Default mode network abnormalities predict cutaneous allodynia in patients with episodic migraine without aura

Marcello Silvestro

Centro cefalee ed algie facciali

Prima Clinica Neurologica e Neurofisiopatologia

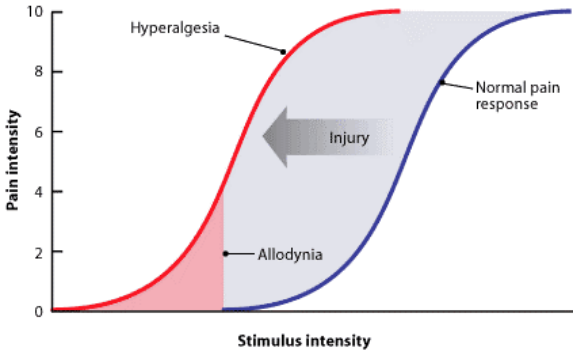
Direttore: prof. G. Tedeschi

Università degli Studi della Campania, “L.Vanvitelli”

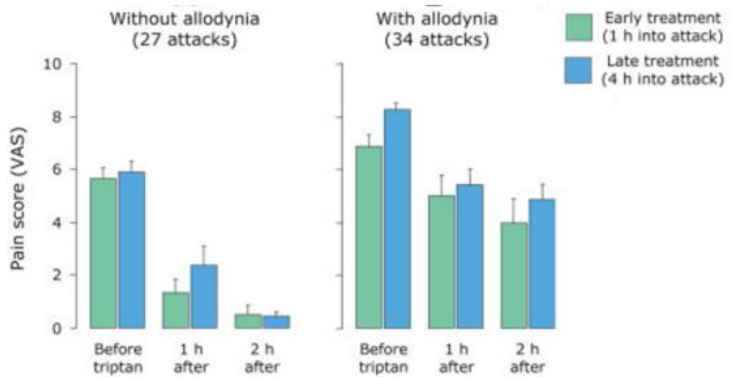
Università
degli Studi
della Campania
Luigi Vanvitelli

BACKGROUND

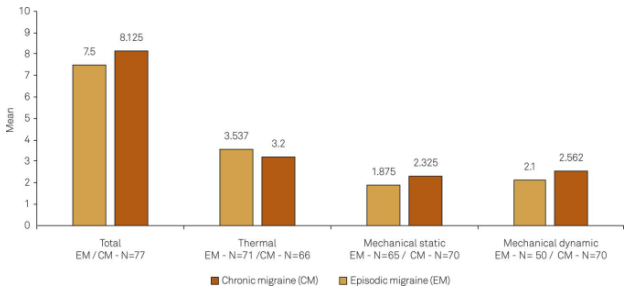
Cutaneous allodynia (CA) is the perception of skin discomfort induced by trivial stimuli



CA represents a negative predictor of response to symptomatic therapy with triptans during a migraine attacks



CA is a prognostic factor for migraine without aura (MwoA) chronification

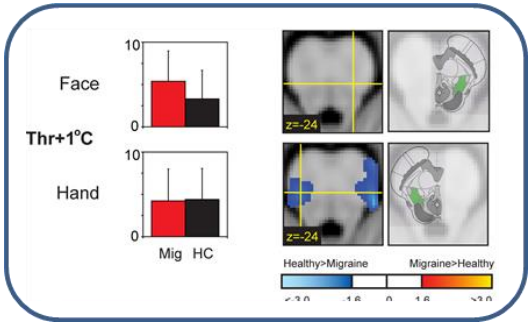


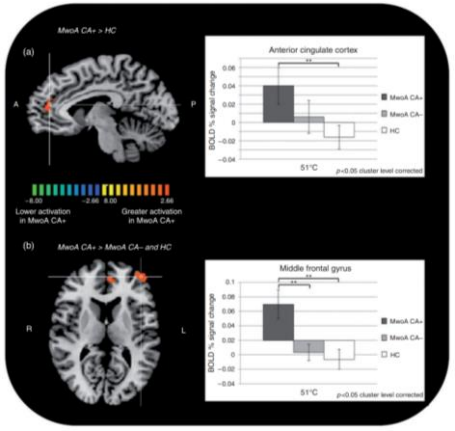
Burstein et al., Ann Neurol. 2004; Louter MA et al., Brain. 2013

BACKGROUND-2

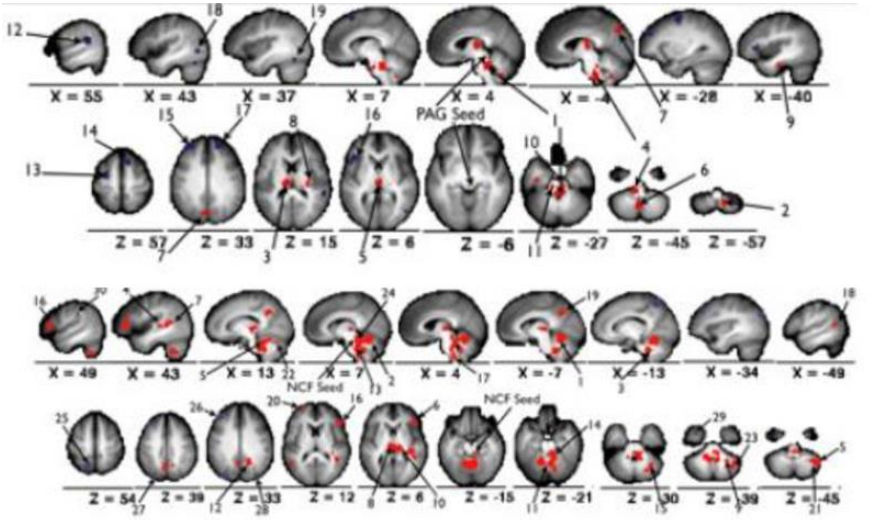
Advanced neuroimaging studies have showed in migraine patients:

