Default mode network and functional connectivity in chronic pain syndromes

Marina de Tommaso

How many types of pain do I know?

❖ Neuropathic pain

Pain caused by a lesion or disease of the somatosensory nervous system.

❖ Nociceptive pain

Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors with a normally functioning somatosensory nervous system

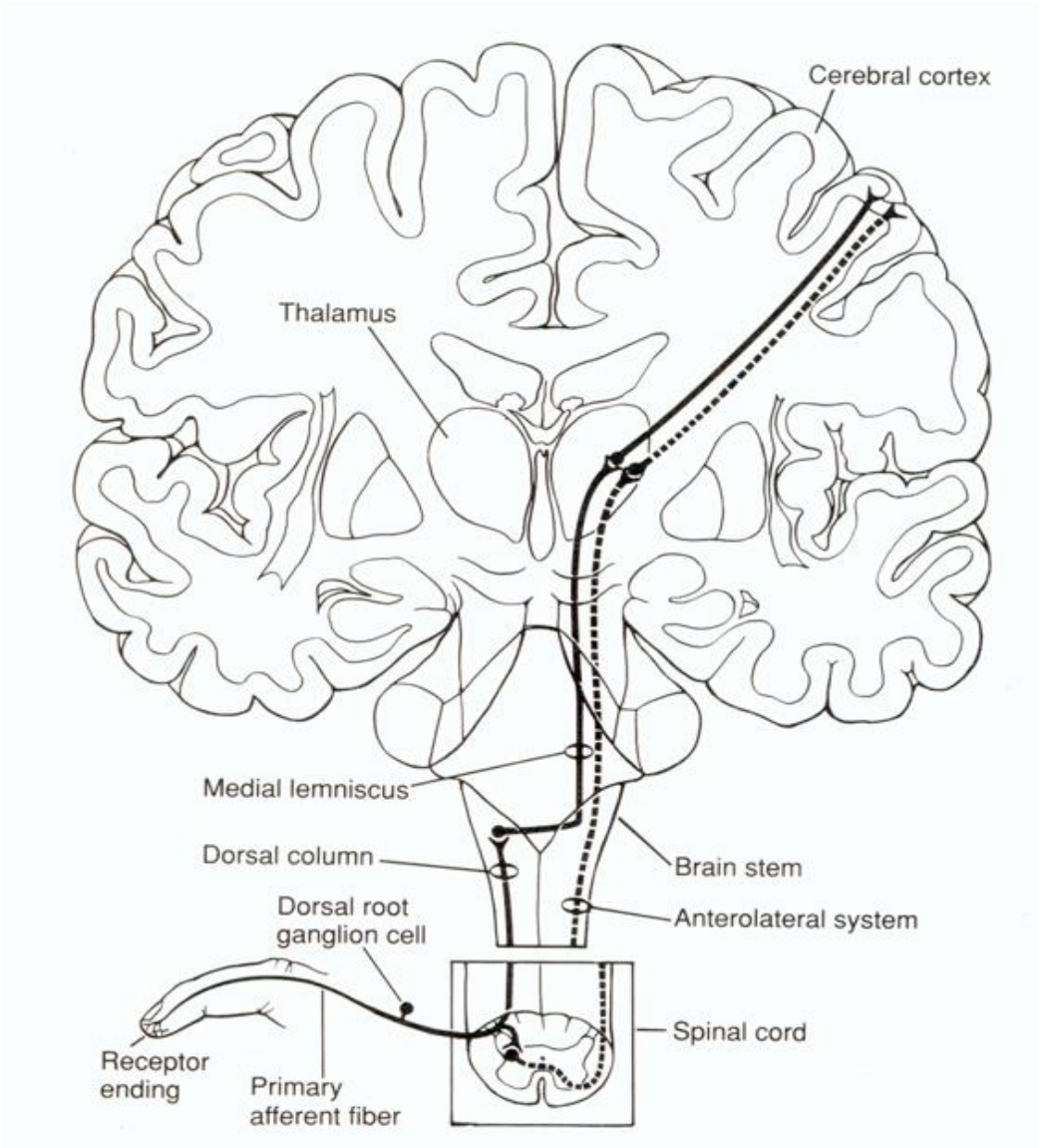
❖ Mixed pain

the *same* disease causes different pains through different pathophysiological mechanisms that are often difficult to separate and quantify

❖ Nociplastic pain

Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. Patients can have a combination of nociceptive and nociplastic pain

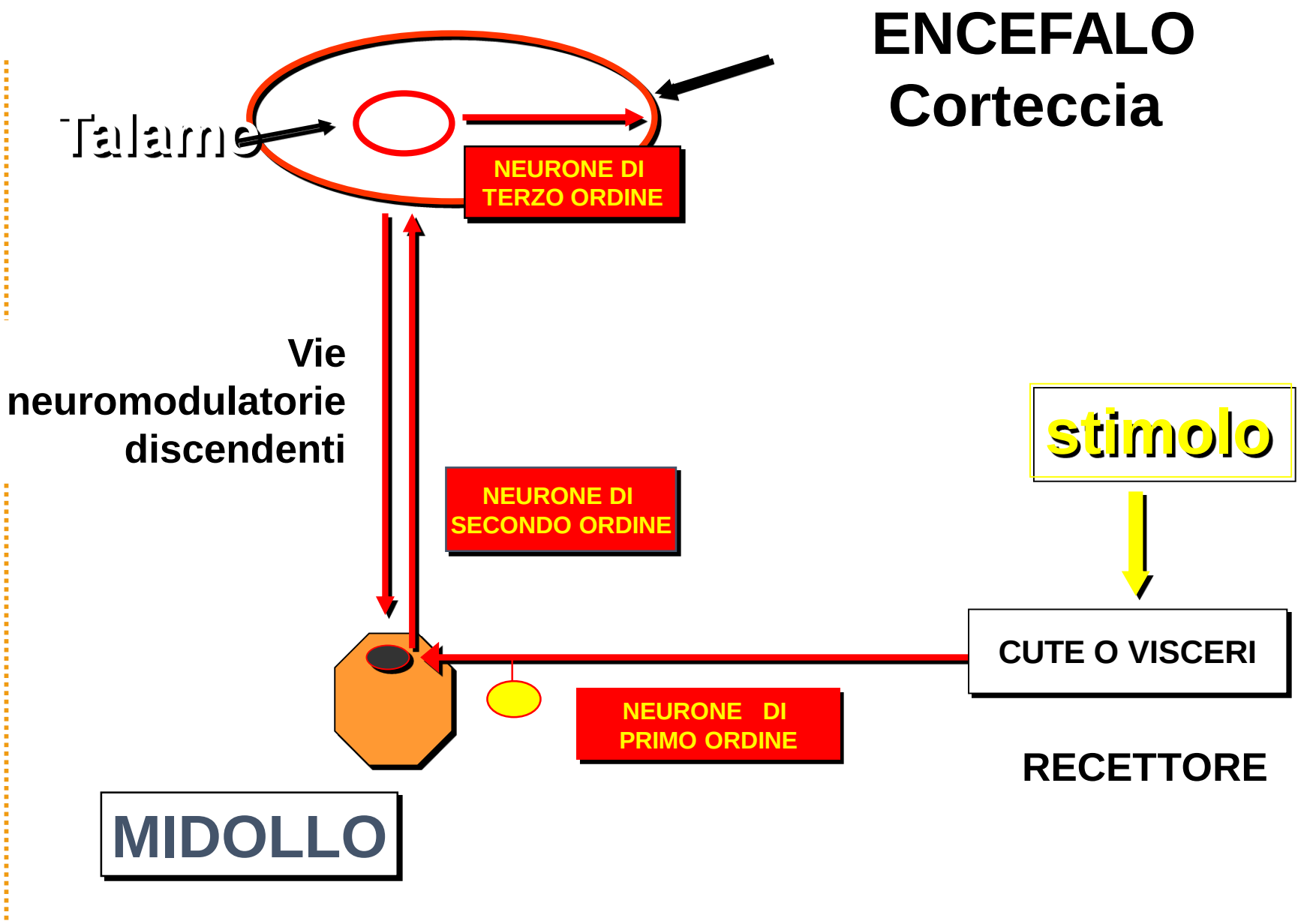
The nociceptive system



Kandel / Schwartz / Jessell:

Principles of Neural Science

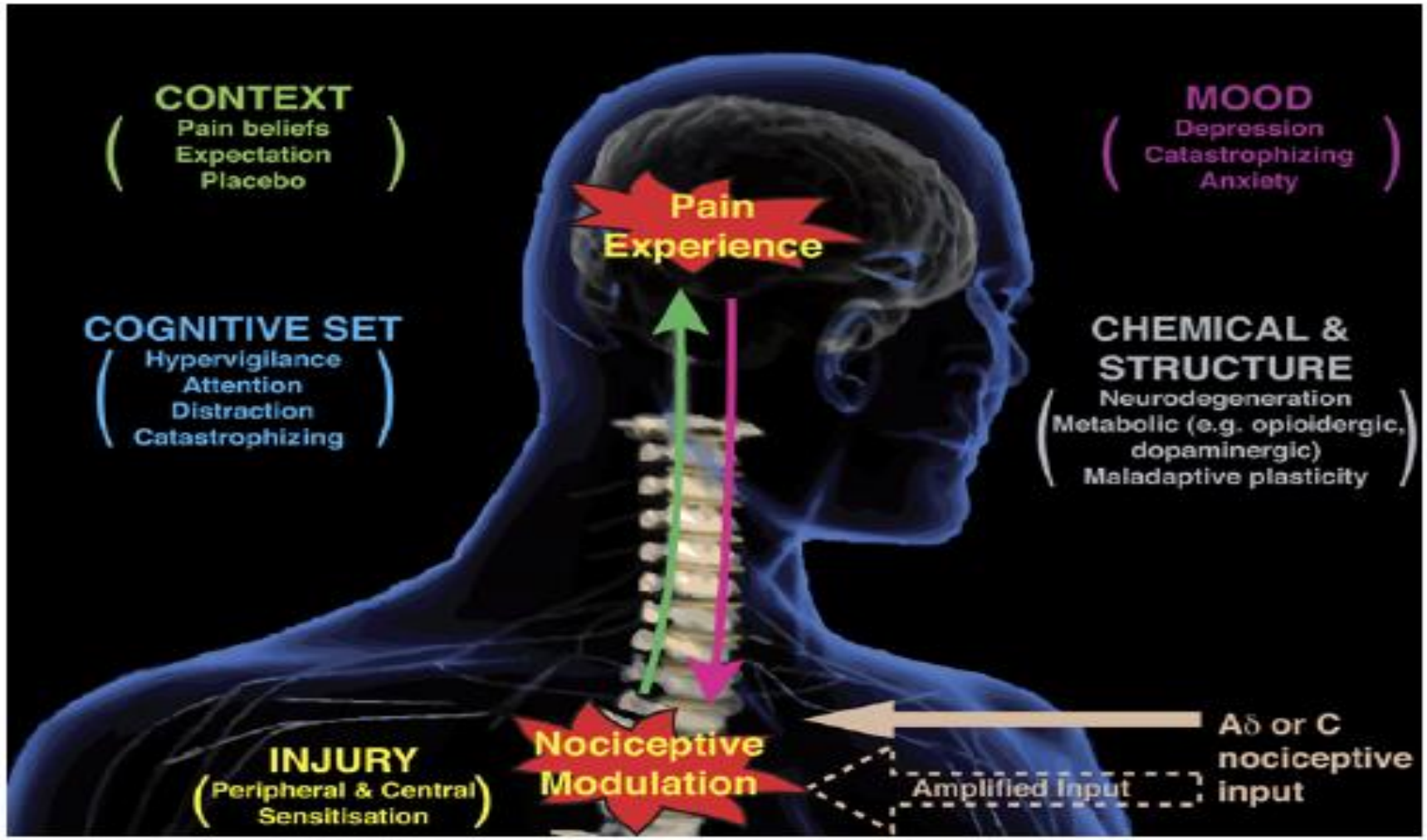
Le informazioni nocicettive sono condotte lungo
il fascio spino-talamico laterale e modulate perifericamente da fibre meccanocettive
(gate-control) e centralmente da strutture del troncoencefalo a funzione inibente e dalla corteccia
nocicettiva con funzione facilitante



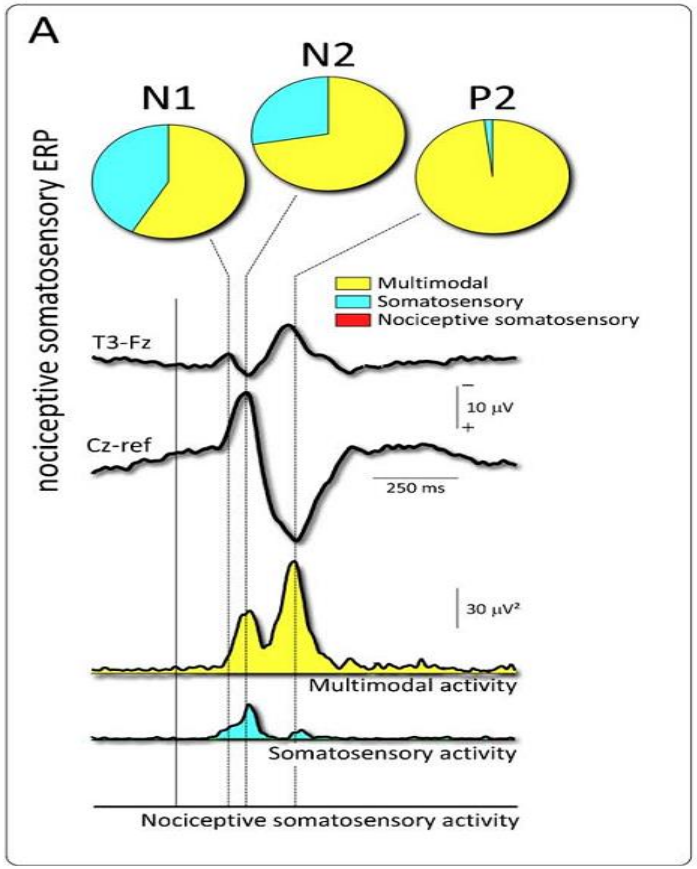
Neuron

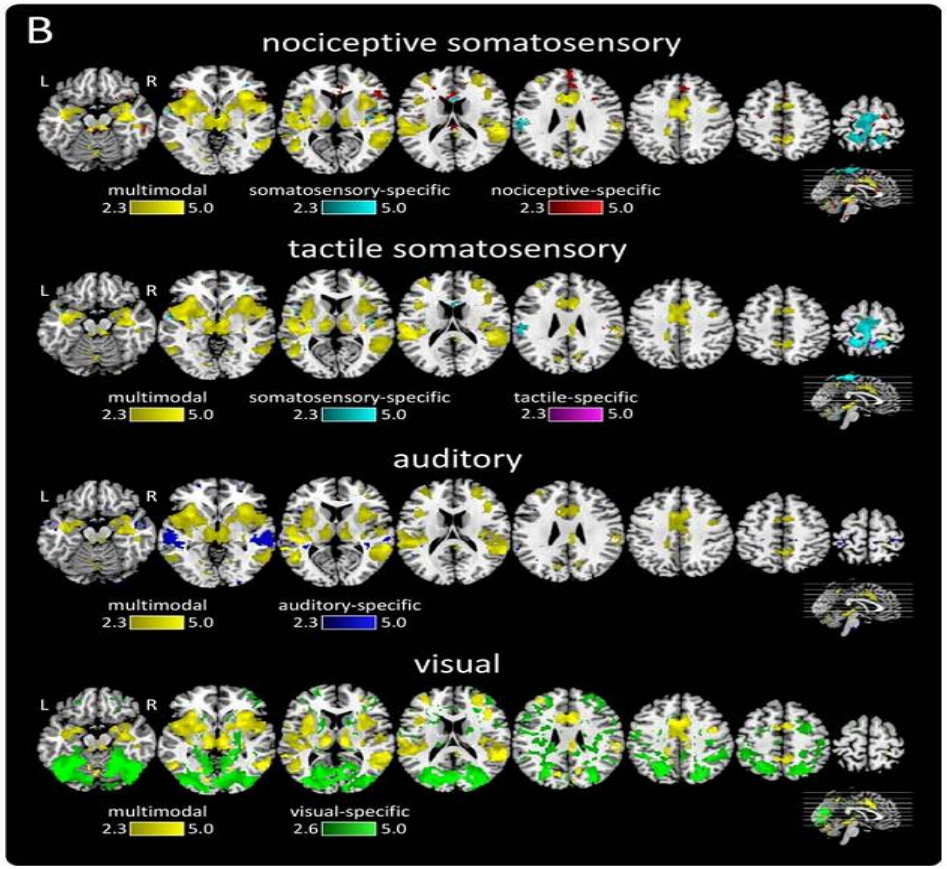
Review

Irene Tracey[1,*] and Patrick W. Mantyh[2,*]



The salience matrix or the pain matrix??





