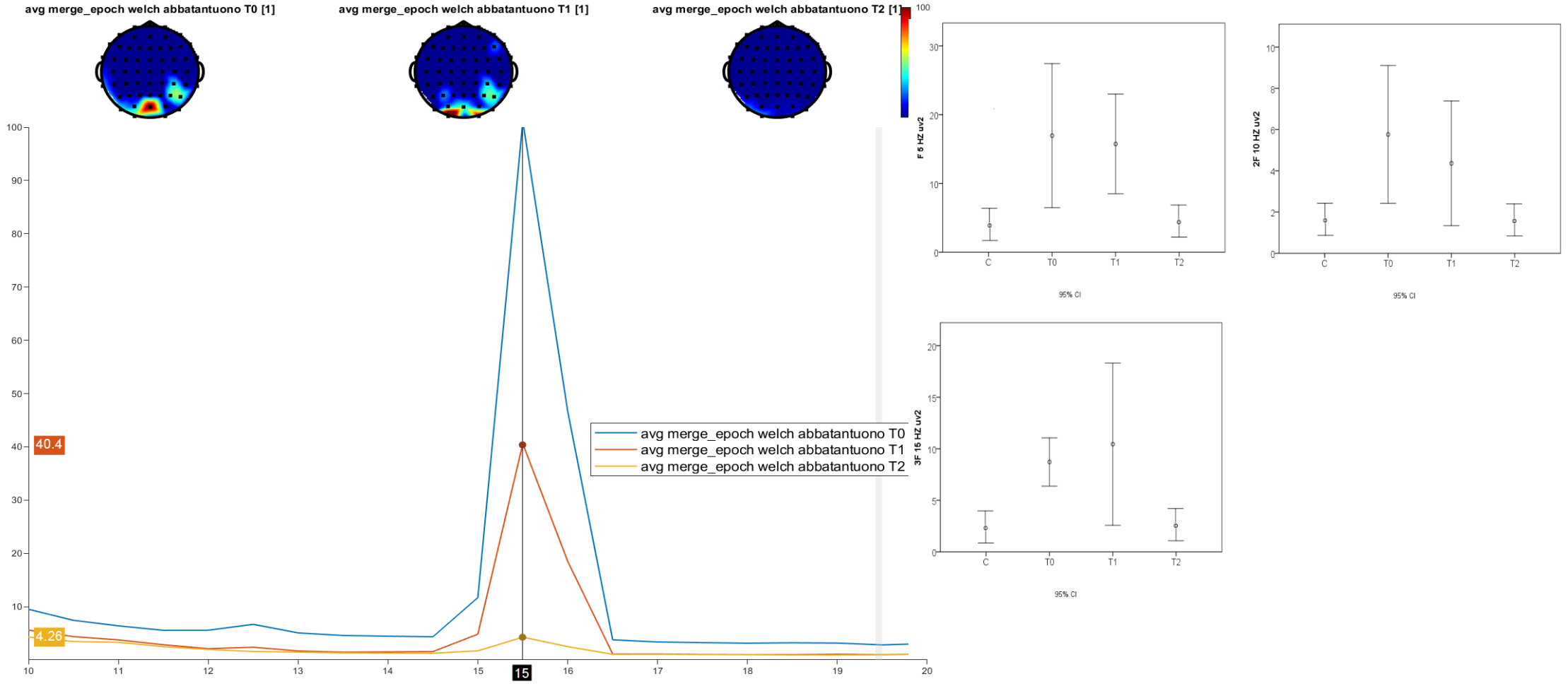
How peripheral modulation of CGRP receptors could prevent migraine?