- ✓ CA may be subtended by both a dysfunctional DPMS and abnormal internal representation of pain





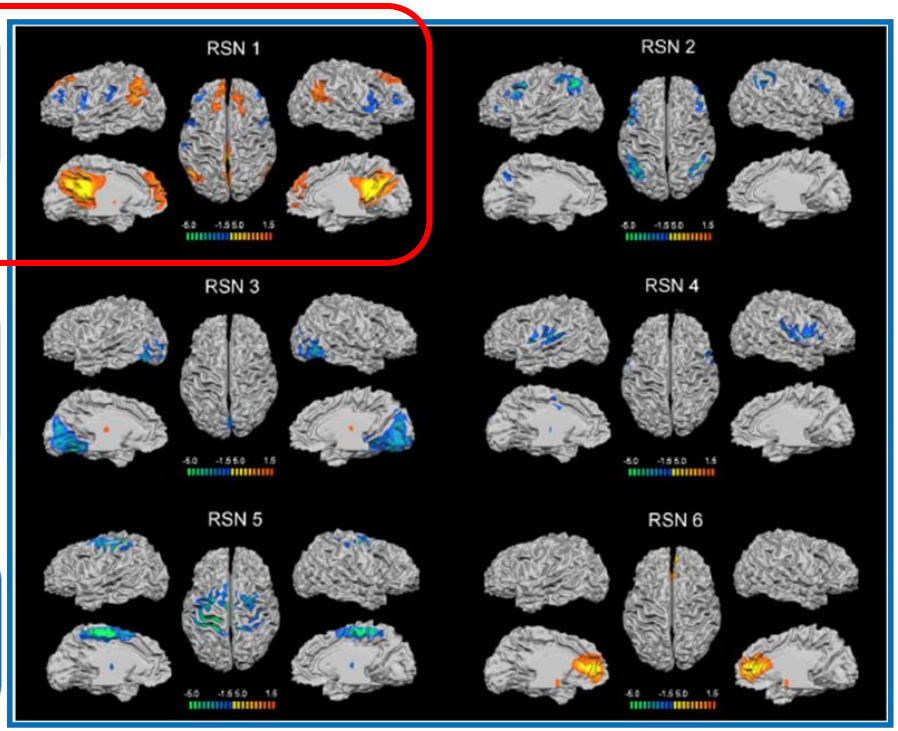
- ✓ CA is correlated to atypical RS-FC within the brainstem and between the brainstem and higher order cortical modulatory pain regions



Moulton EA et al., PLoS One. 2008; Russo A et al., Cephalalgia. 2017; Schwedt et al., Pain Medicine. 2014

RESTING STATE NETWORKS

Although a pletora of studies have been conducted to investigate pattern of intrinsic brain FC in migraine, no studies have been conducted to investigate the prognostic role of specific pattern of intrinsic brain FC in the development of CA in migraine patients