NEUROLOGICAL PROGRESS

A Cortical Network for Directed Attention and Unilateral Neglect

M.-Marsel Mesulam, MD

The pivotal role of anterior cingulate in directed attention, arousal and stimulus novelty

Ann Neurol 10:309–325, 1981

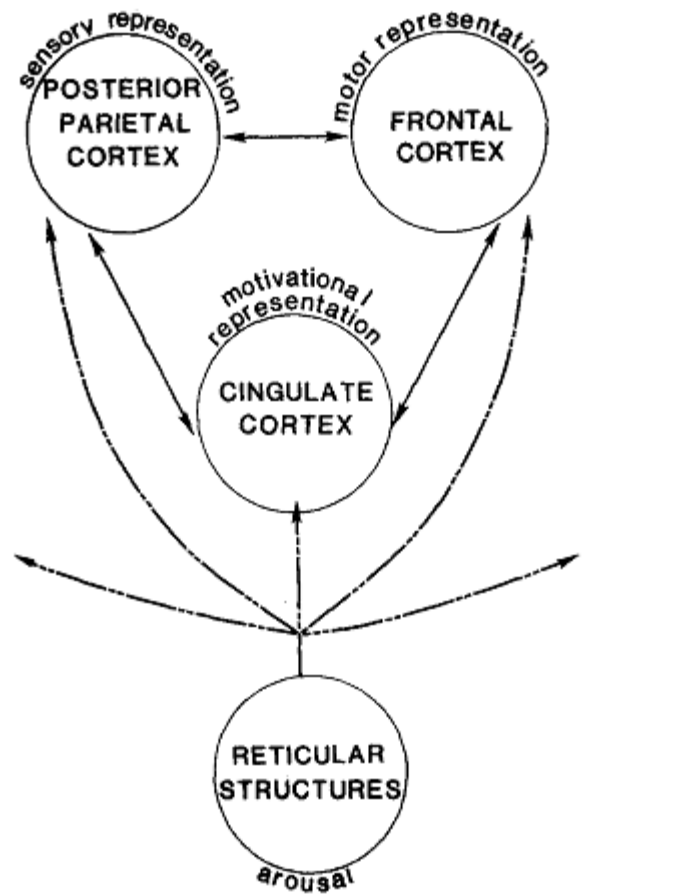
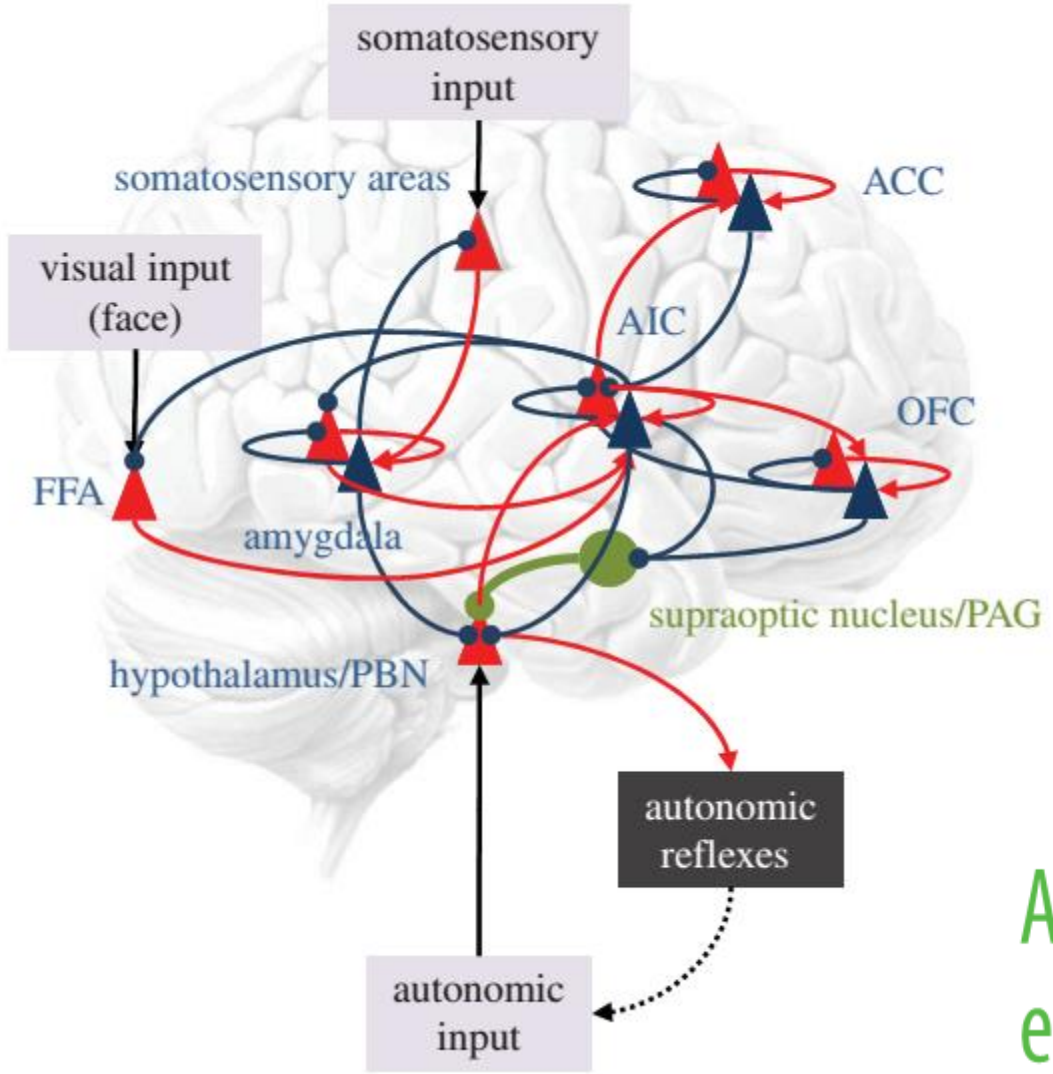


Fig 3. The components of a neural network involved in modulating directed attention.



With respect to an input stimulus, the "uncertainty" network encodes the error of prediction, the waiting and the arousal and activates the motor and reflex behavioral reaction
Exciting circuits in red Inhibitors in blue

Active interoceptive inference and the emotional brain

Anil K. Seth[1] and Karl J. Friston[2]

Phil. Trans. R. Soc. B **371**:

THE ARTIFACT OF FUNCTIONAL NEUROIMMAGING
NOT ALL IS COLORED BY PAIN……IS ONLY PAIN

Phil. Trans. R. Soc. Lond. B (1999)

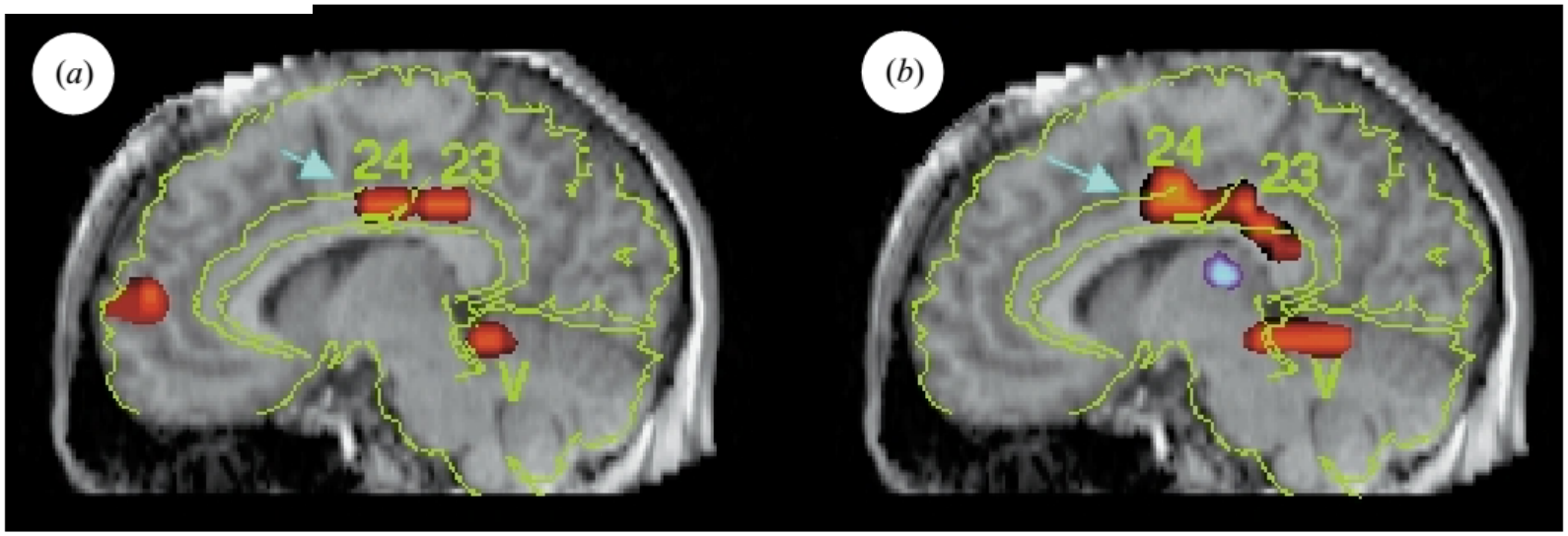
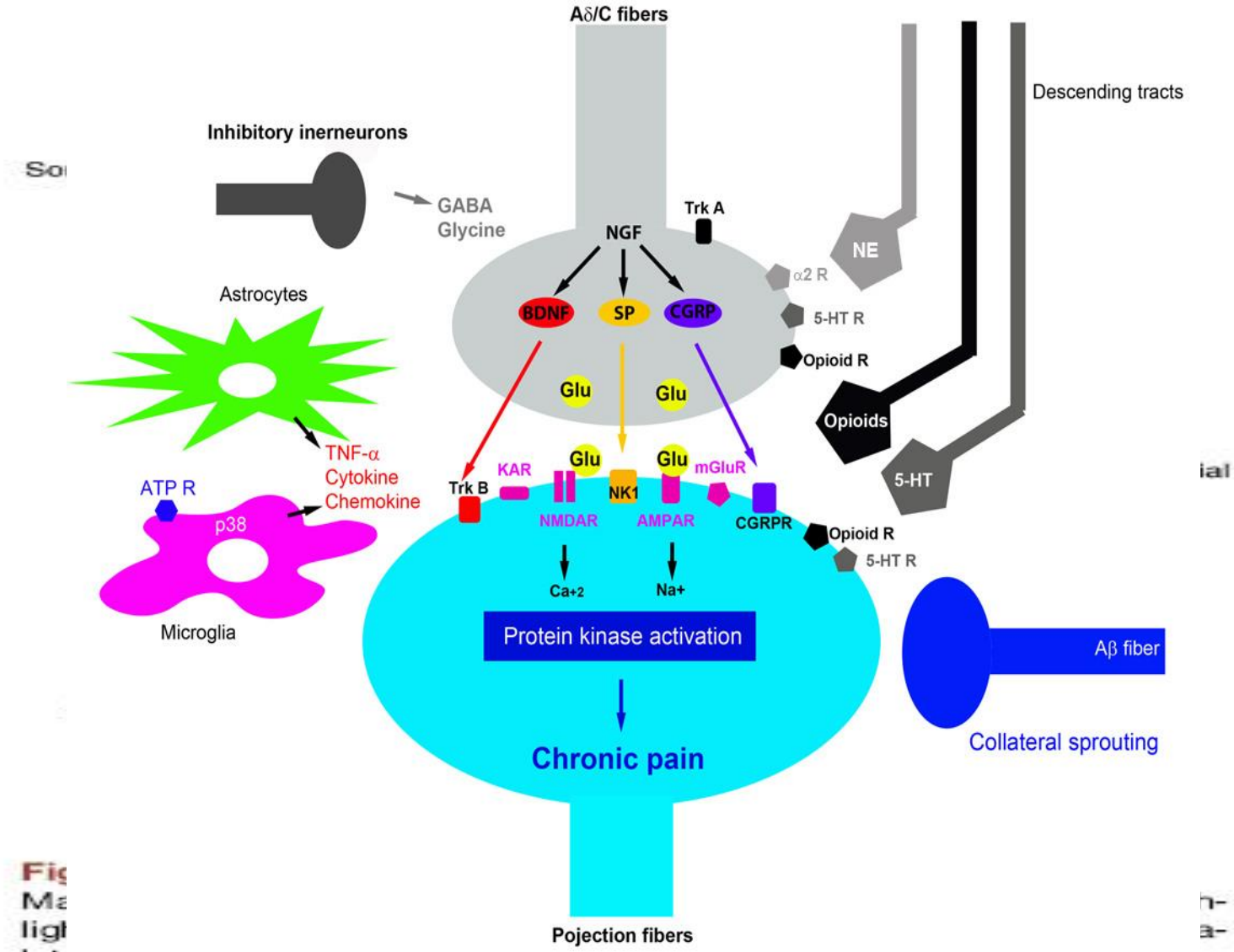
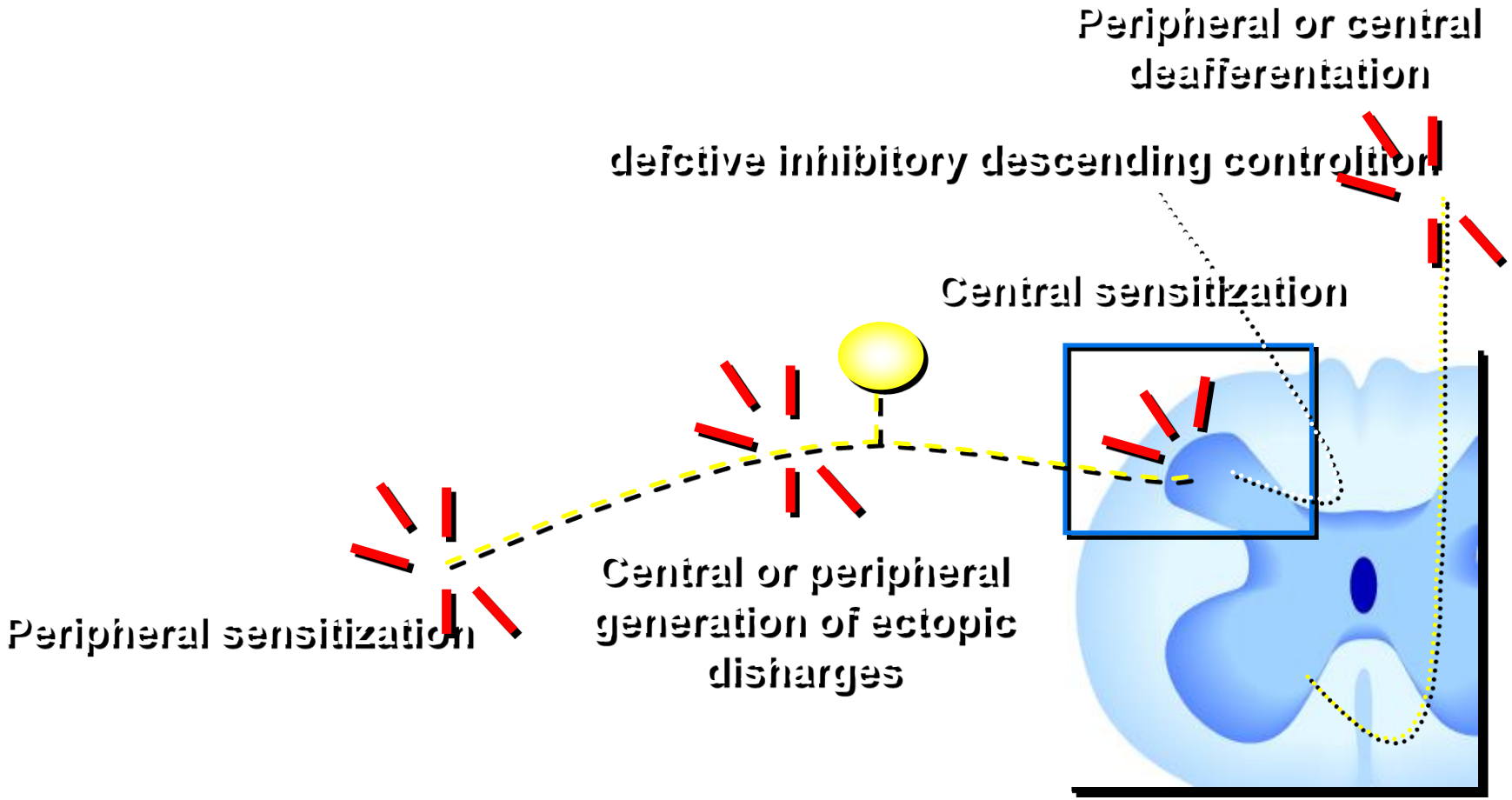


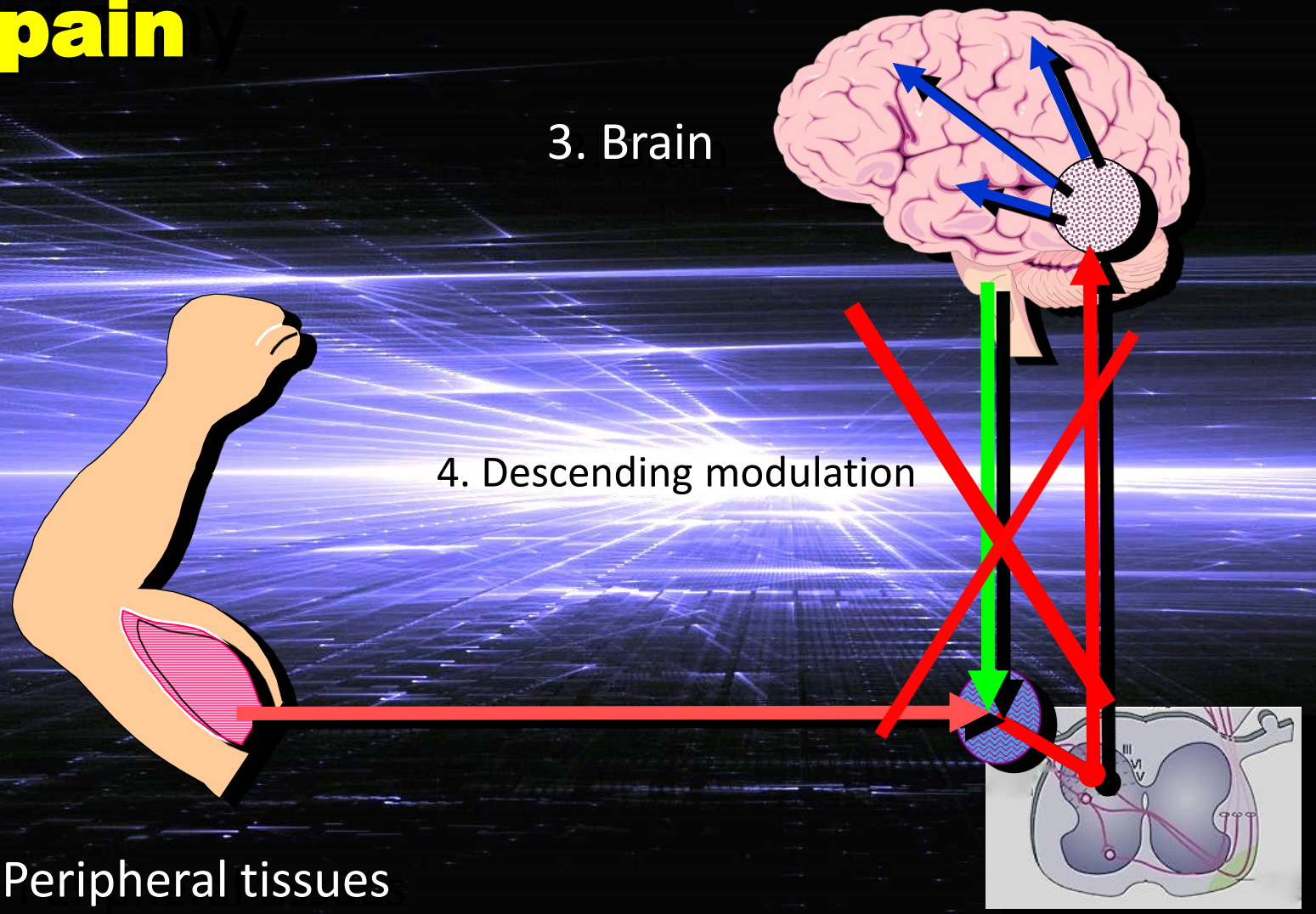
Figure 2. In peripheral neuropathy both right-sided (*a*) and left-sided (*b*) nerve affliction leads to a right-sided activation in the ACC. Sagittal slices through the right ACC in two subgroups with either right- or left-sided affliction. The omnibus significance maps (thresholded at $p<0.01$) were superimposed on a transformed MRI image and were colour coded into four levels defined by $0.001 \leqslant p<0.01$ (increase = red; decrease = blue) and $p<0.001$ (increase = yellow; decrease = light blue). Data from Hsieh *et al.* (1995).