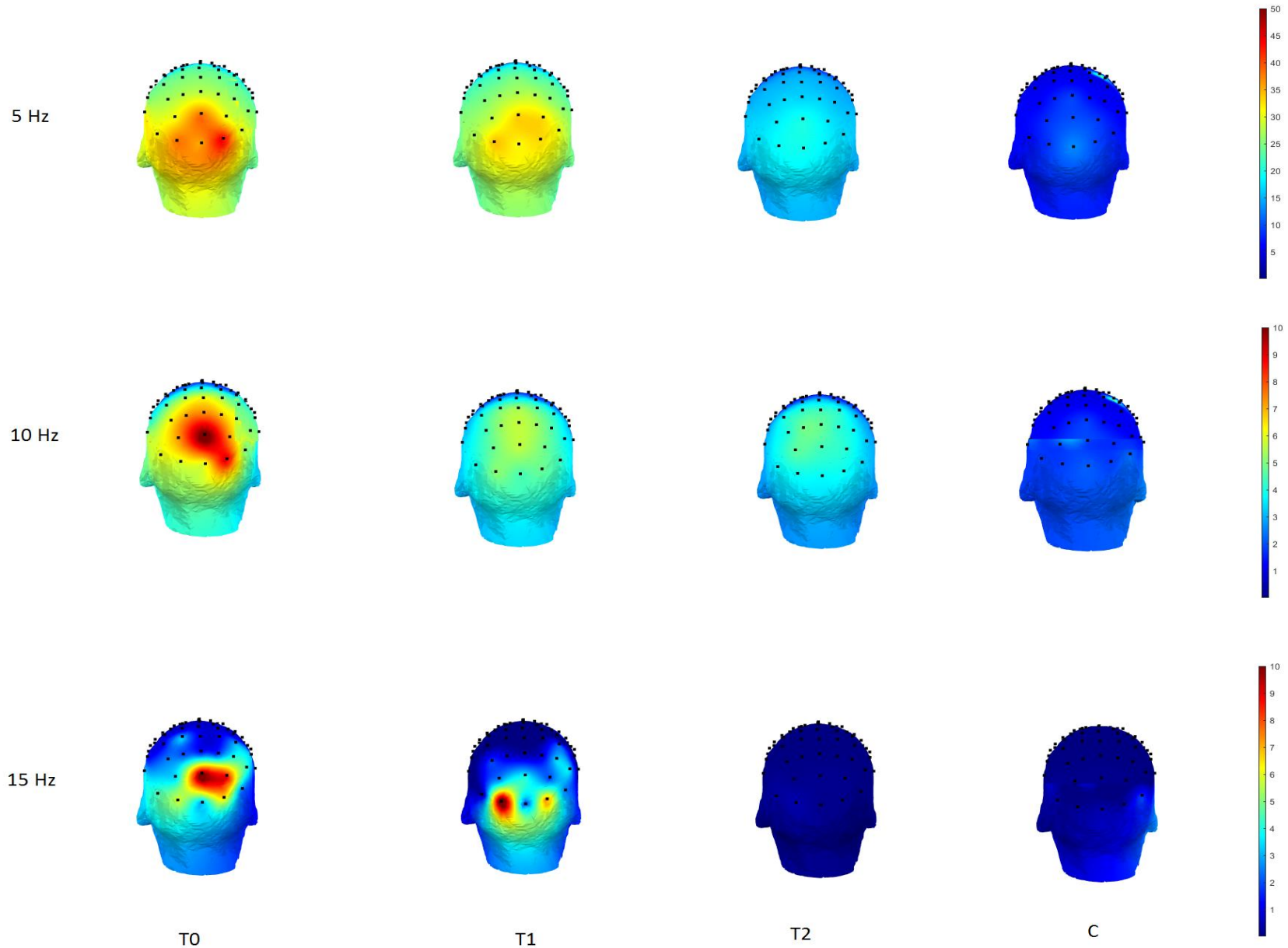
Effect of galcanezumab on SSVEPs in migraine; preliminary results.