"Default mode network" associated with internal processing

"Executive network" mediating goal-directed stimulus-response selection

"Visual network" dedicated to visual processing

"Auditory network" corresponding to the auditory-phonological system

"Sensory-motor network" associated with sensory-motor processing

"Medial ventral-prefrontal network" related to self-referential mental activity

Mantini et al., 2007

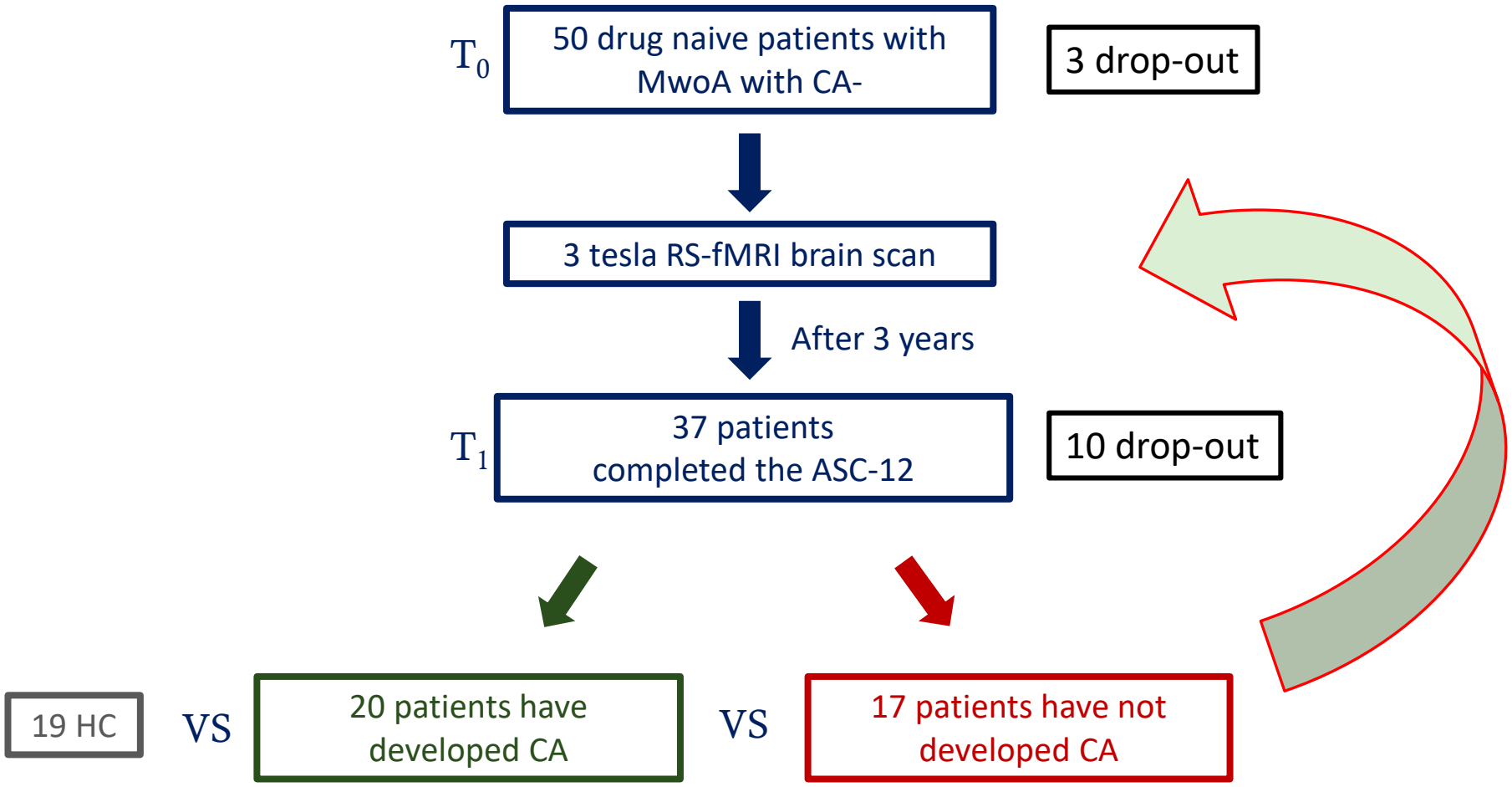
AIMS

To investigate whether a specific pattern of Resting-state (RS) default mode network (DMN) intrinsic functional connectivity (FC), during interictal period, may predict the development of CA in patients with MwoA CA-

HYPOTHESIS

Migraine patients who will develop CA would show an altered resting-state brain FC during interictal period and even before the occurrence of this complication.

STUDY PROTOCOL



POPULATION

Parameter	Group	Mean ± SD	p value
Gender	MwoA CA+	3M; 17F	0.08[a]
	MwoA CA -	7M; 10F	0.23[b]
	HC	6M; 13F	0.56[c]
Age (years)	MwoA CA+	31.3 ± 8.81	0.84[a]
	MwoA CA -	30.7 ± 8.86	0.06[b]
	HC	28.84 ± 6.3	0.18[c]
Disease duration (years)	MwoA CA+	13.80 ± 7.90	0.62
	MwoA CA -	12.35 ± 9.80	
Frequency (days/month)	MwoA CA+	5.11 ± 5.0	0.47
	MwoA CA -	4.0 ± 2.98	
ASC-12 T0	MwoA	0	
ASC-12 T1	MwoA CA+	7.75 ± 4.05	3.04×10^{-8}
	MwoA CA -	0	
MIDAS	MwoA CA+	15.9 ± 10.55	0.30
	MwoA CA -	12.17 ± 11.06	
HIT-6	MwoA CA+	59.7 ± 7.46	0.06
	MwoA CA -	54.41 ± 9.18	
HAM-D	MwoA CA+	5,11 ± 0,82	0.18
	MwoA CA -	4,79 ± 0,76	
HAM-A	MwoA CA+	5,71 ± 0,96	0.28
	MwoA CA -	5,34 ± 0,89	
VAS of attack intensity	MwoA CA+	8.36 ± 1.14	0.11
	MwoA CA -	7.69 ± 1.39	

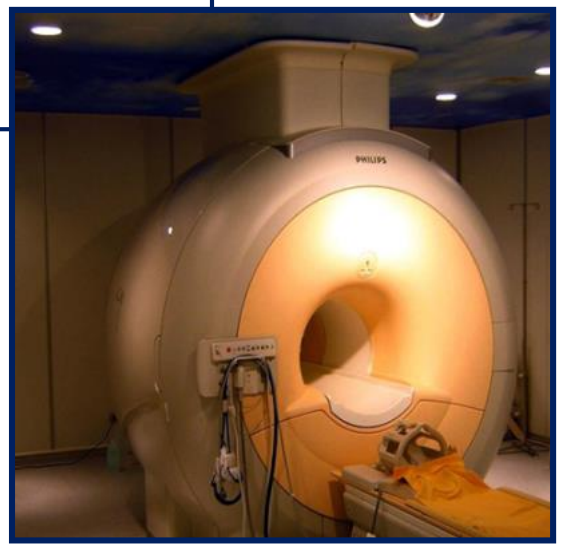
[a] *MwoA CA+ vs MwoA CA-*

[b] *MwoA CA+ vs HC*

[c] *MwoA CA- vs HC*

METHODS

- Magnete 3 Tesla GE (General Electric, Minneapolis, MN, USA)
- Connettività funzionale (*Software Brain Voyager*)
  - Random effects analysis ($p<0.05$)
- Analisi di correlazione post-hoc