Aδ/C fibers
Descending tracts
Inhibitory inerneurons
GABA
Glycine
Trk A
NGF
NE
α2 R
BDNF
SP
CGRP
5-HT R
Opioid R
Astrocytes
Glu
Glu
Opioids
TNF-α
Cytokine
Chemokine
KAR
Glu
Glu
mGluR
ATP R
Trk B
NK1
5-HT
p38
NMDAR
AMPAR
CGRPR
Opioid R
5-HT R
Ca+2
Na+
Protein kinase activation
Aβ fiber
Collateral sprouting
Microglia
Chronic pain
Pojection fibers

Neuropathic pain



Putative or nociplastic pain



Contents lists available at ScienceDirect

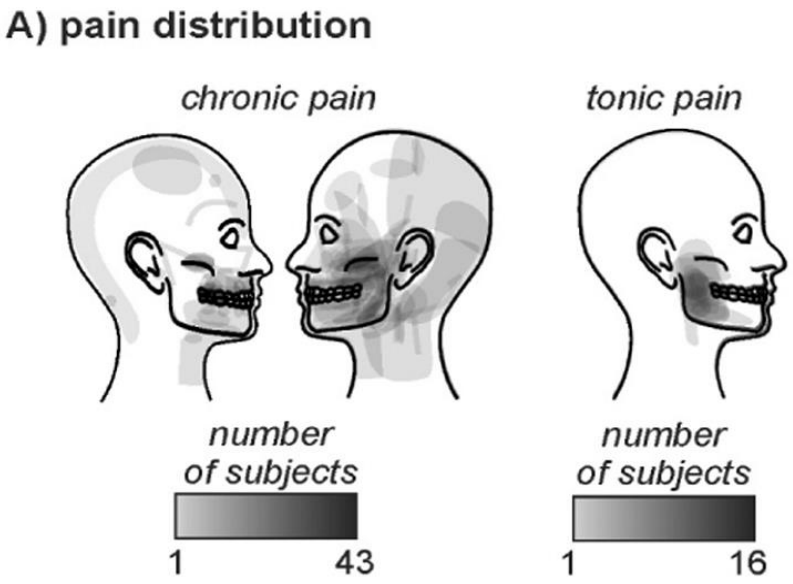
NeuroImage: Clinical

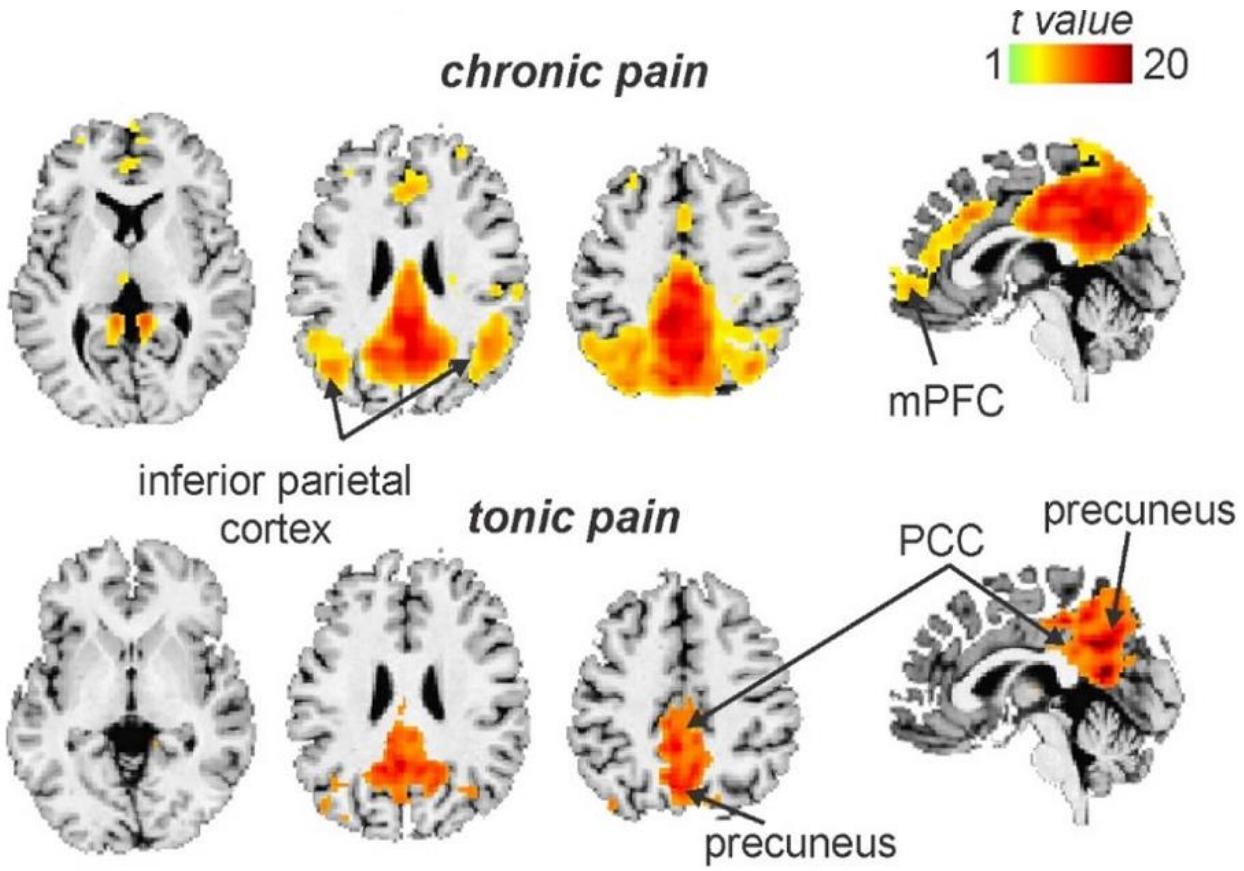
journal homepage: www.elsevier.com/locate/ynicl

Tonic pain causes itself disruption in default mode network

Disruption of default mode network dynamics in acute and chronic pain states

Z. Alshelh[a], K.K. Marciszewski[a], R. Akhter[b], F. Di Pietro[a], E.P. Mills[a], E.R. Vickers[a], C.C. Peck[b], G.M. Murray[b], L.A. Henderson[a,*]





EJP
European Journal of P

ORIGINAL ARTICLE

Altered fMRI resting-state connectivity in individuals with fibromyalgia on acute pain stimulation

E. Ichesco[1,a], T. Puiu[1,a], J.P. Hampson[1], A.E. Kairys[1,2], D.J. Clauw[1], S.E. Harte[1], S.J. Peltier[3], R.E. Harris[1], T. Schmidt-Wilcke[1,4]

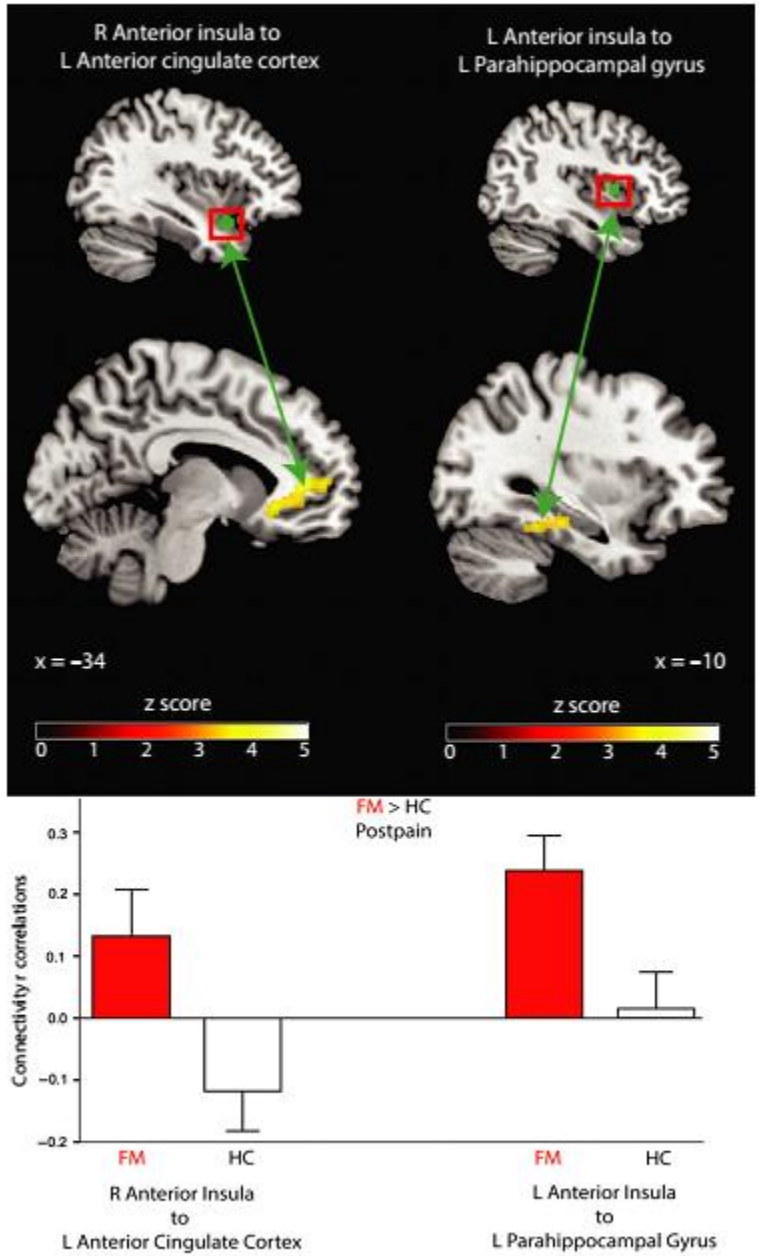


Figure 2 Increased insular cortex connectivity in FM relative to HC post pain. This figure shows FM patients have increased resting state connectivity following experimental pressure pain stimuli between the right anterior insular cortex and the left anterior cingulate cortex as well as increased connectivity between the left anterior insular cortex and the left parahippocampal gyrus. Red rectangles indicate seed location – seed coloured in green; bar graphs display mean degree of group connectivity with 95% confidence interval error bars. FM – Fibromyalgia; HC – Healthy Controls; L – Left; R – Right.

The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity

FREDERICK WOLFE,[1] DANIEL J. CLAUW,[2] MARY-ANN FITZCHARLES,[3] DON L. GOLDENBERG,[4] ROBERT S. KATZ,[5] PHILIP MEASE,[6] ANTHONY S. RUSSELL,[7] I. JON RUSSELL,[8] JOHN B. WINFIELD,[9] AND MUHAMMAD B. YUNUS[10]

Table 4. Fibromyalgia diagnostic criteria

Criteria

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

1) Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9.
2) Symptoms have been present at a similar level for at least 3 months.
3) The patient does not have a disorder that would otherwise explain the pain.

Ascertainment

1) WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.

Shoulder girdle, left	Hip (buttock, trochanter), left	Jaw, left	Upper back
Shoulder girdle, right	Hip (buttock, trochanter), right	Jaw, right	Lower back
Upper arm, left	Upper leg, left	Chest	Neck
Upper arm, right	Upper leg, right	Abdomen	
Lower arm, left	Lower leg, left		
Lower arm, right	Lower leg, right		

2) SS scale score:

Fatigue
Waking unrefreshed
Cognitive symptoms

For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:

0 = no problem
1 = slight or mild problems, generally mild or intermittent
2 = moderate, considerable problems, often present and/or at a moderate level
3 = severe: pervasive, continuous, life-disturbing problems

Considering somatic symptoms in general, indicate whether the patient has:*

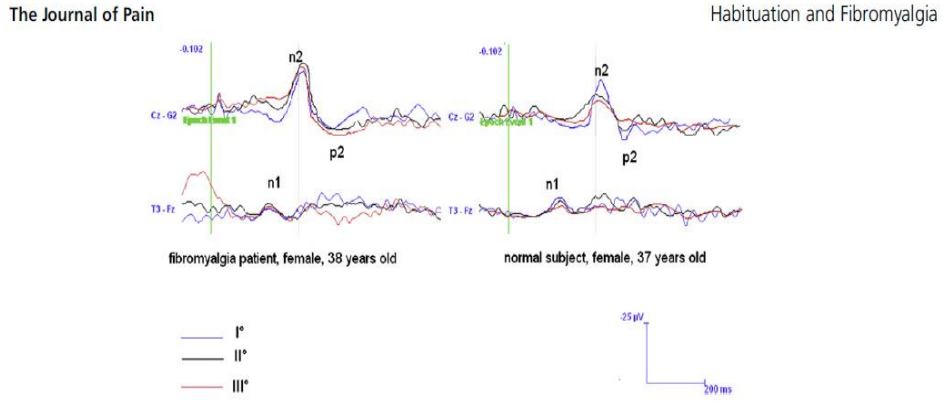
0 = no symptoms
1 = few symptoms
2 = a moderate number of symptoms
3 = a great deal of symptoms

The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

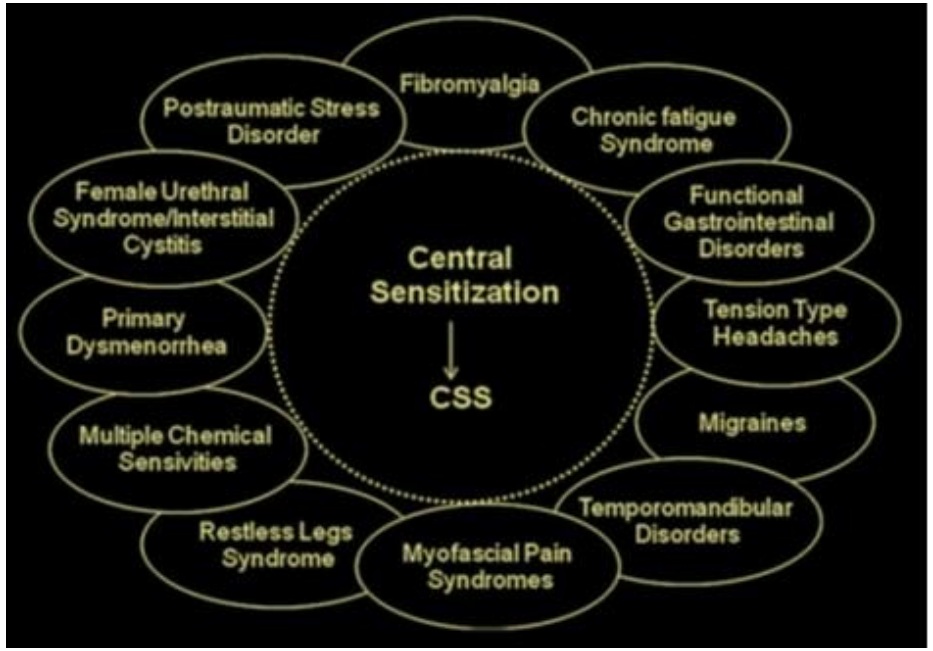
* Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

Fibromyalgia

Reduced habituation of cortical responses to laser stimuli in FM patients suggests alterations in the pattern of cortical excitability



De Tommaso et al, 2011



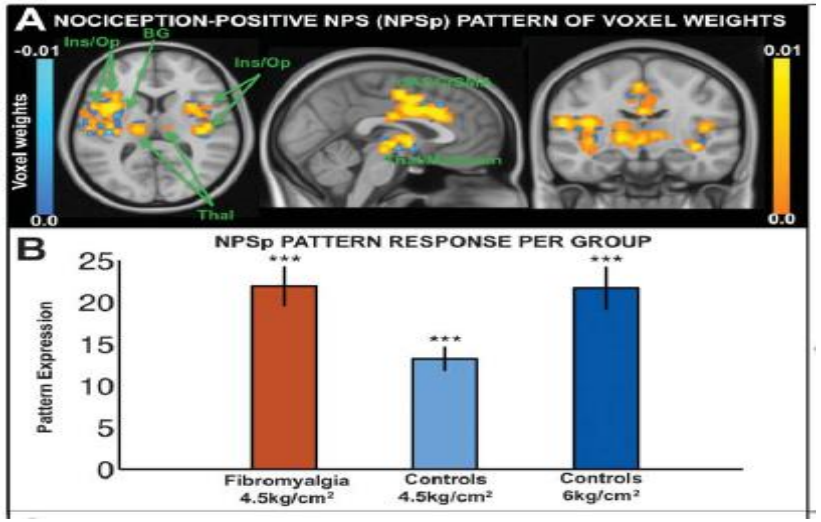
Central sensitization syndromes share a common etiologic mechanism and frequently present with overlapping epidemiologic, clinical and psychological features

Research Paper
PAIN

Towards a neurophysiological signature for fibromyalgia

Marina López-Solà[a,b,*], Choong-Wan Woo[a,b], Jesus Pujol[c], Joan Deus[c,d,e], Ben J. Harrison[f], Jordi Monfort[g], Tor D. Wager[a,b]