	GENDER	AGE	DURATION	DIAGNOSIS	DRUGS	T0	DAYS/30	SIM/30	MIDAS	NRS	T1	DAYS/30	SIM/30	MIDAS	NRS
AI	F	29	20	MA	AED, AD, BB	2	13	13	79	10		17	16	113	10
BA	F	48	30	MA	AED, AD, BB,TB	1	12	12	26	7		8	8	12	4
DD	F	38	22	MA	AED,AD,CA	1	9	9	68	10		4	4	34	10
DE	F	47	25	CM	AED,AD,CA,TB	2	17	17	150	9		17	10	70	6
DI	F	48	25	MA	AED,AD,CA,BB	1	13	13	26	7		10	10	13	6
DL	F	47	24	MA	AED,AD	1	8	12	32	10		3	3	10	6
FA	F	57	40	CM	AED,AD,CA,TB	1	20	20	75	7		4	4	12	8
LE	F	42	30	CM	AED,AD,CA,BB,TB	1	27	27	30	8		6	6	10	6
MA	F	67	50	CM	AED,AD,CA,BB,TB	2	15	4	50	8		15	3	25	5
MO	F	47	30	CM	AED,AD,TB	1	25	25	56	8		12	10	25	7
MN	F	63	45	MA	AED,AD,CA,BB	1	10	12	5	6		5	0	0	4
PN	F	58	10	MA	AED,BB,AD	1	13	13	77	7		8	8	33	7
SM	M	56	30	CM	AED,BB,AD	1	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					

Results: 13 patients. SSVEPs 2 cpd response

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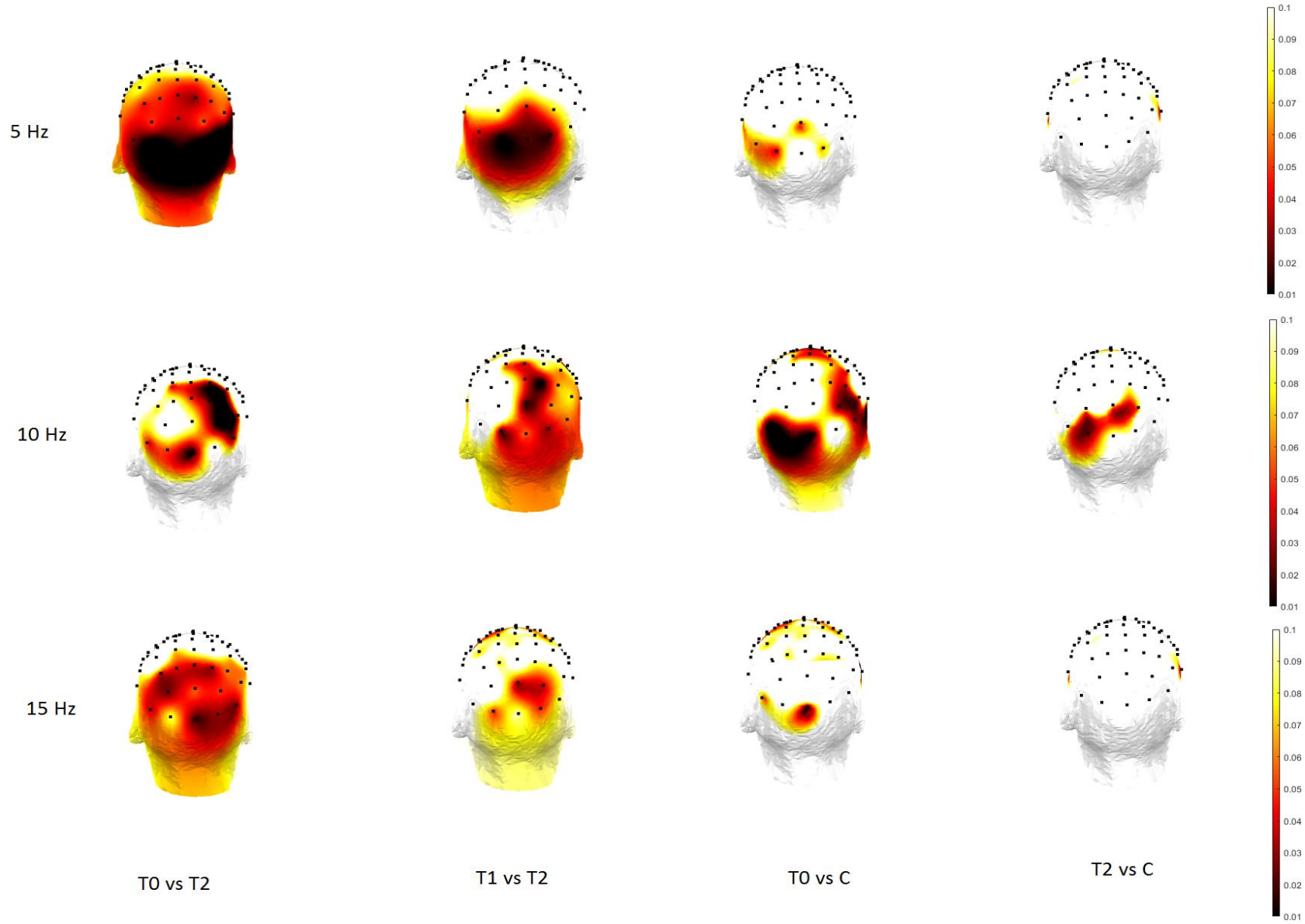
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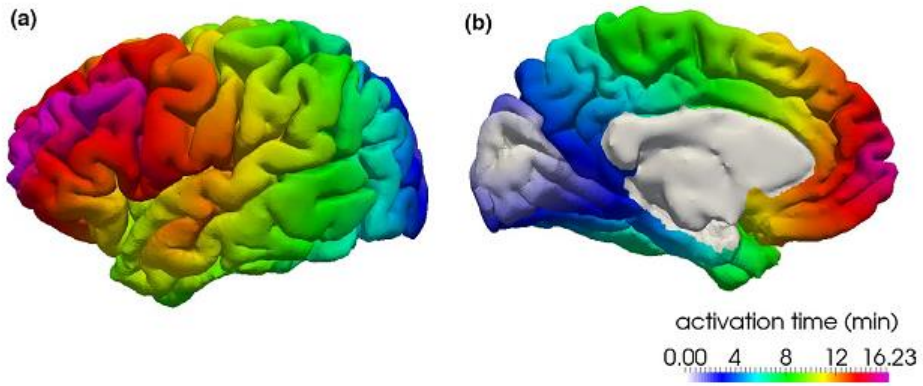
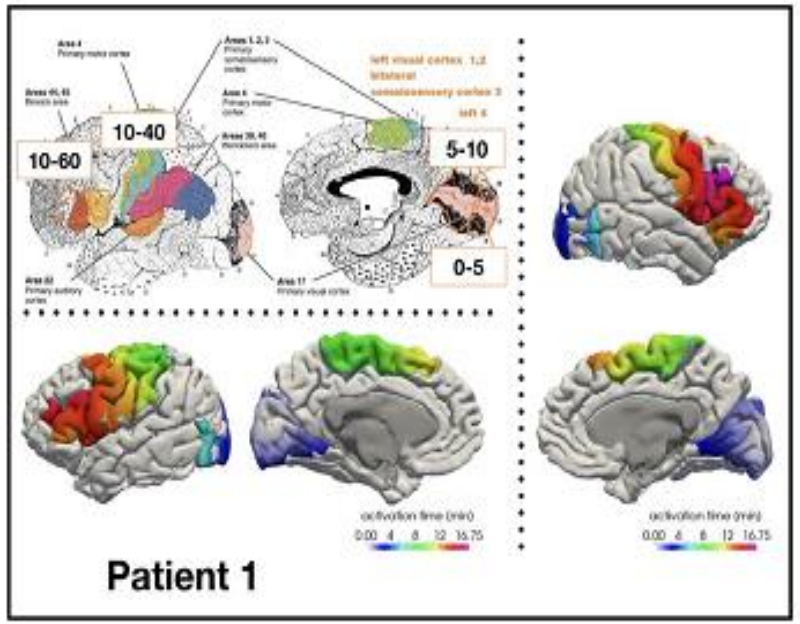
How peripheral modulation of CGRP receptors could prevent migraine?





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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