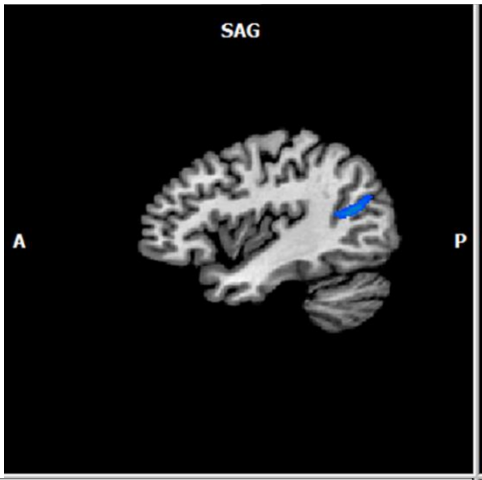
FONDAZIONE ITALIANA SCLEROSI MULTIPLA

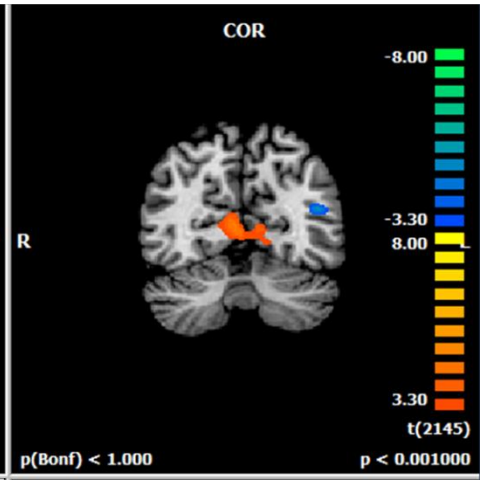
Seconda Università degli Studi di Napoli SUN

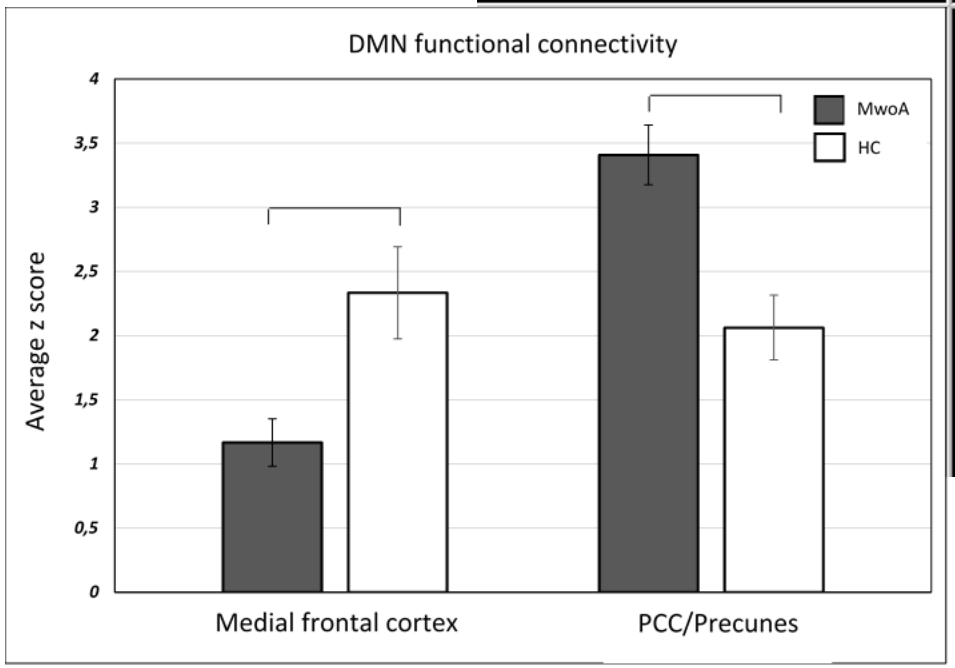
CENTRO di RICERCA
SUN - FISM
di ALTI STUDI IN RISONANZA MAGNETICA
sulla sclerosi multipla e patologie similari