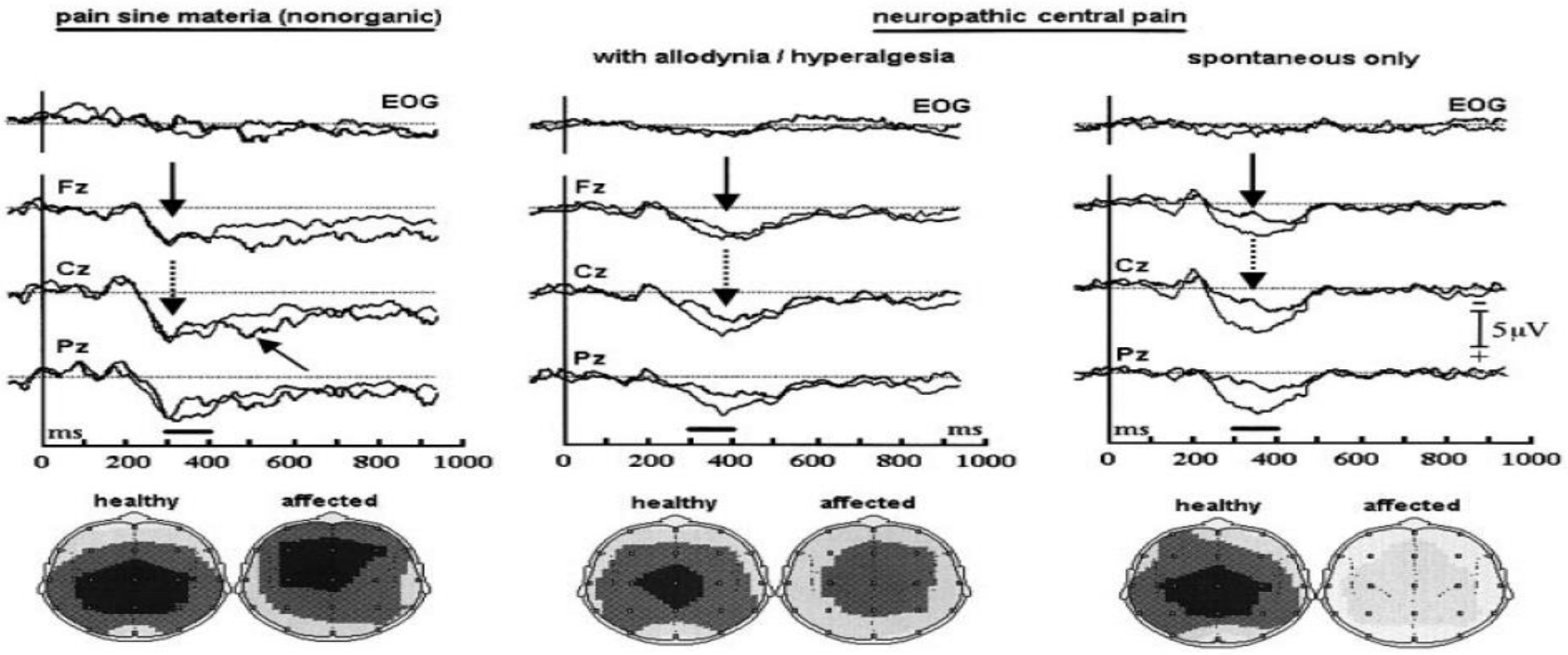
fMR studies revealed augmented responses in sensory integration (insula/operculum) and selfreferential (eg, medial prefrontal) regions in FM and reduced responses in the lateral frontal cortex after painful stimulation



Increased amplitude and reduced habituation of nociceptive evoked responses for an altered activation of pain/salience network in nociplastic/putative pain

Brain (2002), **125,** 2766–2781

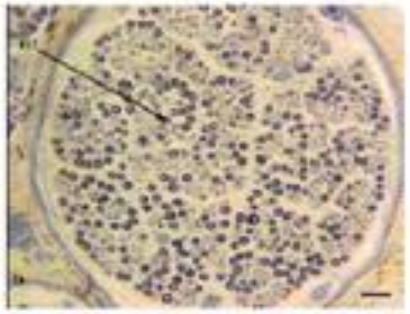
Laser-evoked potential abnormalities in central pain patients: the influence of spontaneous and provoked pain



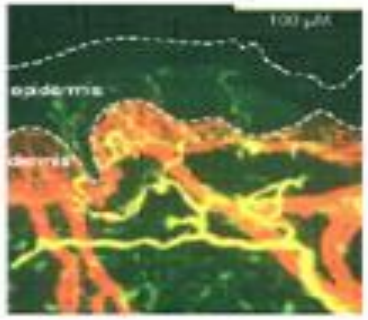
The example of Fibromyalgia: coexistence of peripheral damage and abnormal central pain processing

Diagnostica strumentale: biopsia

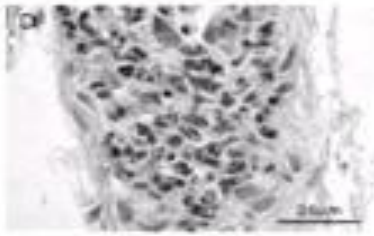
Biopsia nervo surale ed istogramma fibre nervose di vario calibro

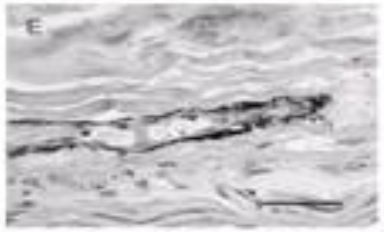


Puntato bioptico della cute con misurazione della densità di terminazioni libere



J Neurol
DOI 10.1007/s00415-013-7211-9





Update on laser-evoked potential findings in fibromyalgia patients in light of clinical and skin biopsy features

Marina de Tommaso · Maria Nolano · Florenzo Iannone · Eleonora Vecchio · Katia Ricci · Marta Lorenzo · Marianna Delussi · Francesco Girolamo · Vito Lavolpe · Vincenzo Provitera · Annamaria Stancanelli · Giovanni Lapadula · Paolo Livrea

Non lenght dependent small fibers neuropathy in FM: how the central processing of pain could change clinical features of neuropathic pain

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 7, July 2014, pp 1945–1954
DOI 10.1002/art.38662

SHORT RE

SMALL
FIBRO

MARIA PIA
PATRIZIA A

[1]Departmen
[2]IRCCS Istitu

Accepted 23 D

wit

Evidence of Abnormal Epidermal Nerve Fiber Density

Clinica

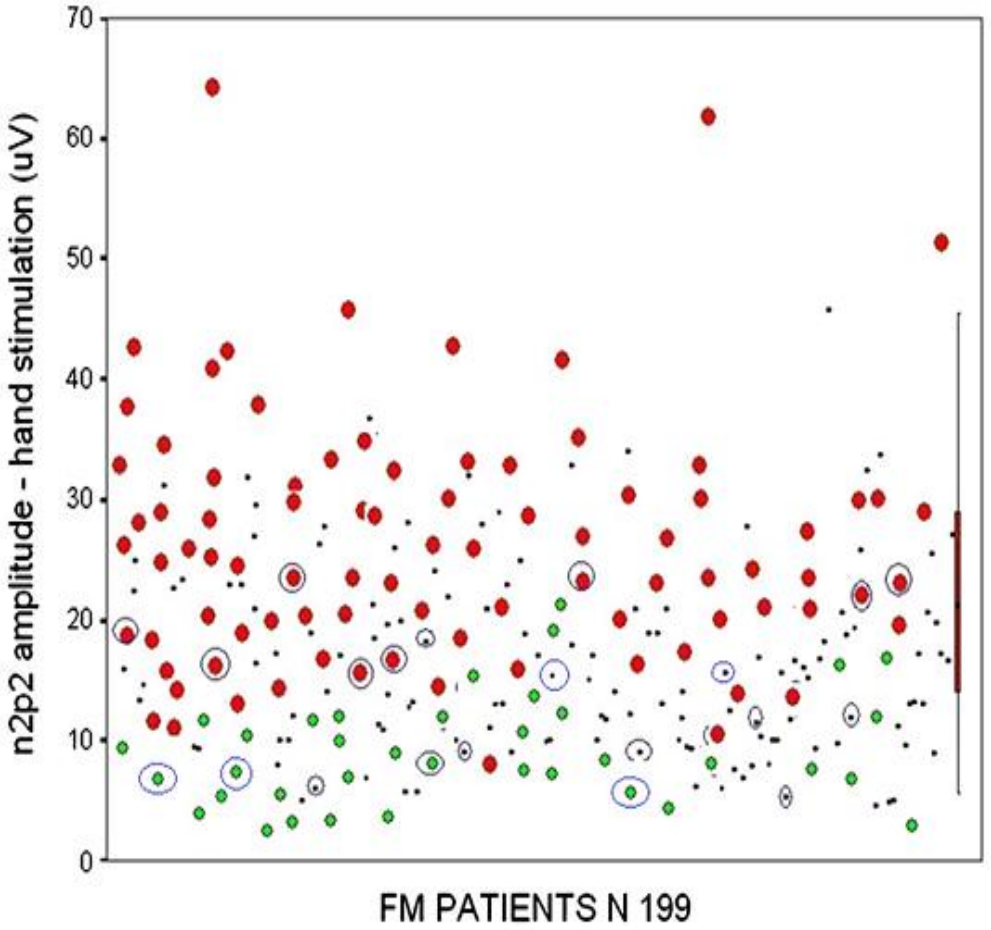
Xa

fibromyalgia sync

Conclusion. **The calf and thigh ENFD in patients with FM is significantly diminished compared with that in control subjects. Advancing age alone cannot explain this finding. Calf ENFD was inversely correlated, although weakly, with serum levels of IL-2R. These findings suggest that small fiber neuropathy is likely to contribute to the pain symptoms of FM; that pain in this disorder arises, in part, from a peripheral immune-mediated process; and that measurement of ENFD may be a useful clinical tool in FM.**

Nurcan Üçeyler,[1] Daniel Zeller,[1] Ann-Kathrin Kahn,[1] Susanne Kewenig,[1] Sarah Kittel-Schneider,[2] Annina Schmid,[1] Jordi Casanova-Molla,[1] Karlheinz Reiners[1] and Claudia Sommer[1]

Dysfunction in the nociceptive system at both the central and peripheral levels may concur to explain phenotypical eterogeneity and clinical symptom complexity in fibromyalgia



LEPs: amplitude variability; reduced habituation
Skin biopsy (32 patients: not lenght dependent small fiber neuropathy)

Small fibers denervation in FM

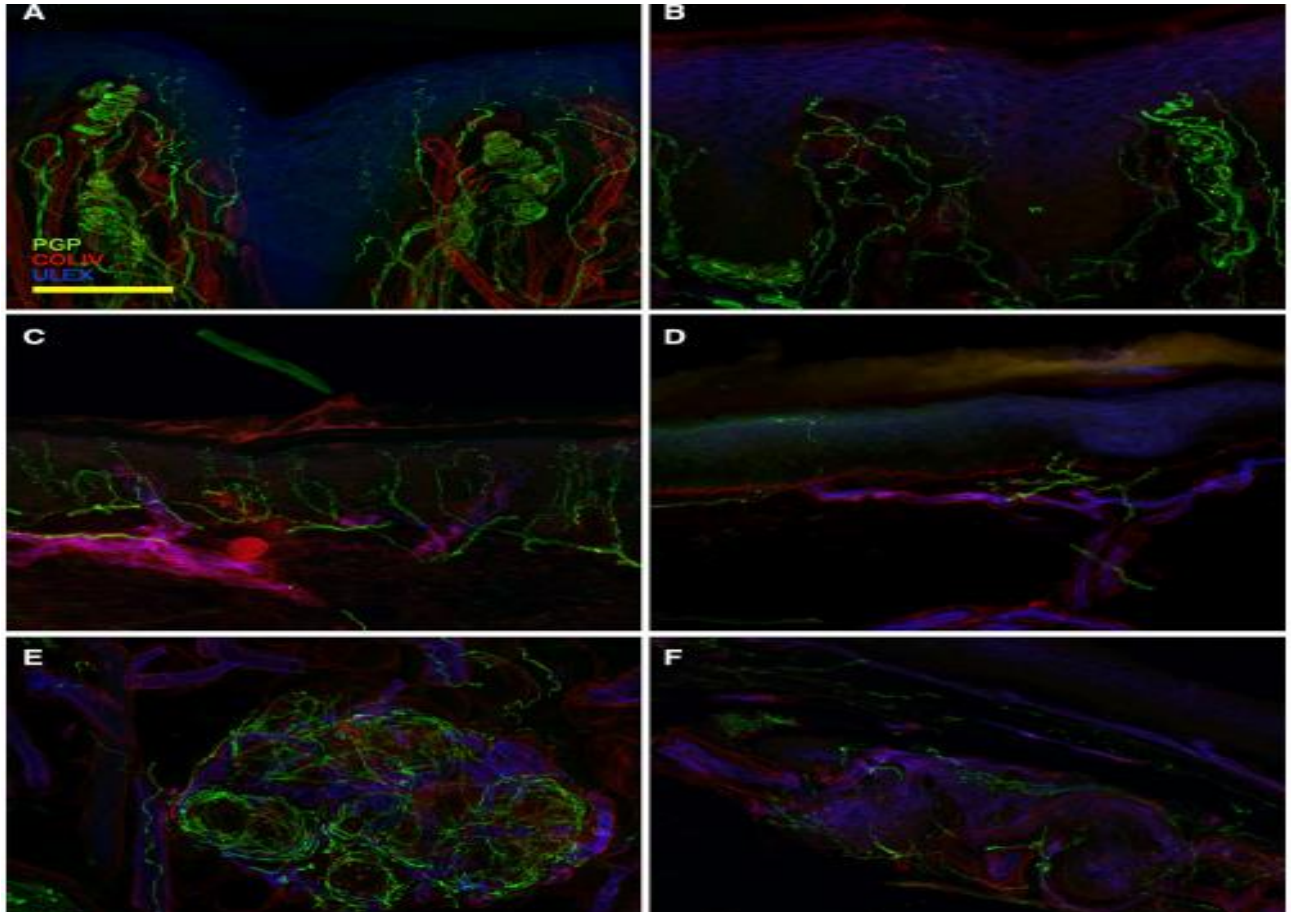


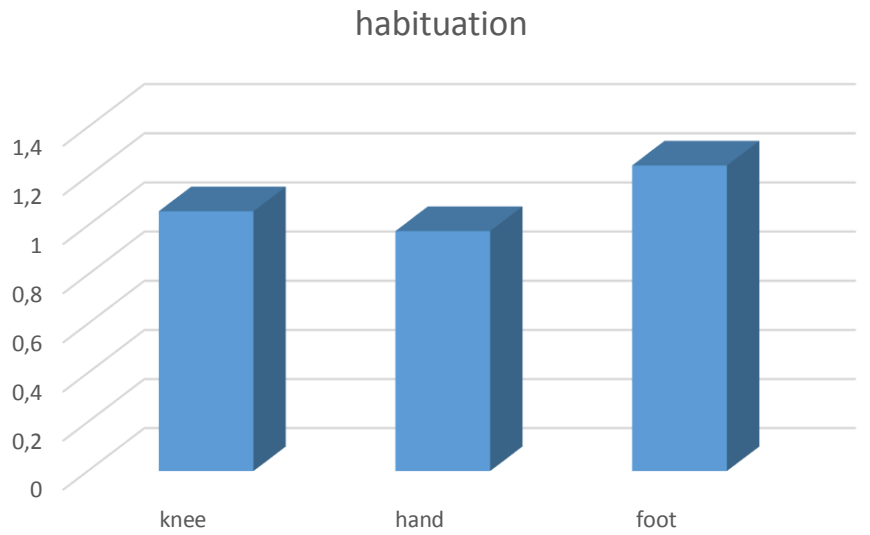
Table 4 Mean values and standard deviations of the number of epidermal nerve fibers (EFN) per linear mm, Meissner corpuscles (MC) per mm^2, and intrapapillar myelinated fibers (IMF) per mm^2

	Sex (M/F)	Age	EFN thigh	EFN leg	EFN fingertip	MC	IMF
Fibromyalgia	3/18	51.0 ± 8.7	17.4 ± 6.9	11.4 ± 4.3	4.5 ± 3.2	9.7 ± 8.3	59.5 ± 25.7
Controls	10/50	52.7 ± 6.3	23.5 ± 3.8	15.0 ± 3.6	6.8 ± 3.0	27.2 ± 7.5	53.1 ± 19.3
p		0.45	**<0.01**	**<0.01**	**<0.05**	**<0.01**	0.33

The results of Student's *t* test are reported

Recent Results: 82 patients

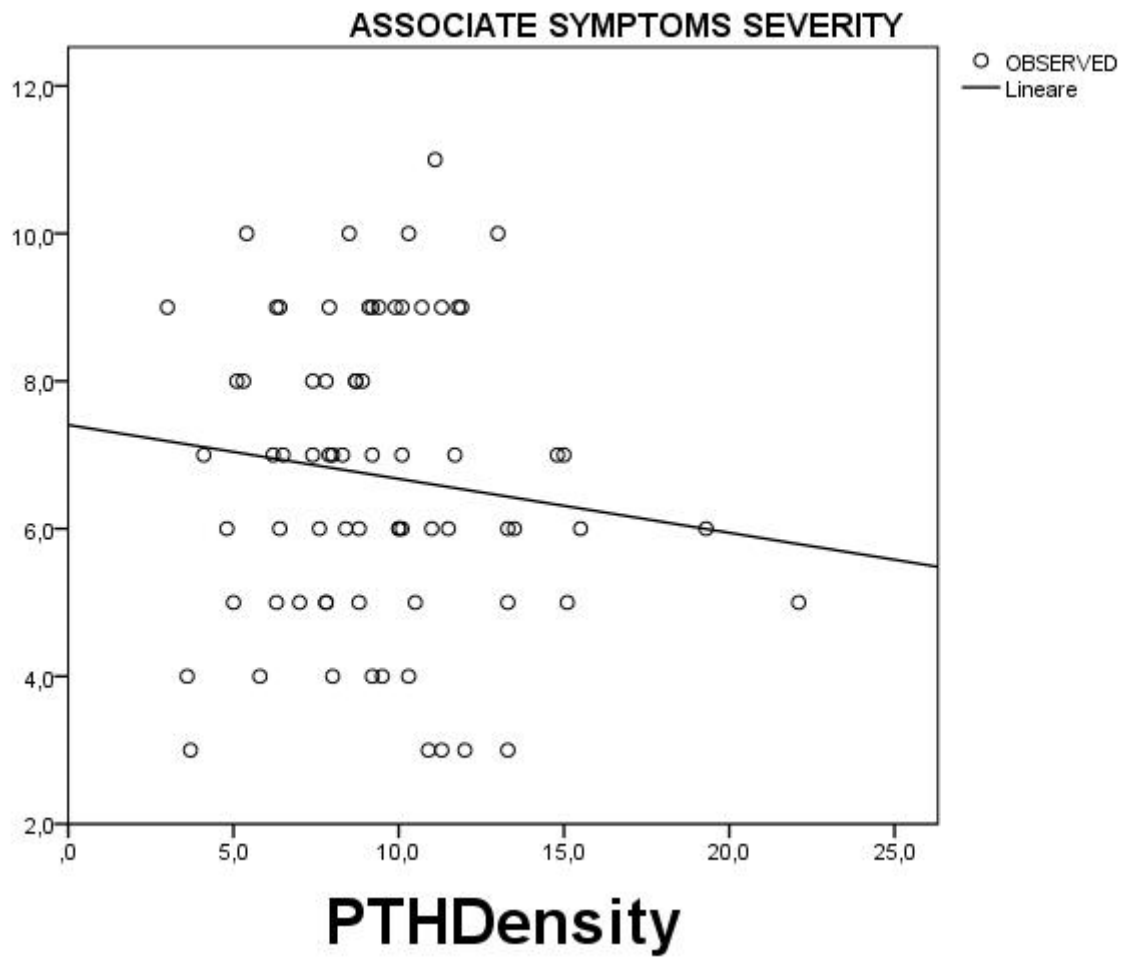
	Impaired %
LEP (N2P2 amplitude)	
Hand	14.7
Knee	26.7
Foot	44.5.
SSR	
Hand	17.2
Foot	59.5
Biopsy	
PTH	85.2
DL	14.8



