



SESSIONE 4

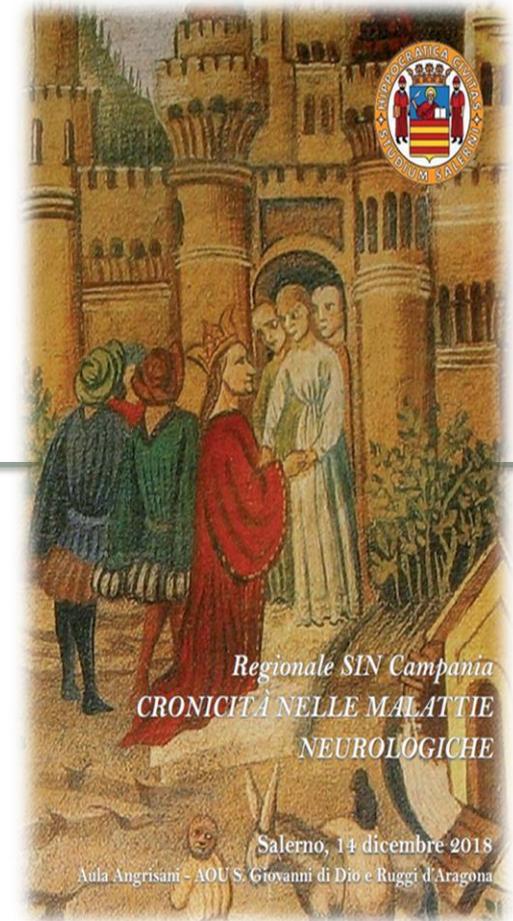
UPDATE SUL DOLORE

Functional imaging nell'emicrania

Gioacchino Tedeschi

Università degli Studi della Campania "Luigi Vanvitelli"

Napoli

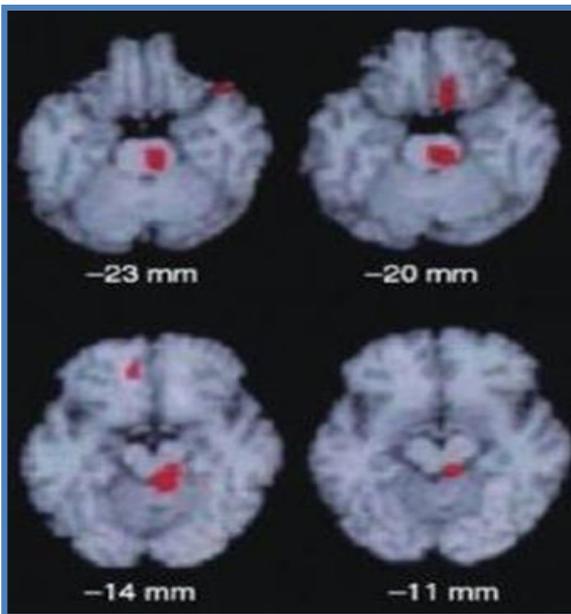




Historical notes

Brainstem activation in spontaneous human migraine attacks

Weiller C et al, Nat Med. 1995



- ✓ 9 migraine pts
 - ✓ CBF: ^{15}C -labelled- O_2 inhalation
- Scan:
- ✓ during attack (within 6 h after migraine onset)
 - ✓ only the brainstem activation persisted **after the injection of sumatriptan** had induced complete relief from headache and phono- and photophobia.



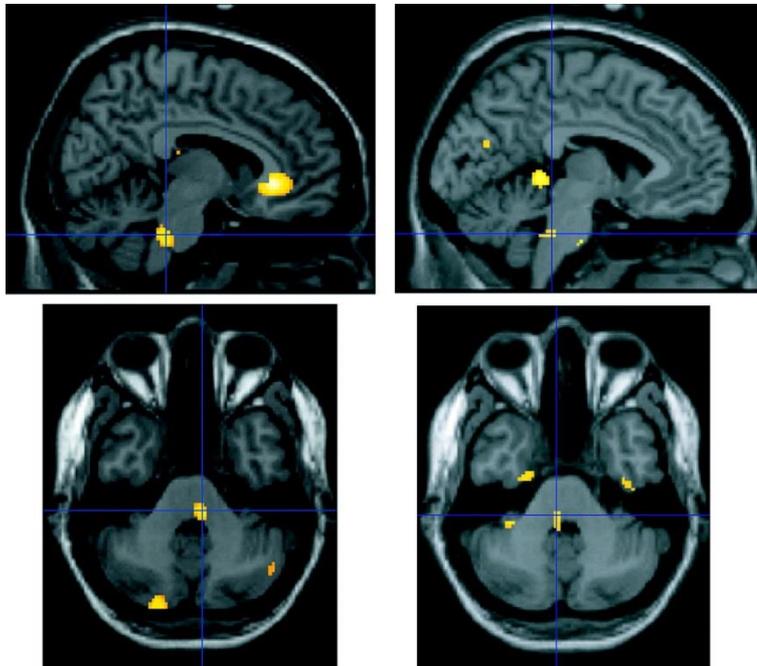
"... pathogenesis of migraine is related to an imbalance in activity between brainstem nuclei regulating antinociception and vascular control..."