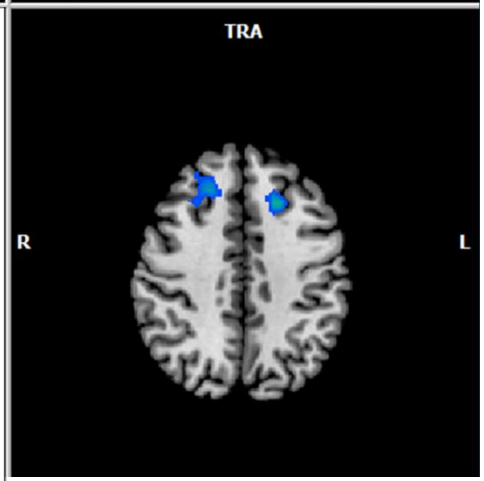
RESULTS-1

Patients with MwoA *vs* HC



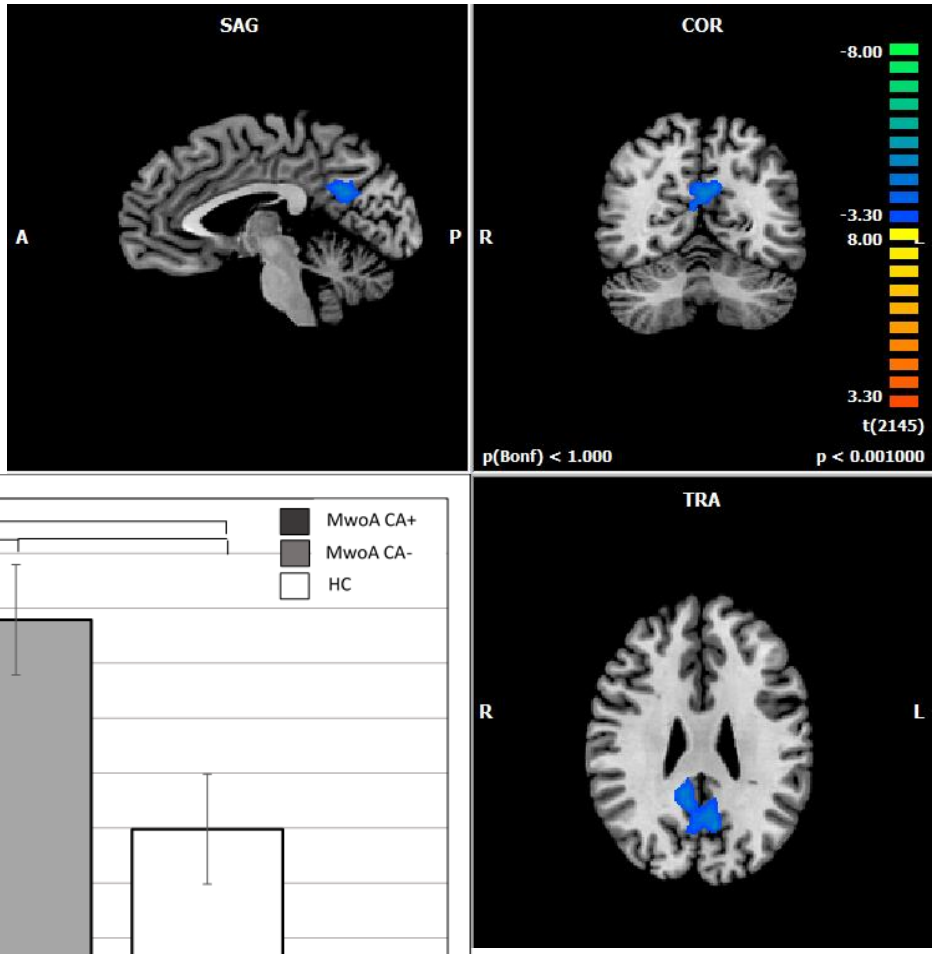


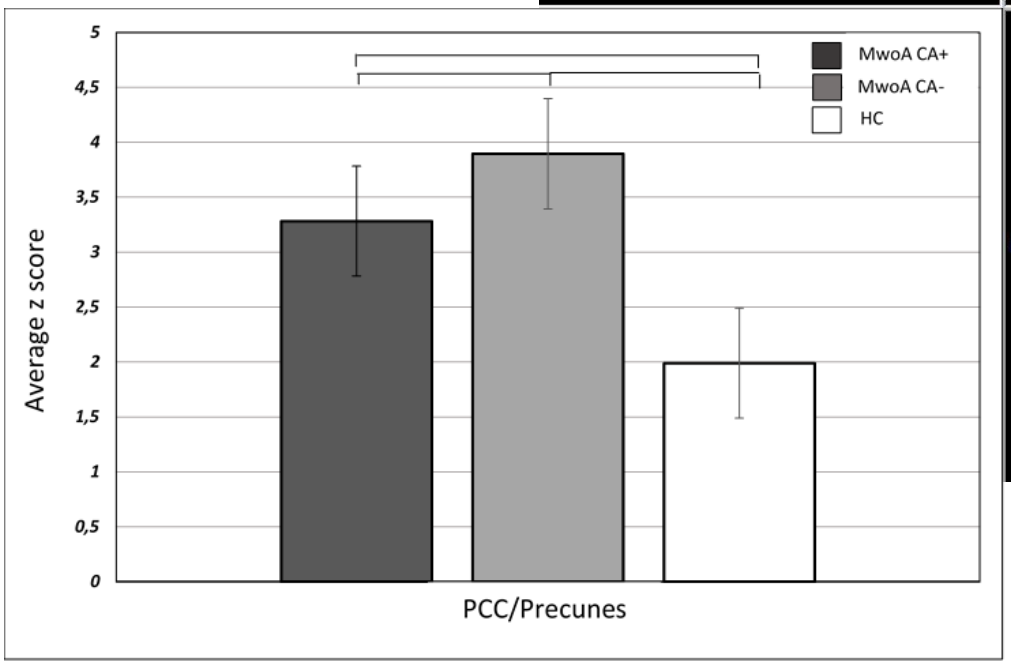




RESULTS-2

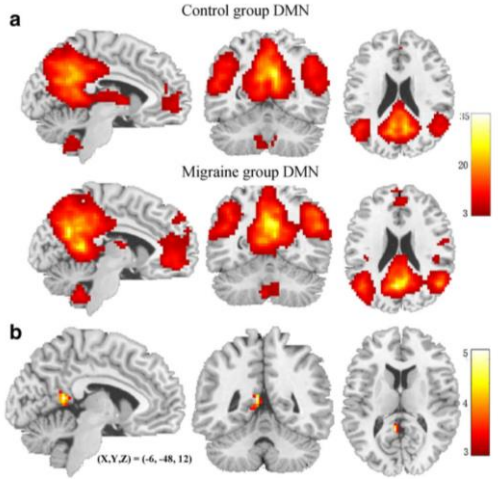
Patients with MwoA CA+ *vs* MwoA CA- *vs* HC