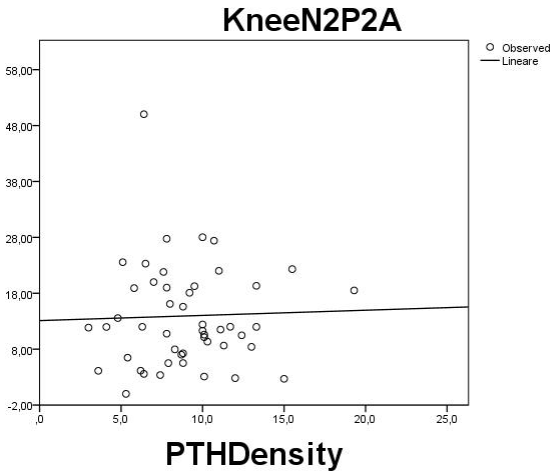
THE MOST OF PATIENTS PRESENTED WITH PROXIMAL EFN REDUCTION
ALL PATIENTS HAD REDUCED LEPs HABITUATION

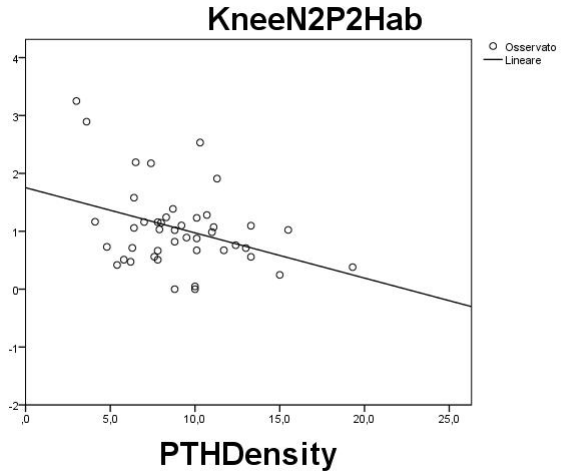
Vecchio et al, in preparation

NO CORRELATION BETWEEN ASSOCIATE SYMPTOMS SEVERITY AND EFNd

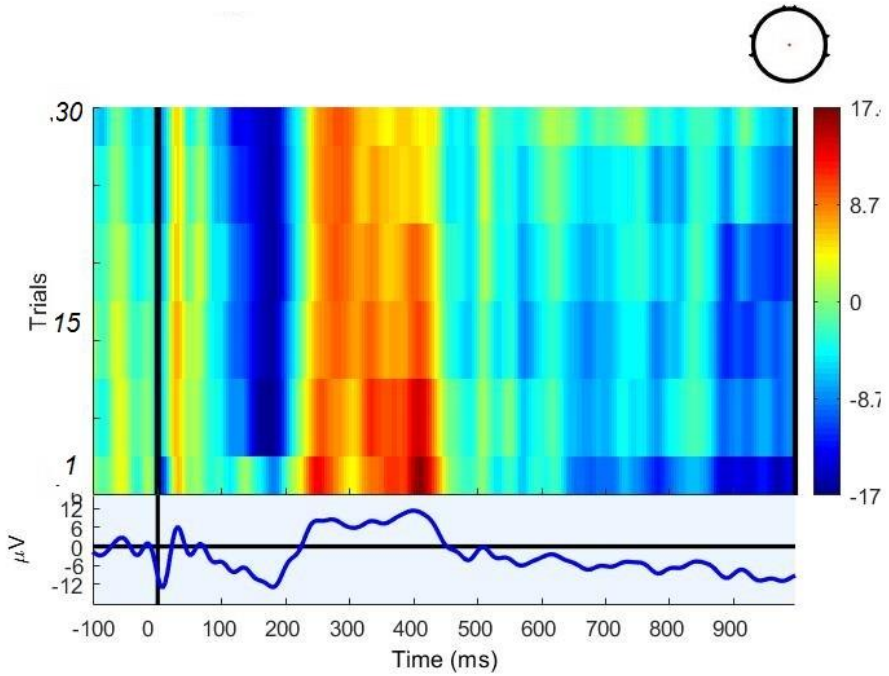


INVERSE CORRELATION BETWEEN EFNd AND HABITUATION INDEX

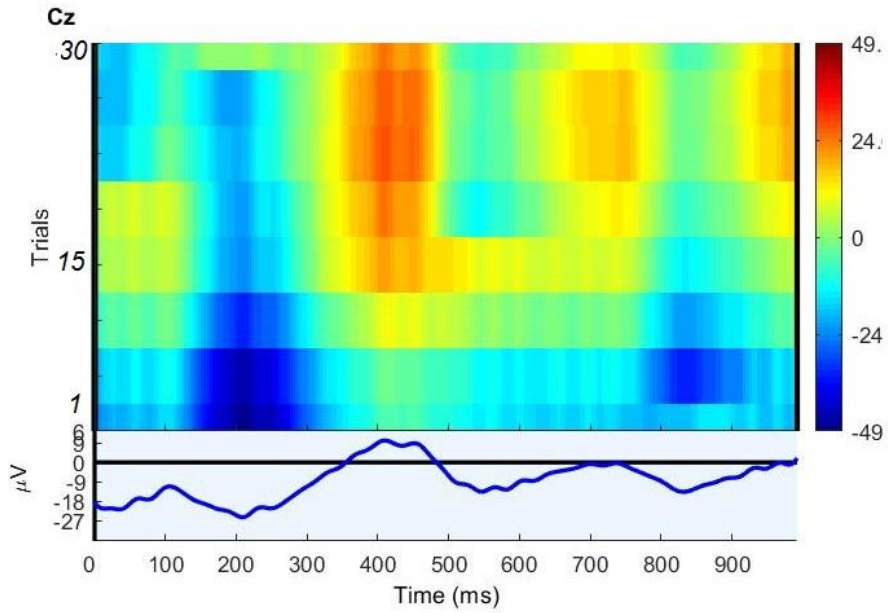




The amplification of peripheral signal by pain/salience matrix via reduced habituation mechanism cause a recover of cortical response amplitude



EFN density
22-12 (n°14)



EFN density
3-7 (n°18)

LEPs findings :

- *Peripheral afferent dysfunction could influence the central processing of pain* ***--_Reduced habituation to contrast reduced small fibers input_***

These findings high spot that in FM the disinhibition of the DPMS is positively correlated with the dysfunction in peripheral sensory neurons assessed by QST and conversely with serum BDNF.

Brietzke et al. Medicine (2019) 98:3

Observational Study

Medicine®

OPEN

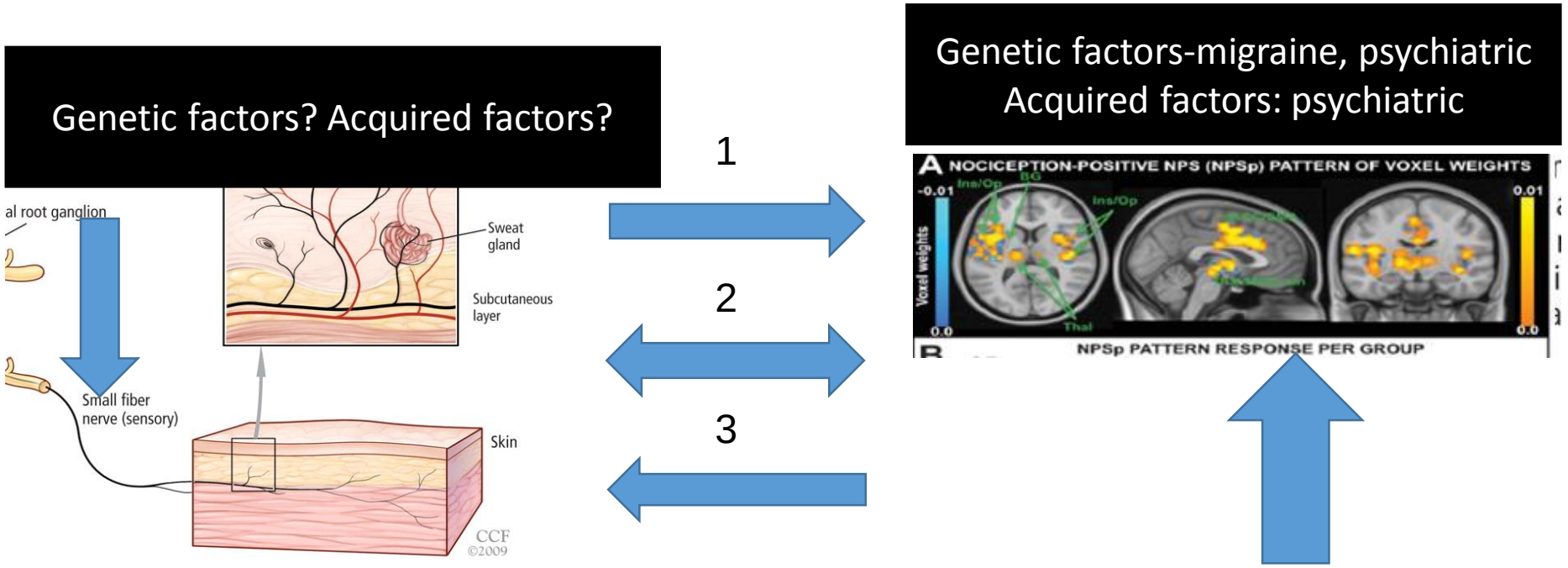
Potency of descending pain modulatory system is linked with peripheral sensory dysfunction in fibromyalgia

An exploratory study

Aline Patrícia Brietzke, PhD[a,b], Luciana Conceição Antunes, PhD[a,b], Fabiana Carvalho, PhD[a,b], Jessica Elkifury[a,b], Assunta Gasparin[a,b], Paulo Roberto Stefani Sanches, PhD[c], Danton Pereira da Silva Junior, PhD[c], Jairo Alberto Dussán-Sarria, MD, PhD[b], Andressa Souza, PhD[b], Iraci Lucena da Silva Torres, PhD[b], Felipe Fregni, MD, PhD[d], Wolnei Caumo MD, PhD[a,b,e,f,*]

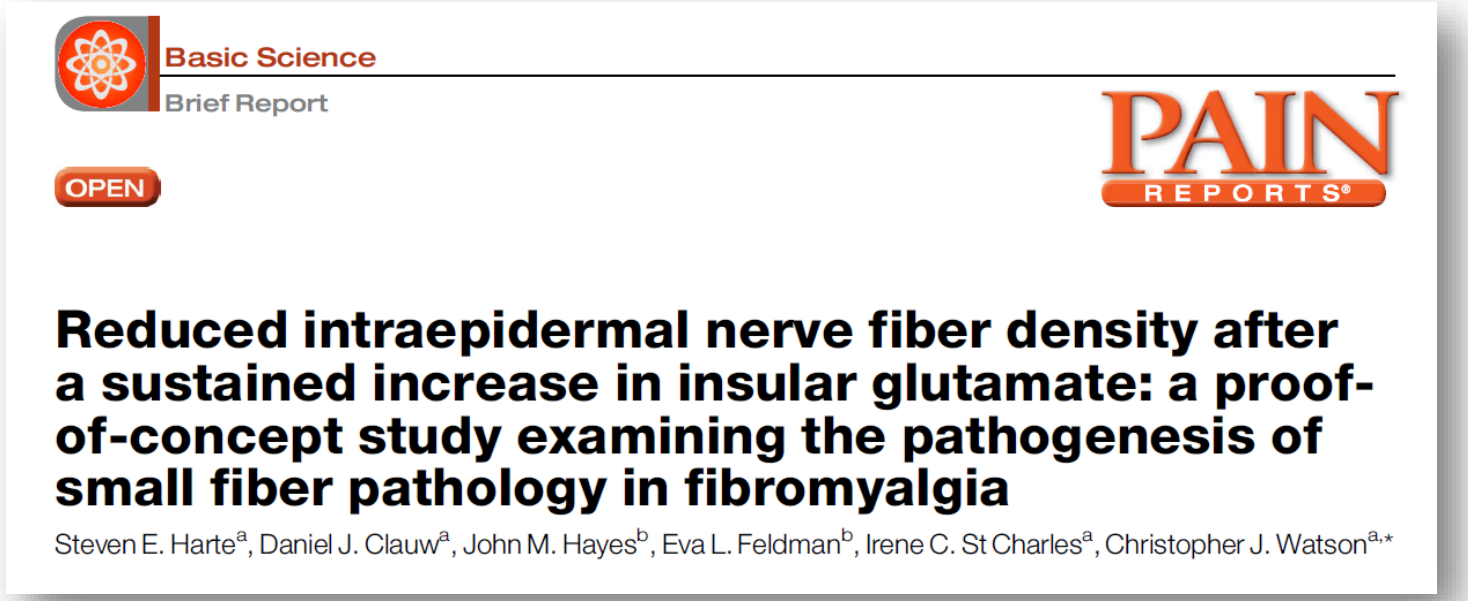
Questions:

- ***Well, what we face here is the question of which comes first, the chicken or the egg.***



3 ??????

- *the peripheral involvement of the small fibers may be the consequence of the central alteration of pain processing*



Basic Science

Brief Report

OPEN

PAIN REPORTS®

Reduced intraepidermal nerve fiber density after a sustained increase in insular glutamate: a proof-of-concept study examining the pathogenesis of small fiber pathology in fibromyalgia

Steven E. Harte[a], Daniel J. Clauw[a], John M. Hayes[b], Eva L. Feldman[b], Irene C. St Charles[a], Christopher J. Watson[a,*]

Clinical picture of chronic pain is influenced by the mutual inference between peripheral and central nervous system: reduced habituation within the pain-salience network could change the features of neuropathic pain

EJP
European Journal of P

ORIGINAL ARTICLE

Reduced laser-evoked potential habituation detects abnormal central pain processing in painful radiculopathy patients

P. Hüllemann[1], C. von der Brelie[2], G. Manthey[1], J. Düsterhöft[1], A.K. Helmers[2], M. Synowitz[2], R. Baron[1]

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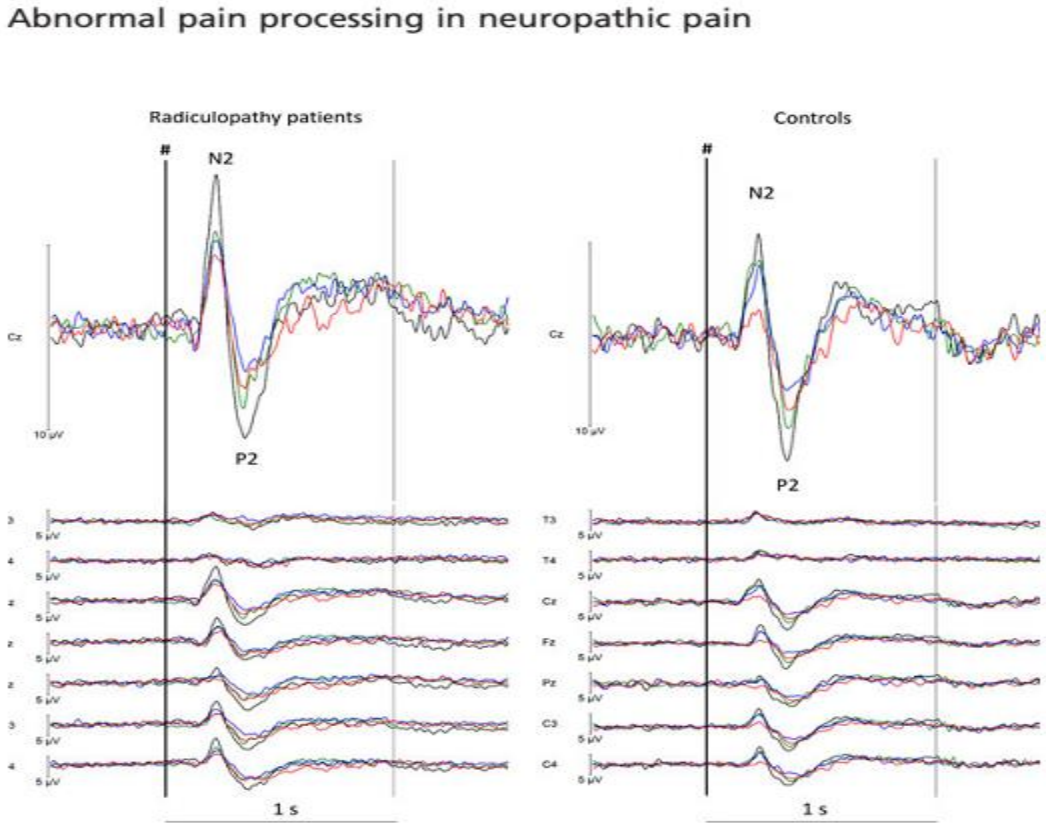


Figure 1 N2/P2 amplitudes – EEG data. The grand-average of the time course of N2/P2 amplitudes is shown here. In the upper part of the image, we magnified the relevant Cz electrode. The lower part shows all included EEG electrodes. Black line = block I (first 25 stimuli); green line = block II (second 25 stimuli); blue line = block III (third 25 stimuli); red line = block IV (forth 25 stimuli). LEPs of radiculopathy patients are indicated on the left, healthy controls on the right. The stimulus onset is indicated with the #-sign.