**BRAIN** A JOURNAL OF NEUROLOGY

(2005), 128, 932-939

A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate

S. K. Afridi,¹ M. S. Matharu,¹ L. Lee,² H. Kaube,¹ K. J. Friston,² R. S. J. Frackowiak²
and P. J. Goadsby¹



before sumatriptan

after sumatriptan

- Brainstem activation in **the dorsal pons** and rostral medulla.
- Involvement of ACC, insula, cerebellar hemispheres, prefrontal cortex and putamen.
- Following abortion of the migraine with sumatriptan, the **dorsal pons remained activated**.

Brainstem is not simply related to *headache (pain phase of a migraine attack)* but to the whole migraine phenomenon



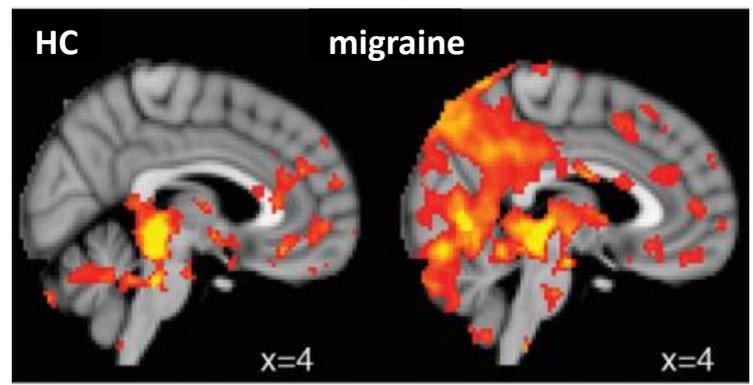
Pons is not the only one in the Brainstem !

Annals of NEUROLOGY

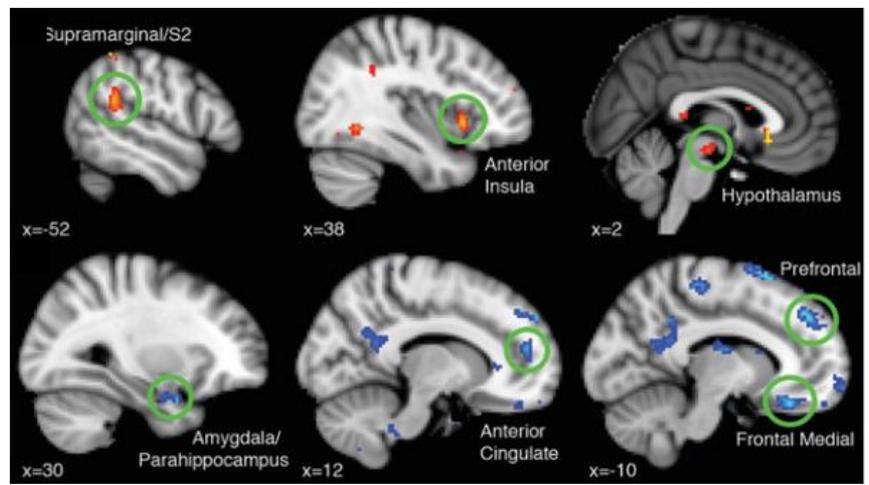
Altered functional MRI resting-state connectivity in periaqueductal gray networks in migraine

Caterina Mainero, MD, PhD¹, Jasmine Boshyan¹, and Nouchine Hadjikhani, MD, PhD^{1,2}