No correlations between RS-FC PCC and clinical parameters of disease severity

DISCUSSION-1

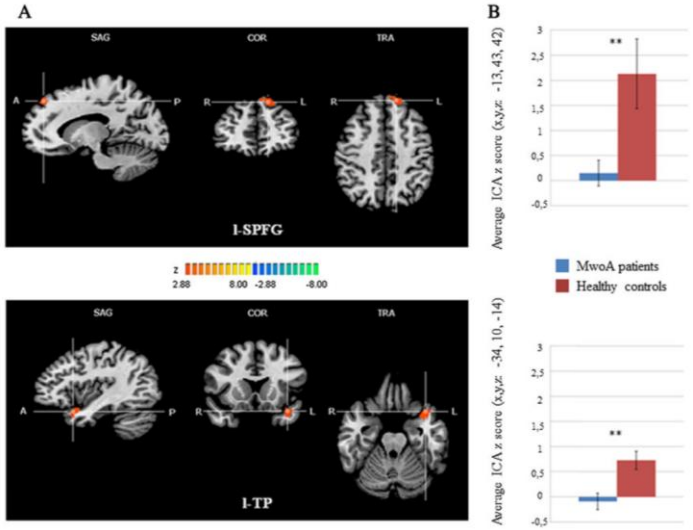


✓ Increased DMN–FC in patients with MwoA

Precuneus and post. cingulate cortex (PCC)

✓ Decreased DMN-FC in patients with MwoA

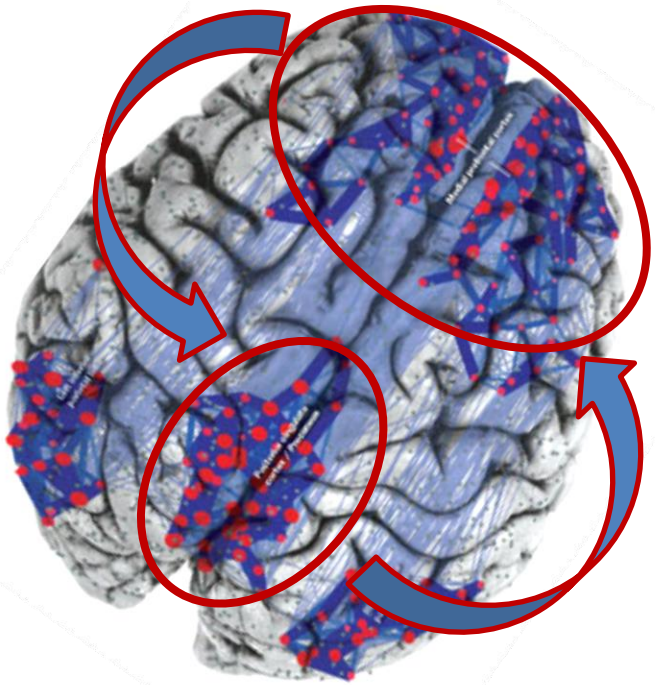
Medial prefrontal (mPFC) and temporal cortex



Zhang et al., J Headache and Pain 2014; Tessitore et al. J Headache Pain. 2013

DISCUSSION-2

Functional differentiation within DMN comes from task-based studies



✓ **mPFC**

- recall best action/emotional response to specific events
- leading role in decision making/coping

✓ **PCC/precuneus**

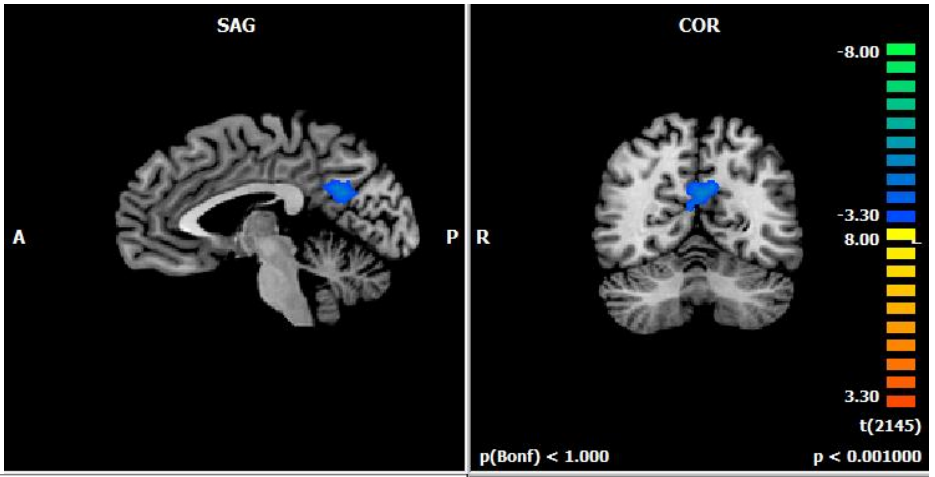
- state of arousal
- internally/externally focused attention
- pain sensitivity/perception
- *multisensory integration*