..abnormal functional connectivity in the salience/pain matrix is the counterpart of reduced habituation

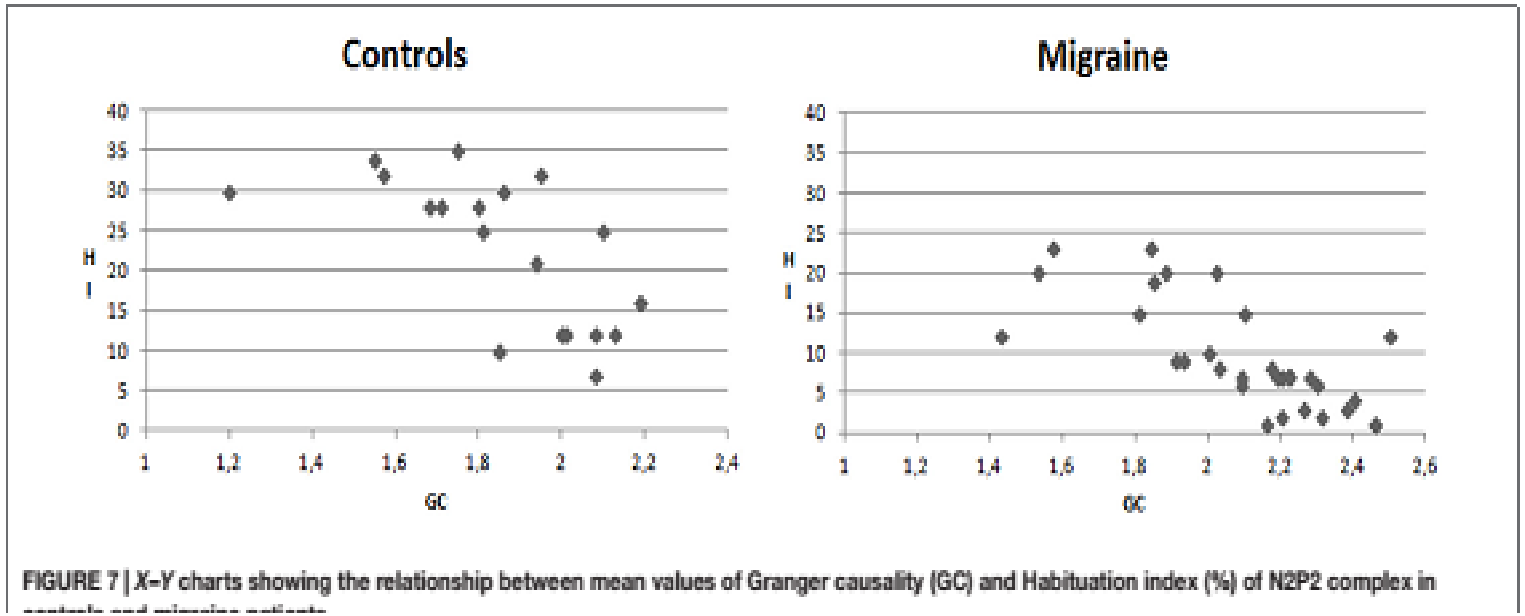
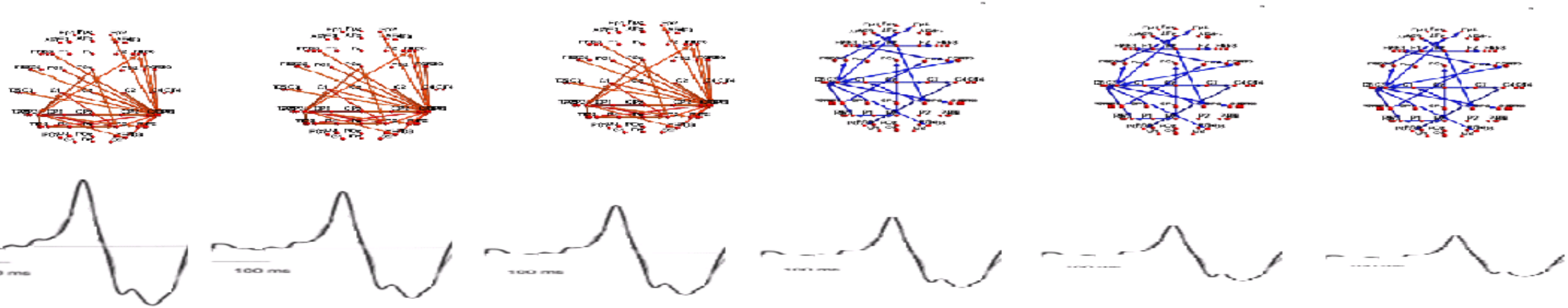


FIGURE 7 | *X–Y* charts showing the relationship between mean values of Granger causality (GC) and Habituation index (%) of N2P2 complex in

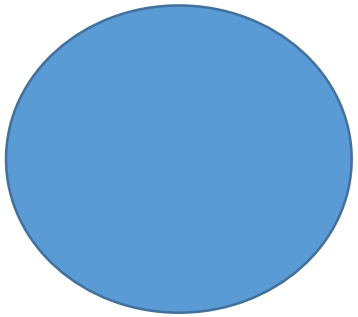


Any type of chronic pain- nociceptive, putative and neuropathic- cannot be explained without considering the status of salience/pain matrix

Pain is never segregated in the periphery

The relationships between pain-salience and motor cortical networks

- Possible mutual relationship between motor function and pain control.
- Motor cortex activation seems to reduce the pain perception and the amplitude of nociceptive evoked responses.



Pain-related modulation of the human motor cortex

Simona Farina, Michele Tinazzi, Domenica Le Pera & Massimiliano Valeriani

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The use of repetitive transcranial magnetic stimulation (rTMS) in chronic neuropathic pain

J.P. Lefaucheur

Pain Research and Treatment

Indexed in Web of Science

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Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia

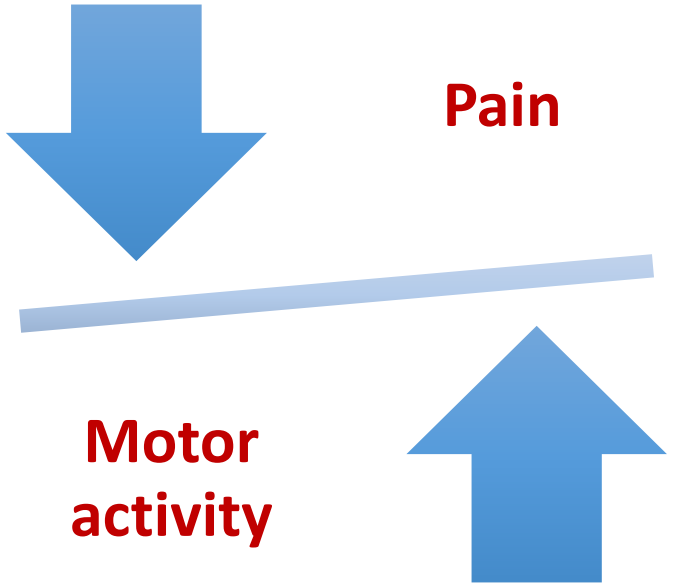
A. Passard,[1] N. Attal,[1] R. Benadhira,[2] L. Brasseur,[1] G. Saba,[2] P. Sichere,[3] S. Perrot,[4] D. Januel[2] and D. Bouhassira[1]

Motor Cortex Function in Fibromyalgia: A Study by Functional Near-Infrared Spectroscopy

Eleonora Gentile, [1] Katia Ricci, [1] Marianna Delussi, [1] Filippo Brighina, [2] and Marina de Tommaso [1]

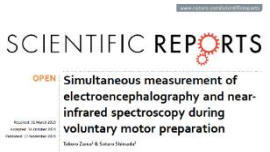
Pain and motor functions

- Motor activity is indicated for the treatment of chronic pain.
- Pain reduces motor activity, inhibiting motor cortex in a self-sustained mechanism of chronic symptoms maintenance.



How to study the salient-pain and motor networks mutual interference: the co-recording of EEG/fNIRS activity Functional Near-Infrared Spectroscopy

- 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.
- Thanks to its portability and movement tolerance, the fNIRS is a useful tool in experimental neuroimaging studies on motor functions (Morais et al., 2018).


SCIENTIFIC REPORTS

OPEN

Simultaneous measurement of electroencephalography and near-infrared spectroscopy during voluntary motor preparation


NeuroImage

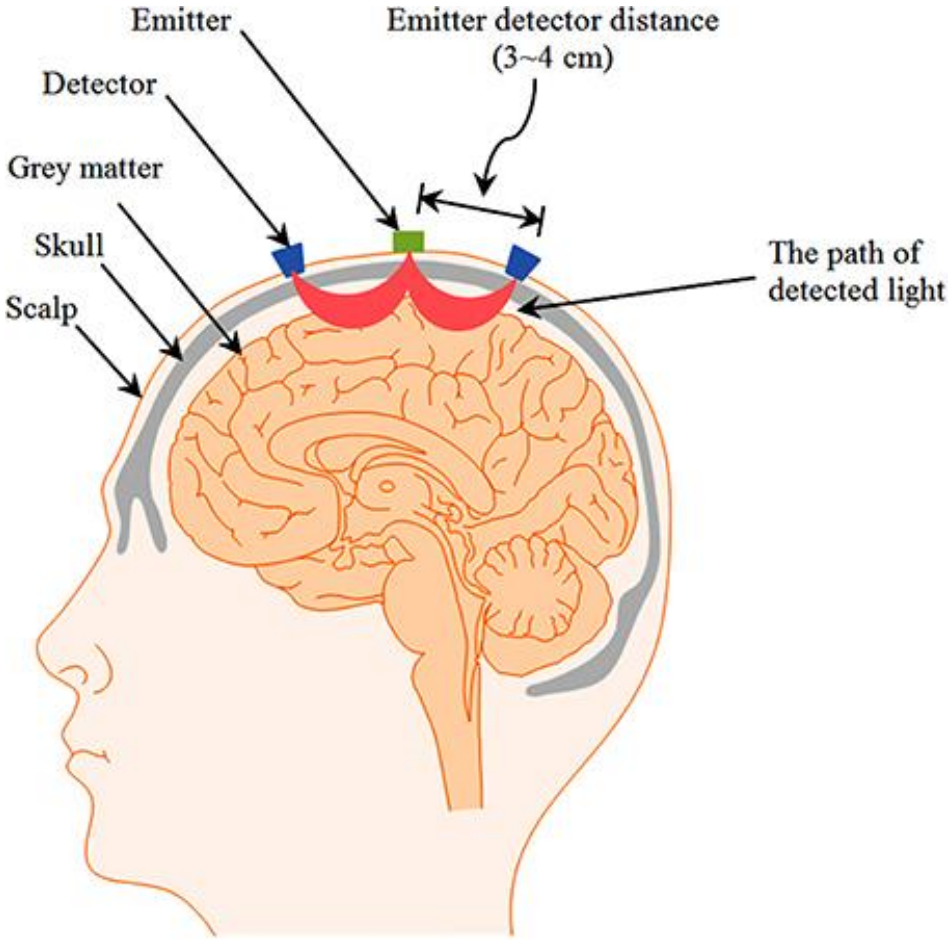
Task complexity relates to activation of cortical motor areas during uni- and bimanual performance: A functional NIRS study


Optical Imaging of Motor Cortical Hemodynamic Response to Directional Arm Movements Using Near-infrared Spectroscopy


The Effect of Maximal Finger Tapping on Cerebral Activation

The fNIRS

- The Near-infrared light can penetrate cerebral tissue without significant degradation of the optical signals (Tam et Zouridakis, 2013).
- The skin, skull and tissues are trasparent to NIR wavelenghts, while O2Hb and HHb absorb these spectra.
- By this method we can see the brain activation and the oxygen consumption during a motor task.



Hemodynamic activity

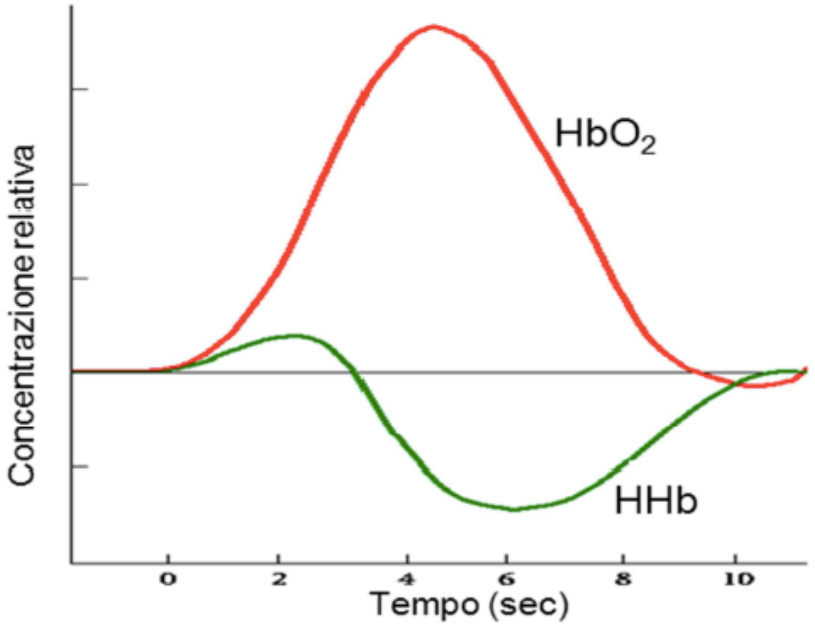
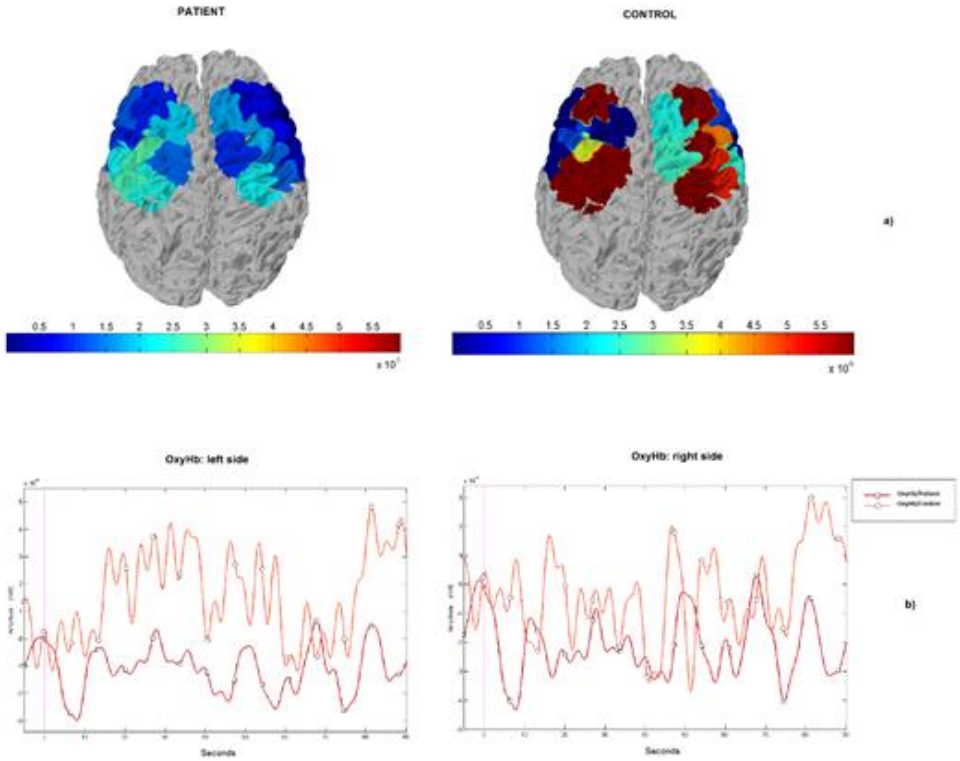
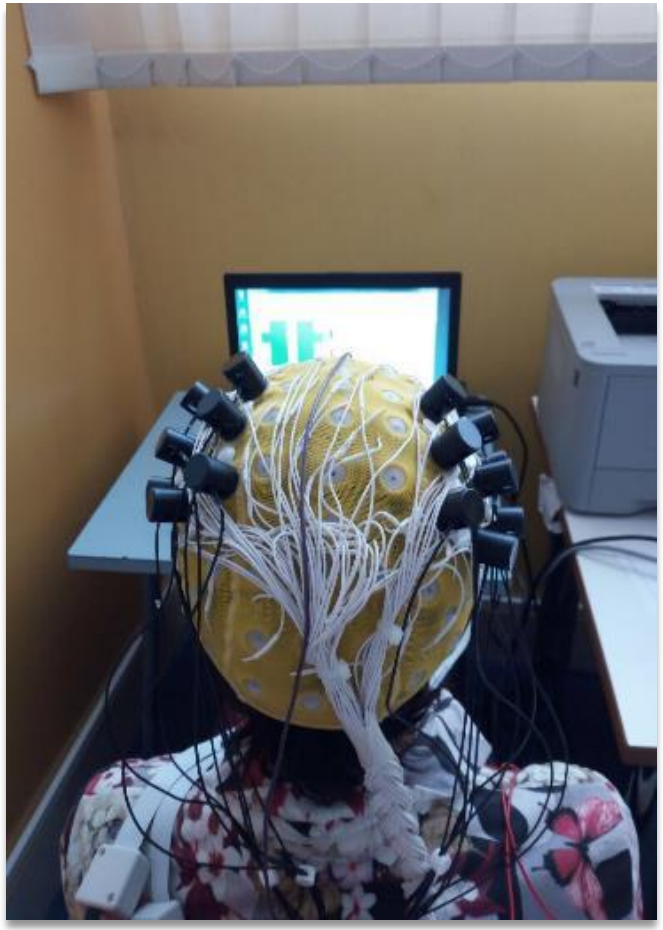
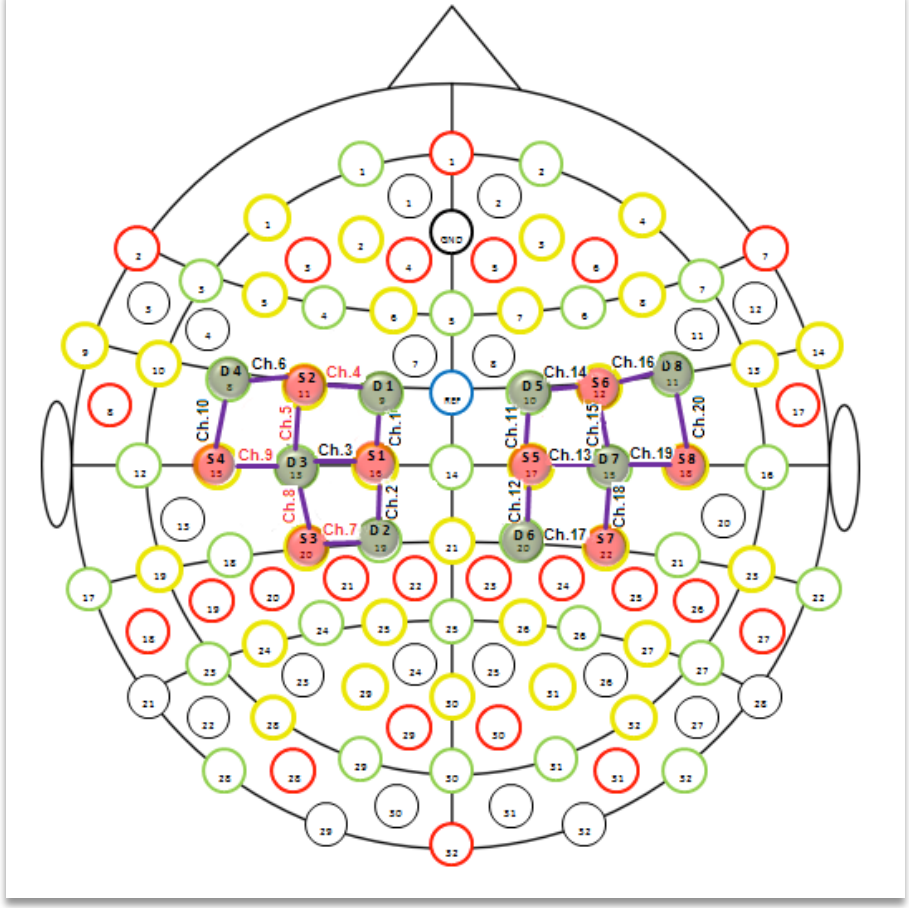


Fig. 2.1.c – Risposta emodinamica attesa per HbO_2 e HHb



Calculation of HbO and HbR variations: the most widely used method is the modified Beer-Lambert law.