2011 November ; 70(5): 838-845.



RS-fc with the **PAG** and nearby structures in HC and patients with migraine



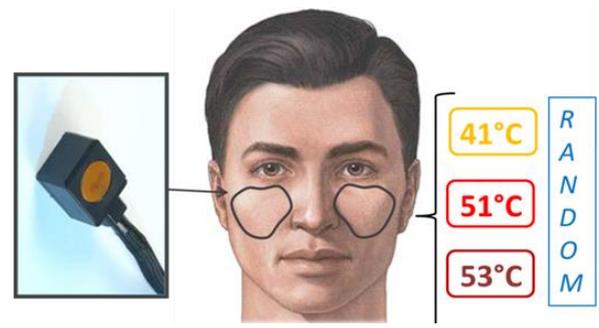
RS-fc with the PAG *correlates with the frequency of migraine attacks*



Pain processing in patients with migraine: an event-related fMRI study during trigeminal nociceptive stimulation

Antonio Russo · Alessandro Tessitore · Fabrizio Esposito · Laura Marcuccio · Alfonso Giordano · Renata Conforti · Andrea Truini · Antonella Paccone · Florindo d'Onofrio · Gioacchino Tedeschi

Published online: 18 February 2012



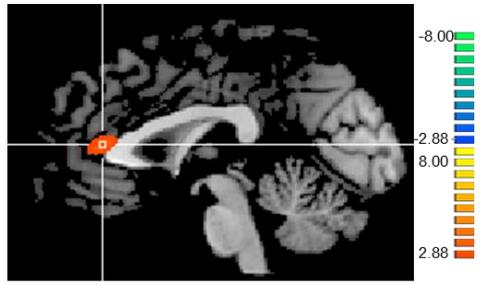
Anterior cingulate cortex

Analgesic compensatory mechanism, or alternatively a prominent affective and emotive response, to pain
"si mette paura"

Bilateral somatosensory cortex

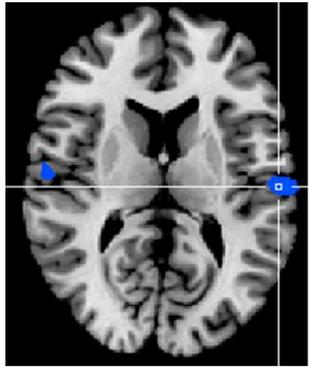
Functional down-regulation at reducing high-noxious painful input to the cortex
"s'arrangia"

This adaptive responses may become progressively less efficient over time



51°C

Patients > Controls



53°C

Controls > Patients



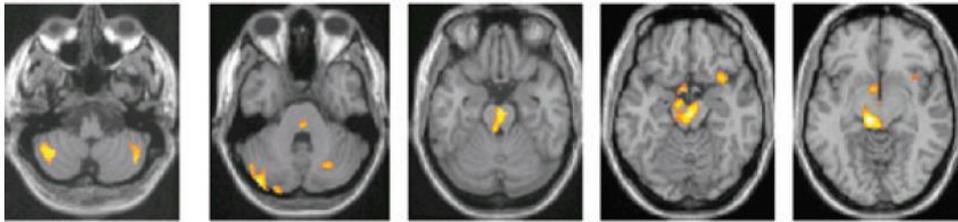
Brainstem is not the only one !

Headache
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Journal compilation © 2007 American Headache Society

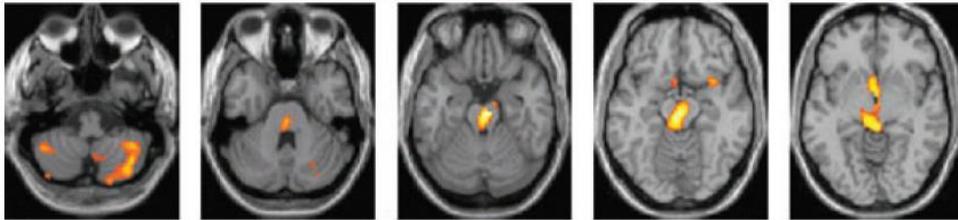
Hypothalamic Activation in Spontaneous Migraine Attacks

Marie Denuelle, MD; Nelly Fabre, MD; Pierre Payoux, MD; Francois Chollet, MD;
Gilles Geraud, MD