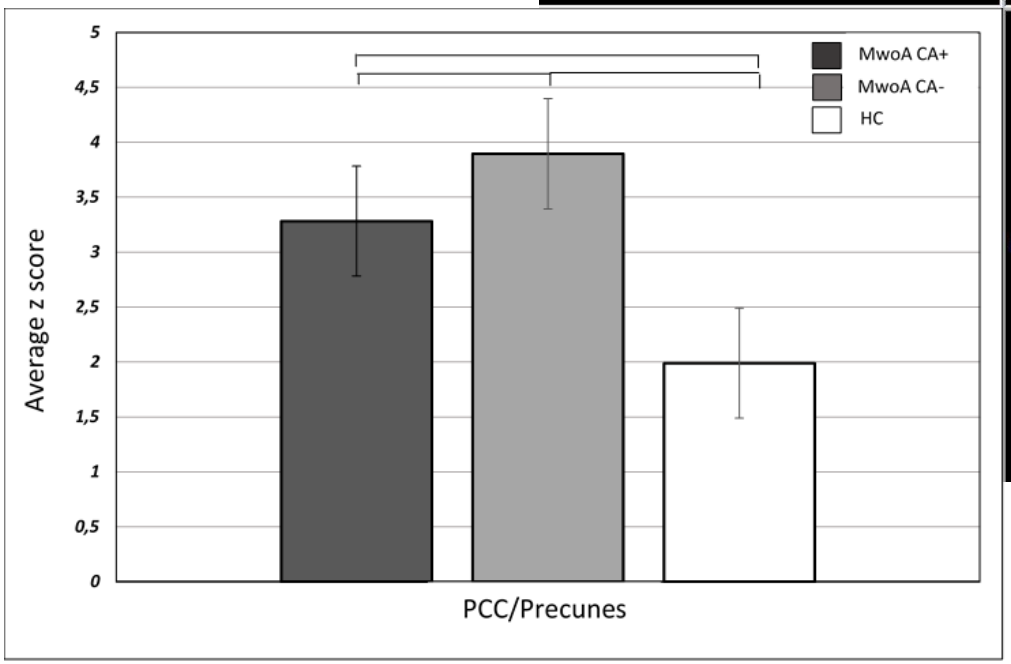
Increased PCC-FC could represent an effort of adaptive response to stressful events and repetitive migraine attacks

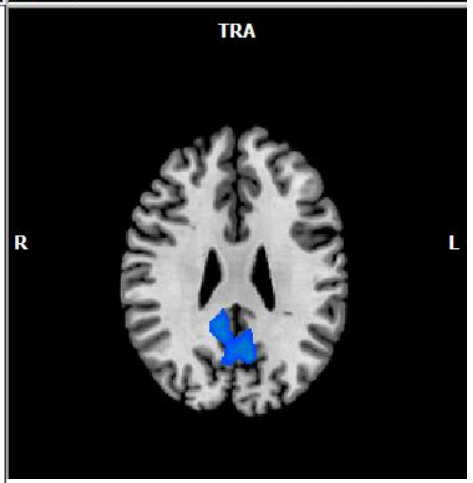
Uddin et al., Hum Brain Mapp. 2009; Coppola et al., Cephalalgia 2018