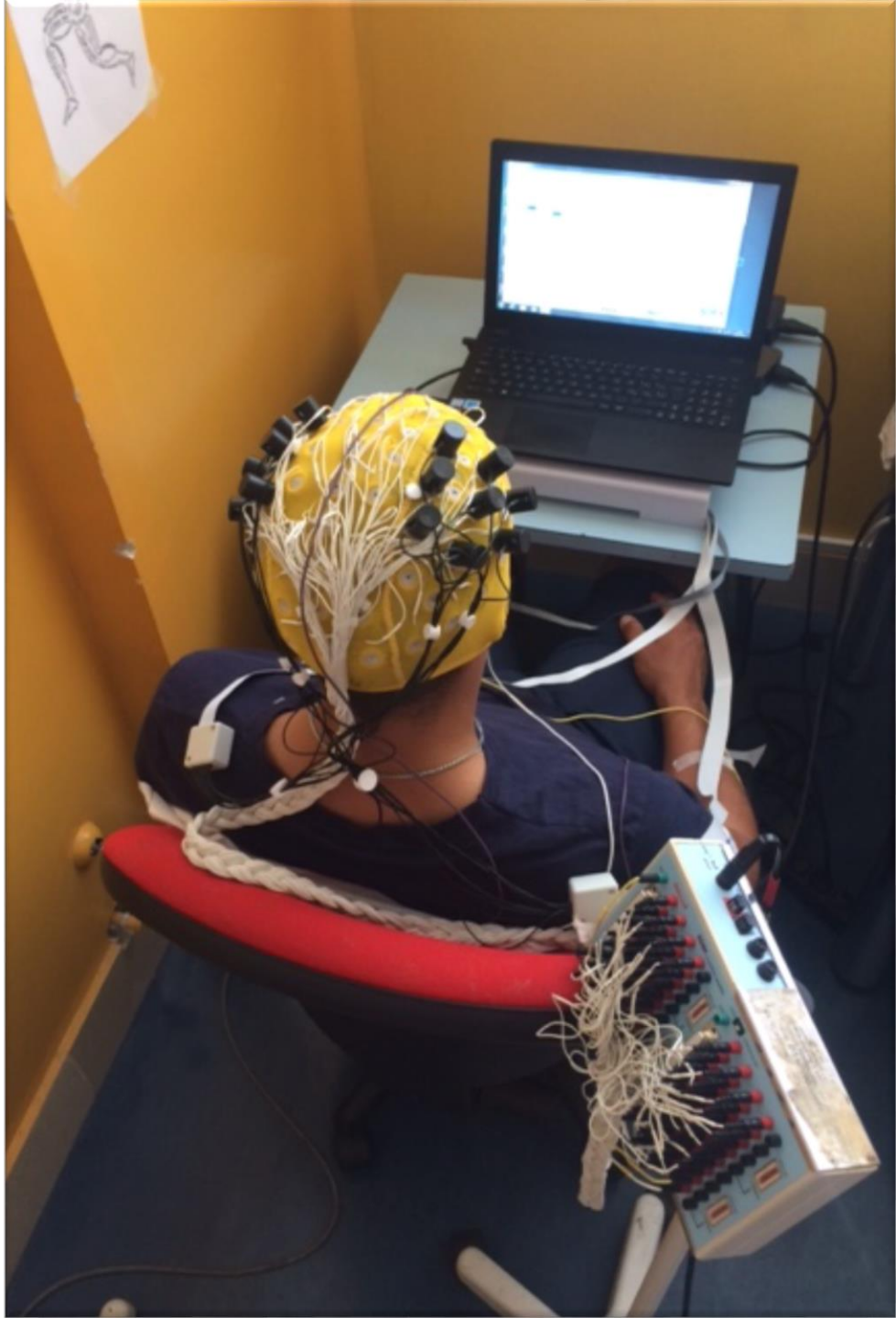
The multimodal EEG/fNIRS to study the co-activation of salience and motor networks

Method

- The participants in this study are 21 healthy subjects (aged from 19 to 60) and 38 patients with fibromyalgia (aged from 19 to 60).

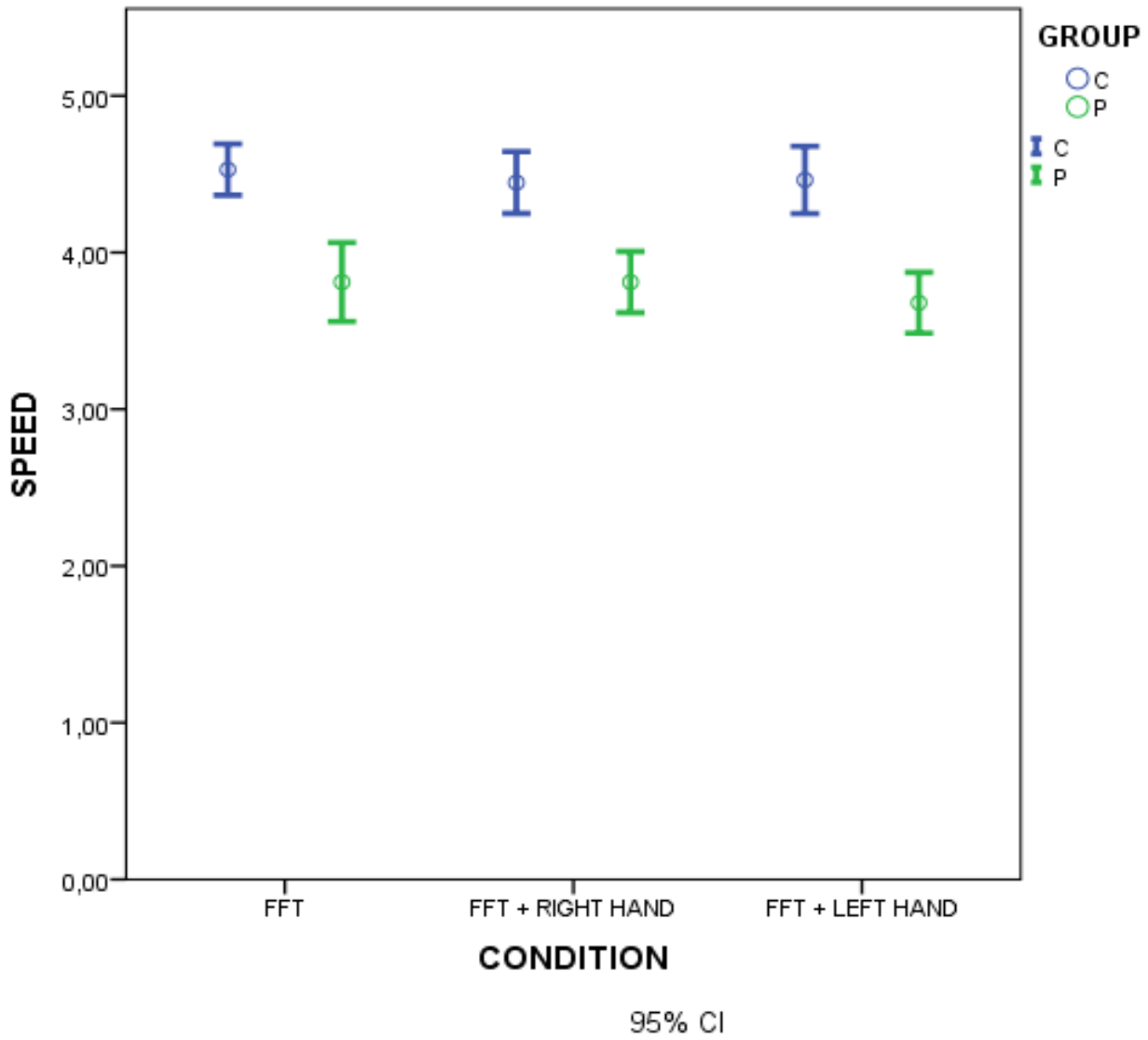
Experimental study design

RESTING STATE	• 1 minute resting state
LASER STIMULATION ON THE RIGHT HAND	• 1 minute resting state
LASER STIMULATION ON THE LEFT HAND	• 1 minute resting state
SLOW FINGER TAPPING TASK (SFT)	• 1 minute resting state
SFT + LASER ON THE RIGH HAND	• 1 minute resting state
SFT + LASER ON THE LEFT HAND	• 1 minute resting state
FAST FIGER TAPPING (FFT) TASK	• 1 minute resting state
FFT + LASER ON THE RIGHT HAND	• 1 minute resting state
FFT + LASER ON THE LEFT HAND	

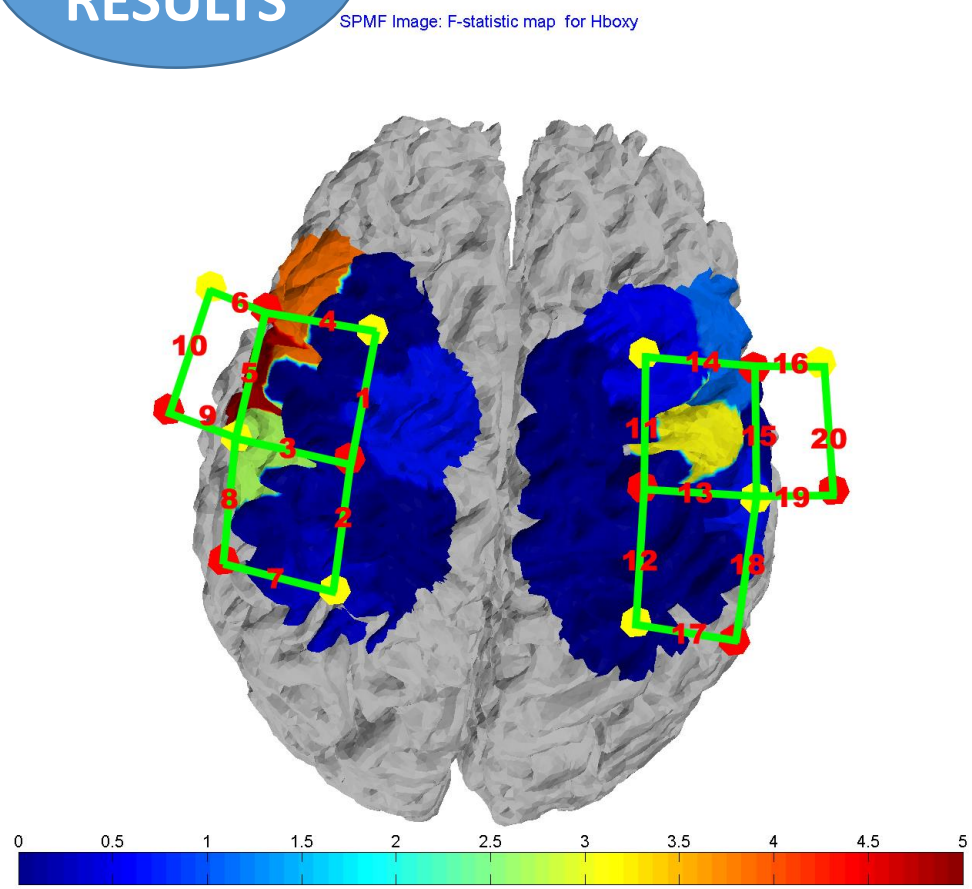


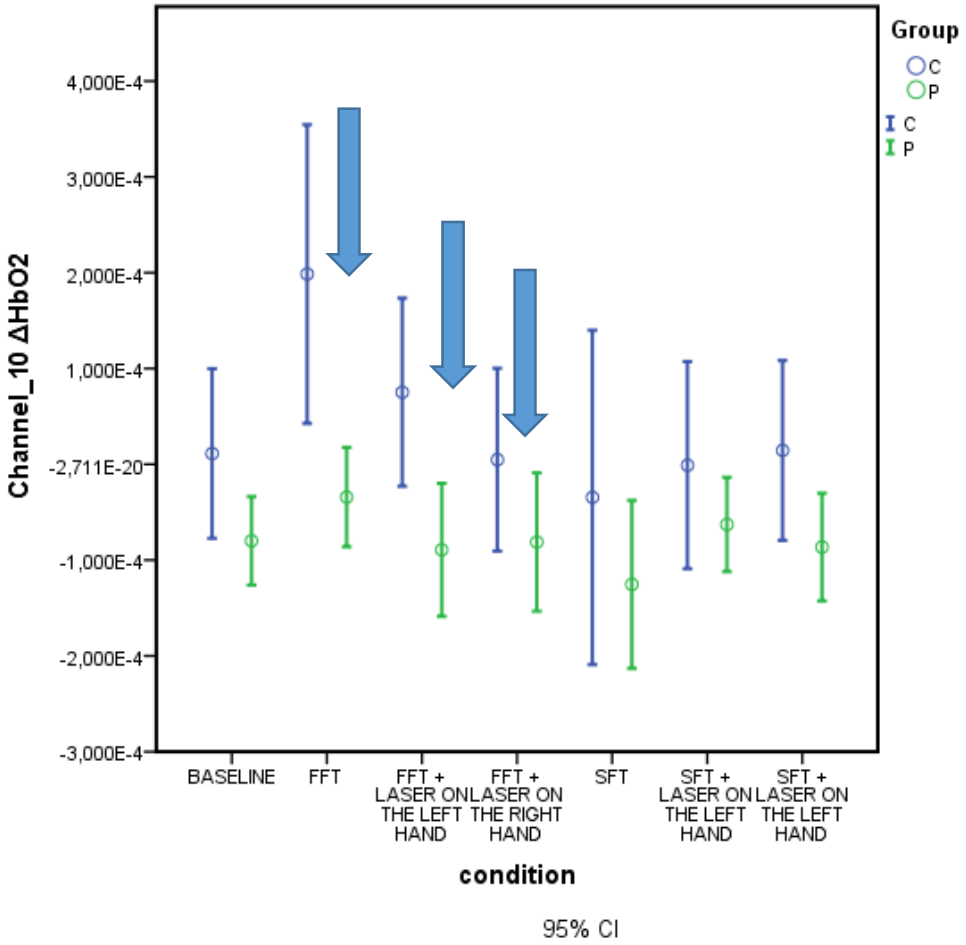
Finger tapping performance

SIGNIFICANT REDUCTION OF FINGER TAPPING SPEED IN PATIENTS , INDEPENDENT FROM LASER STIMULATION



FNIRS RESULTS



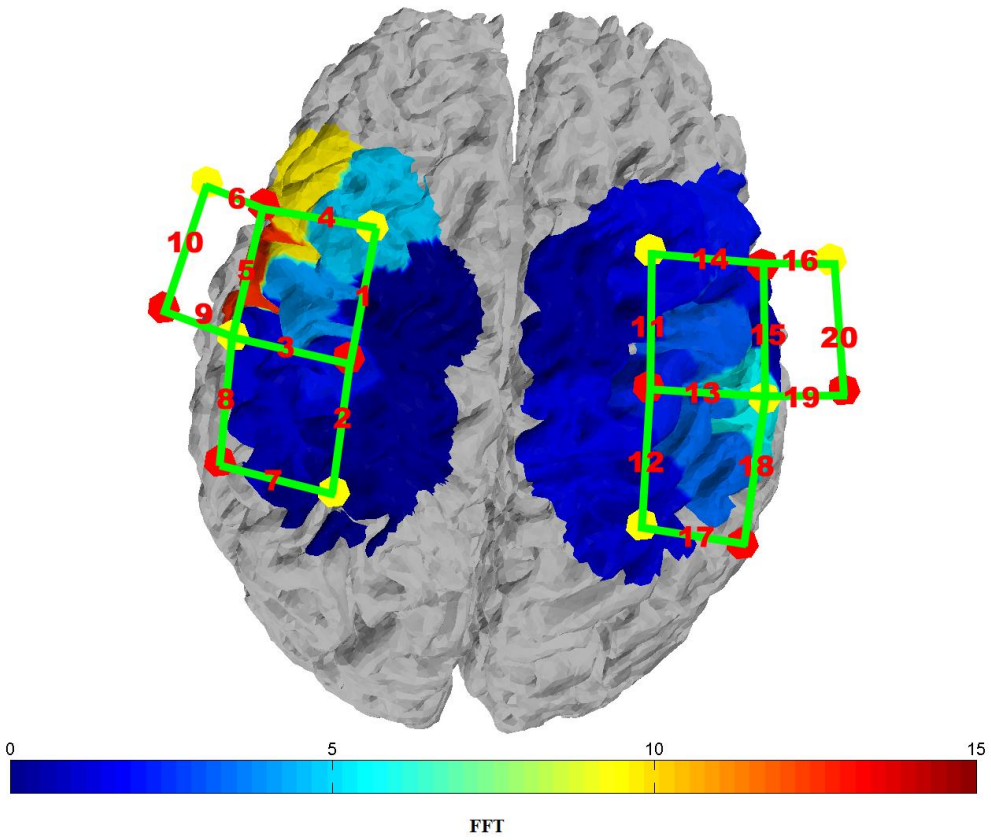


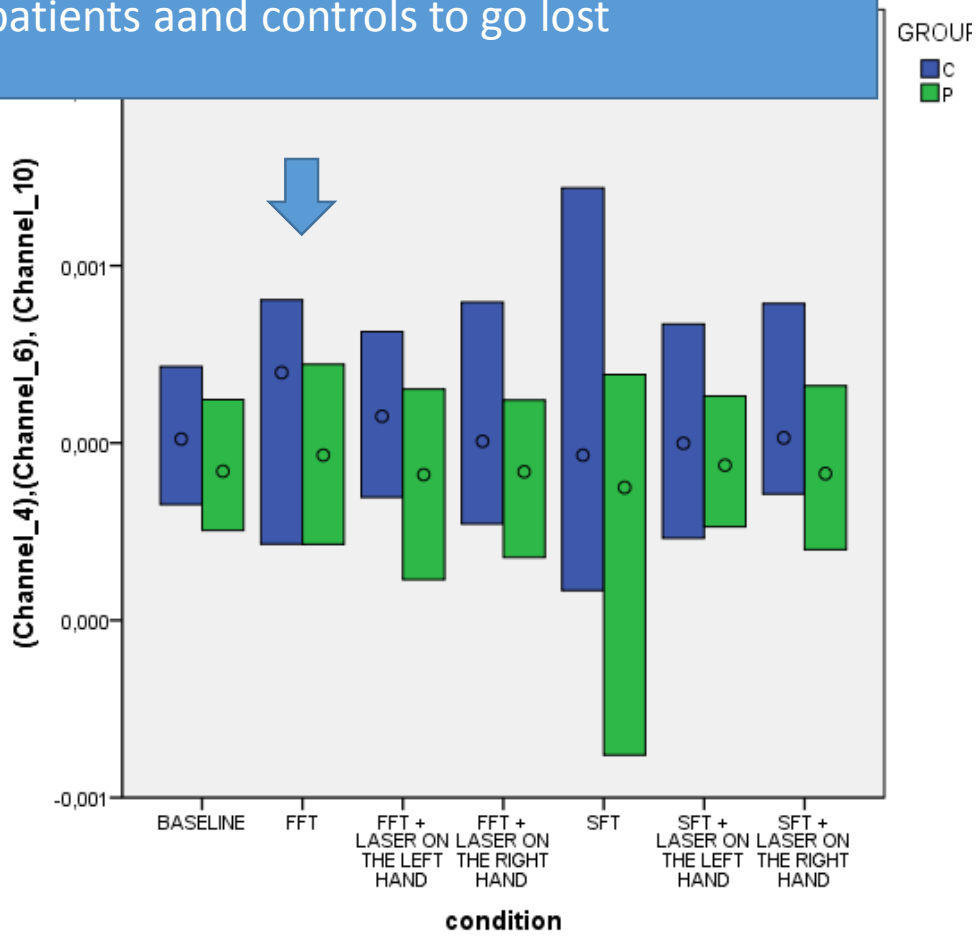
- **Reduced tone of motor cortex in resting state in chronic pain patients**
- **Reduced activation of motor cortex during fast movement in chronic patients**
- **The concomitant painful stimulation, reduced the motor activation in controls, abolishing any difference between groups**
- **The slow movement did not change the activation of motor cortex either in patients or in controls**