RESULTS-2

Patients with MwoA CA+ *vs* MwoA CA- *vs* HC





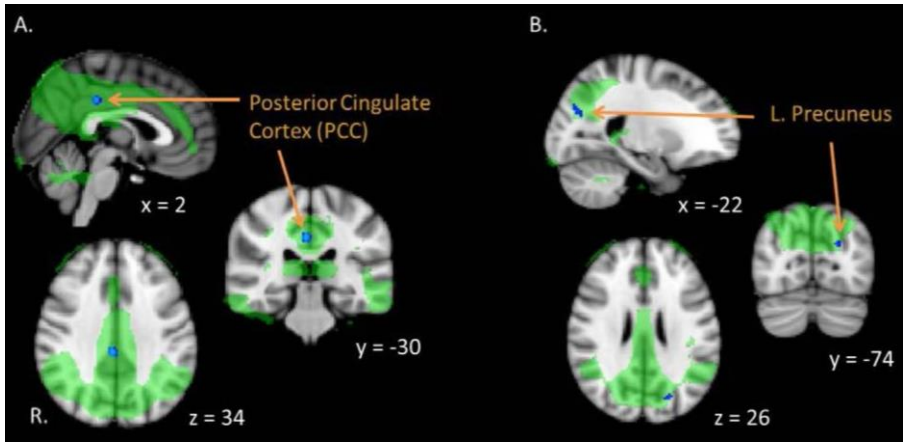


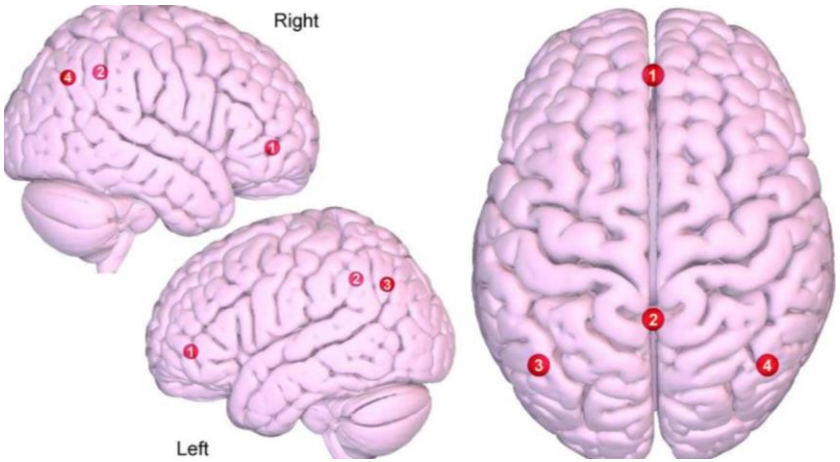
DISCUSSION-3

Reduced PCC-FC makes less effective this adaptive attempt, leading to abnormal

- internally/externally focused attention
- pain sensitivity/perception
- *multisensory integration* → from "touch" to pain → CA

Reduced PCC-FC in MwoA CA+ is similar to DMN changes observed in several *chronic* pain condition as well as in CM





Martucci et al., Pain. 2015; Androulakis et al., Neurology. 2017

CONCLUSIONS

We believe that:

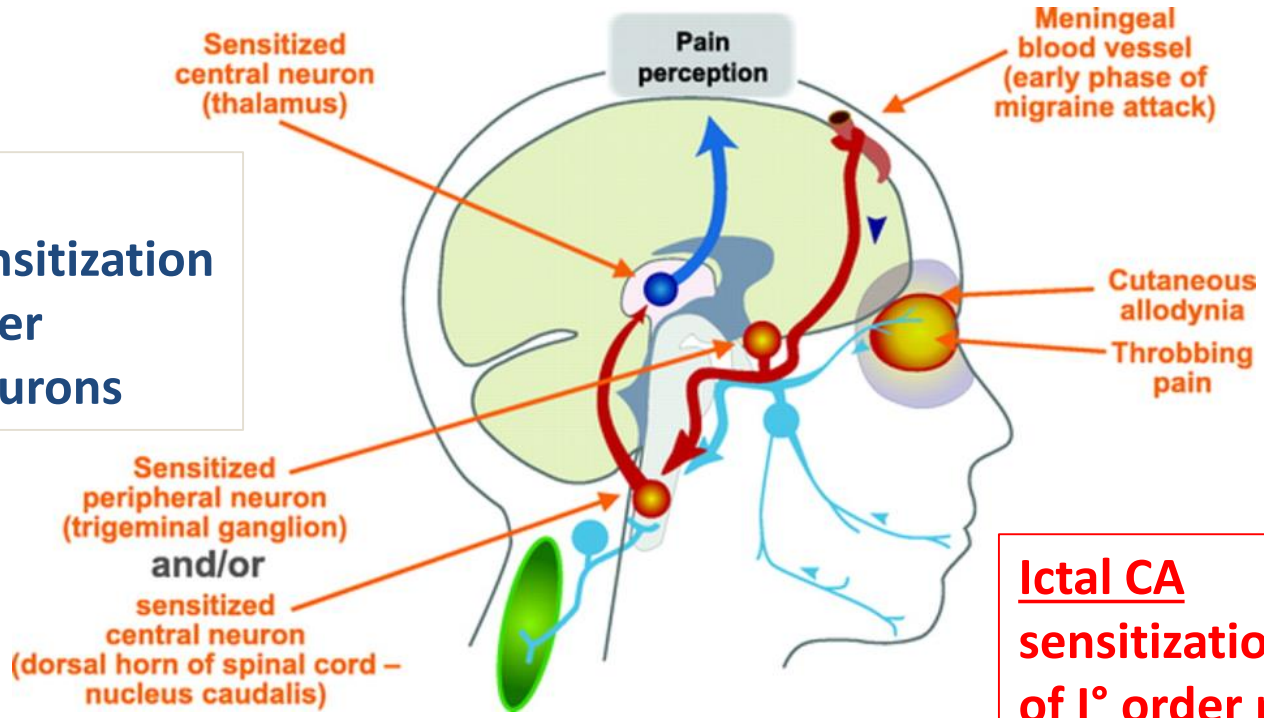
- ✓ Reduced PCC-FC observed in patients with MwoA (who will develop CA) could represent a putative “phenotypic/prognostic biomarker” able to identify migraine sub-groups in research scenario and clinical
- ✓ DMN-FC findings are not correlated with clinical parameters of disease severity, therefore abnormal PCC-FC may be *“per se”* and not related to years lived with migraine, migraine frequency, attacks severity, etc.

Neurologi	*Neuroradiologi*	*Ingegneri e fisici*
G. Tedeschi	S. Cirillo	F. Esposito
A. Tessitore	M. Cirillo	F. Di Nardo
A. Russo	R. Conforti	D. Corbo
A. Giordano	F. Tortora	G. Caiazzo
A. De Mase		A. Paccone
L. Marcuccio		

Grazie per l'attenzione

BACKGROUND-2

Interictal CA
ascending sensitization of II°- III° order trigeminal neurons



Ictal CA
sensitization of I° order nociceptive trigeminal neuron

Burstein et al., Ann Neurol. 2004; Burstein et al., Brain 2000