FNIRS RESULTS

During fast finger tapping, chronic pain patients showed reduced tone of motor cortex activation The concomitant painful sti,ulation caused the difference between patients aand controls to go lost

FFT





PATIENTS:
REDUCED MODULATION OF MOTOR CORTEX.

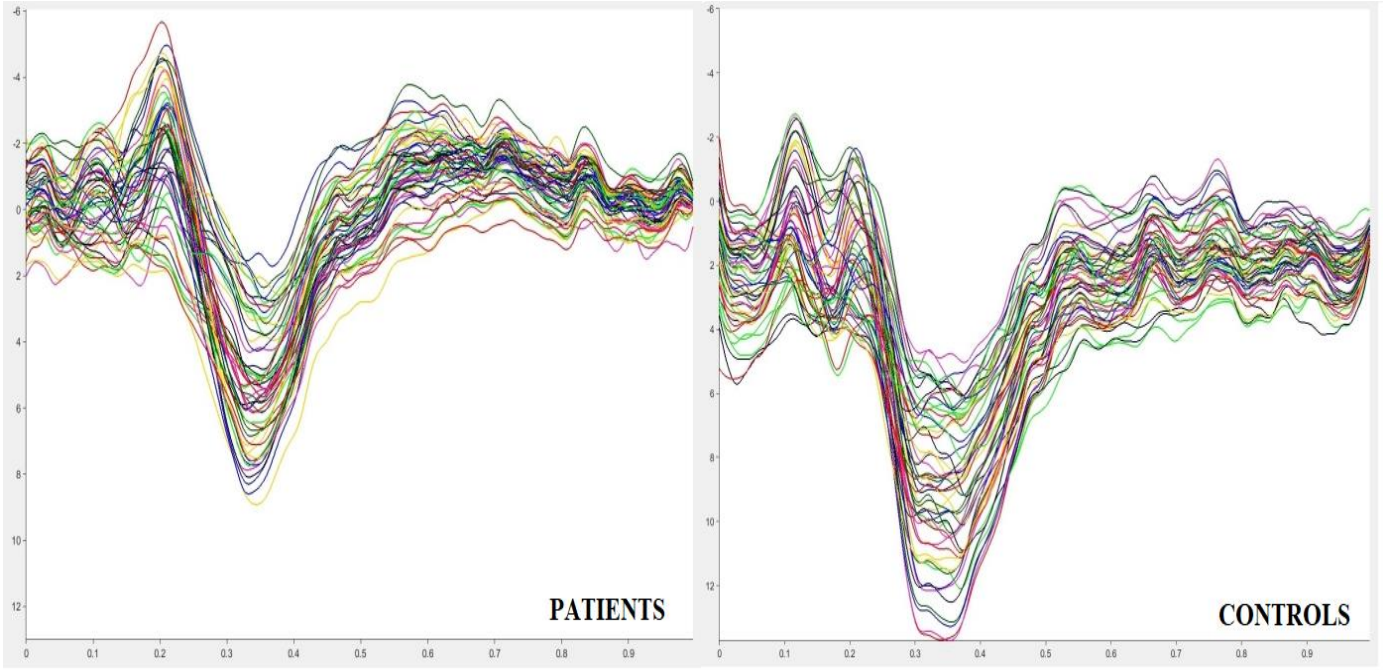
l groups activation maps using canonical HRF model.

Statistical significant difference Group*condition at channels: 4, 6, 10.

RIGHT and LEFT HAND

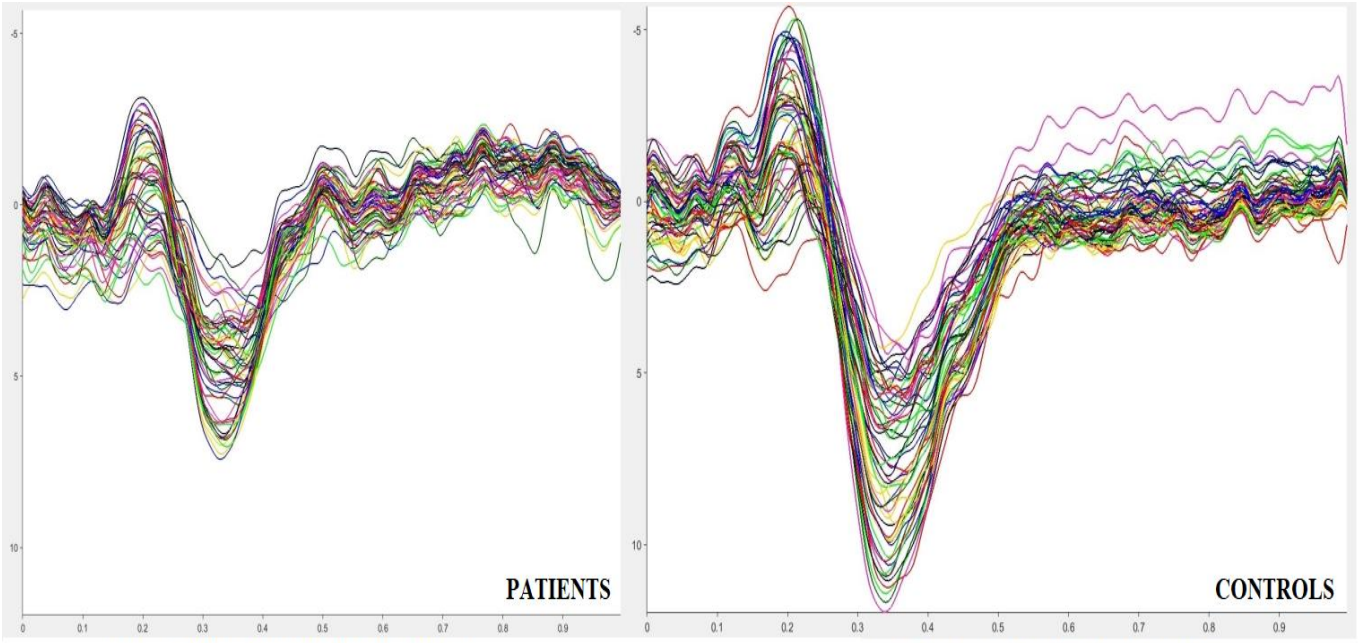
LEPs results

- Finger Tapping task did not reduce the cortical response to laser stimulation in patients and controls



LASER ON THE RIGHT HAND

LASER ON THE RIGHT HAND

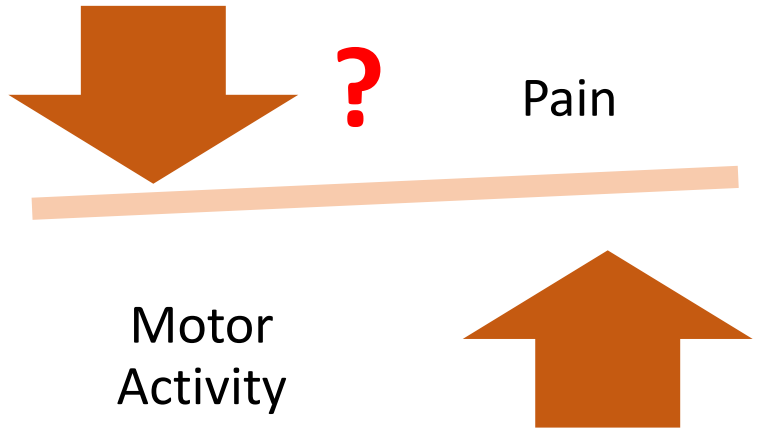


FFT + LASER ON THE RIGHT HAND

FFT + LASER ON THE RIGHT HAND

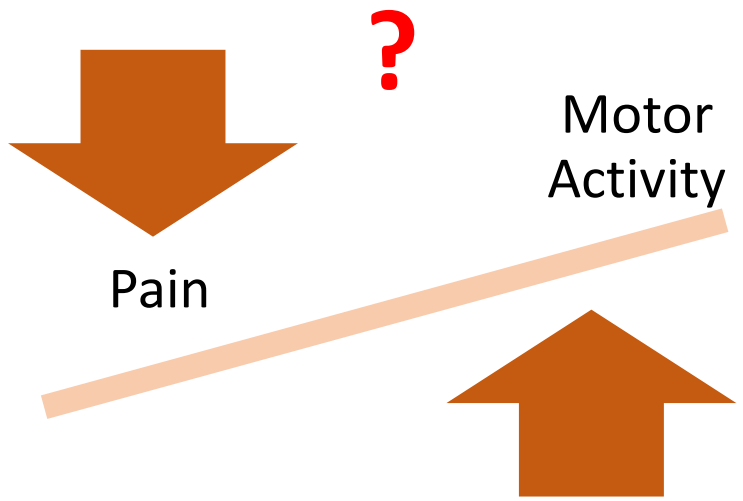
in chronic pain patients, motor cortex appears inhibited with low ativation during finger tapping
concurrent painful stimulation, reduced motor cortex activation in controls

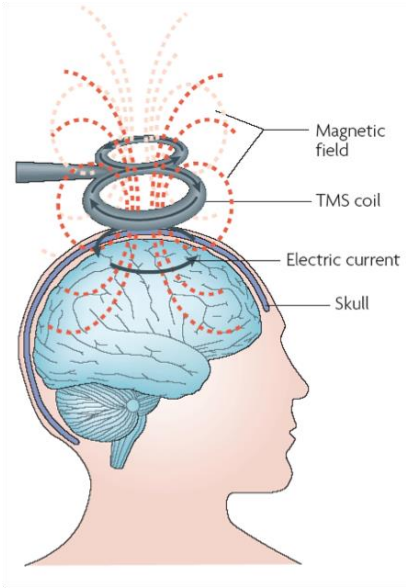
acute *pain could reduce the tone of motor cortical activation*
in chronic pain patients, motor cortex is basically inhibited



The simple and repetitive movement did not reduce pain-related cortical responses

In FM patients and controls
, there
no siginficant inhibition of Leps
during finger tapping task.





- Probably the finger tapping task dose not produces an efficacious inhibitory effect on phasic pain both in patients and controls.

Could a more complex motor task, such as a finalized action, have a modulatory effect on pain?

- When we observe the actions of other people, we activate the same neural circuit responsible for the planning and execution of our actions (Gallese et al., 1996; Rizzolatti et al., 1996).
- The observation of an action is an effective way to learn or improve the performance of a specific motor skill (Rizzolatti and Craighero, 2004).

Background
Motor Resonance-
experimental protocol

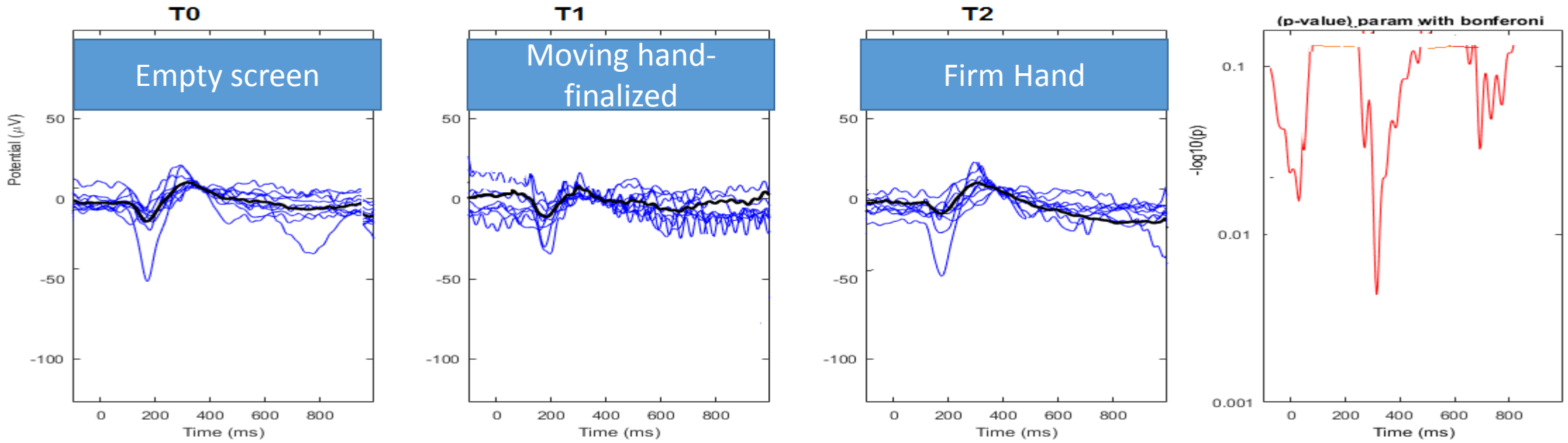
Work in progress

Experimental design

- **Resting state**
- **Action observation:** video with movement task and concomitant laser stimulation
- **Observation**: a still frame with an object to grab during concomitant laser stimulation.
- **Motor Execution**: subjects will press a spacebar when the hand in the video reaches and touches the object

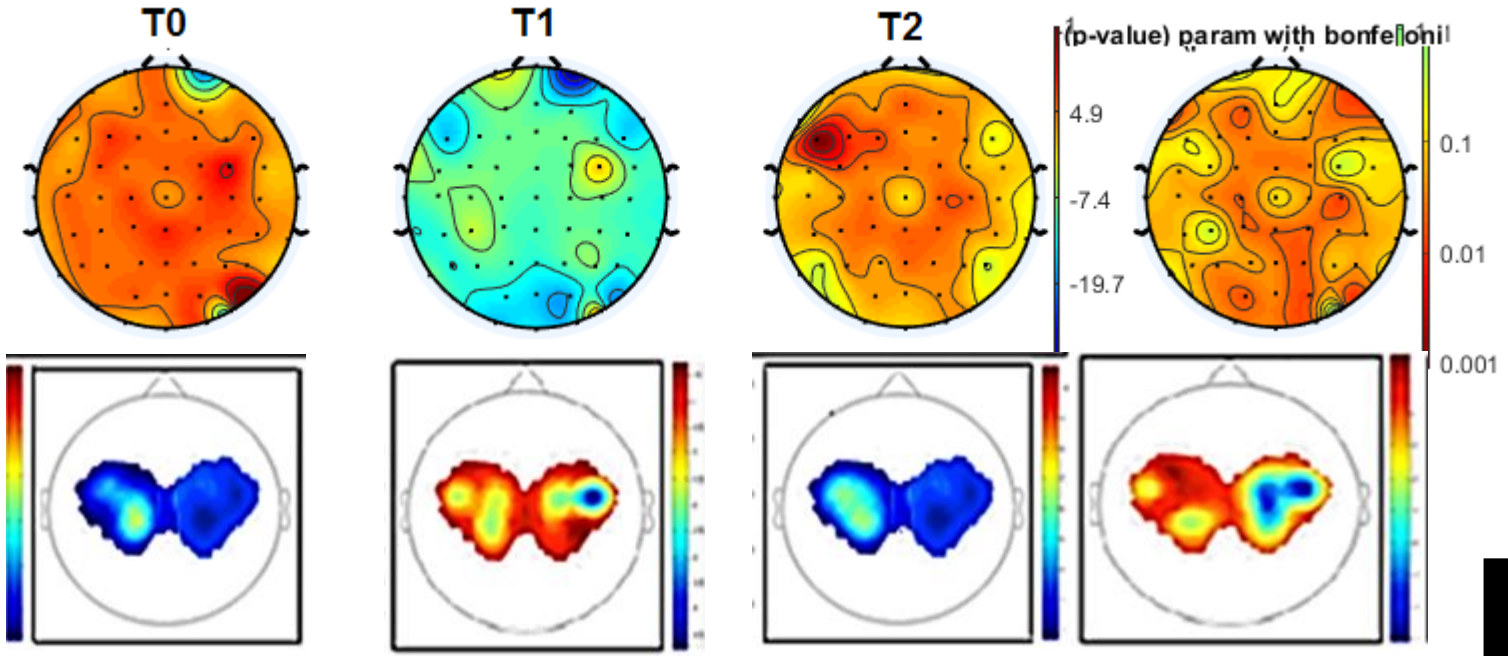
Work in progress

Work in progress



LEPs

fNIRS



EXPECTED RESULTS…
TO BE CONFIRMED