Before sumatriptan



After sumatriptan

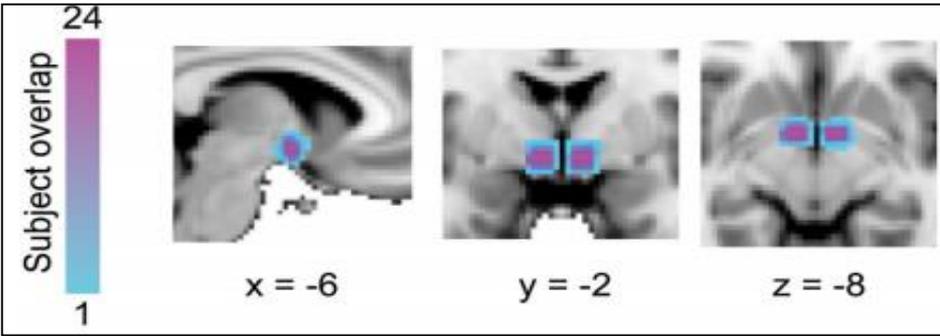


- ✓ Significant activations in the midbrain and pons but also in the *hypothalamus*
- ✓ Hypothalamic activation persisted after complete relief of headache from sumatriptan

Again... the hypothalamus is not simply related to *headache (pain phase of a migraine attack)* but to the whole migraine phenomenon !!!

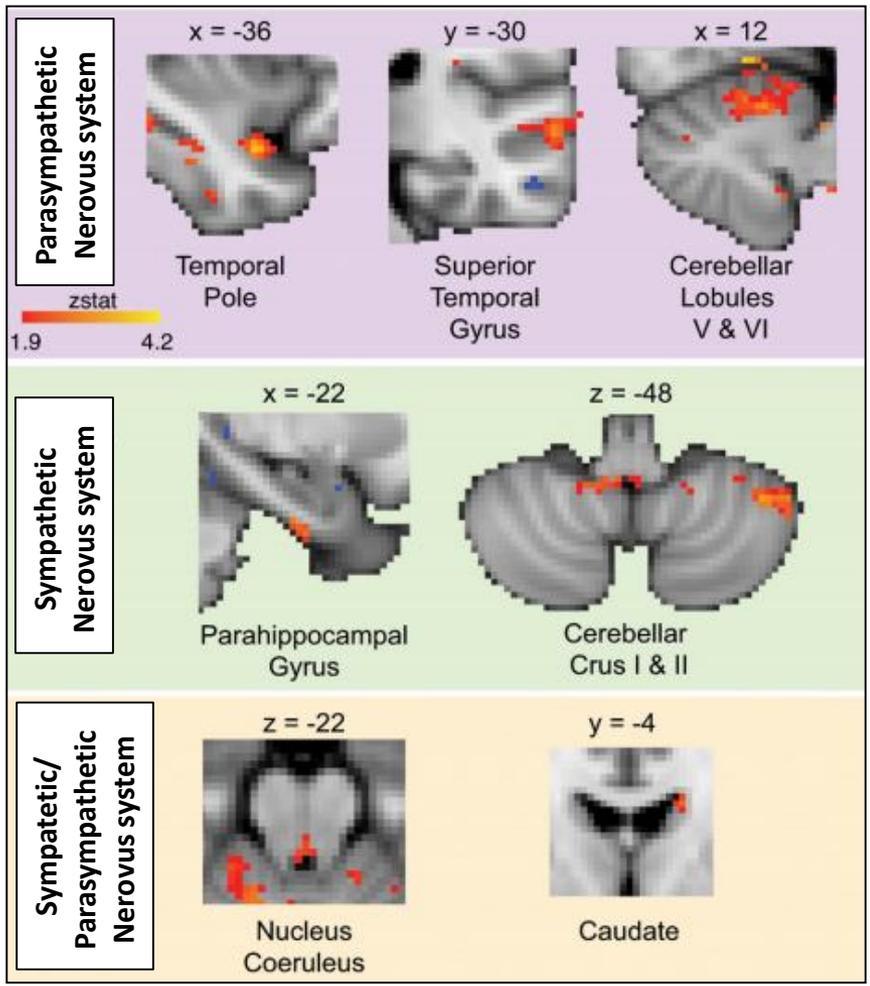


PLOS ONE
Altered Hypothalamic Functional Connectivity with Autonomic Circuits and the Locus Coeruleus in Migraine
 Eric A. Moulton^{1*}, Lino Becerra^{1,2}, Adriana Johnson¹, Rami Burstein⁴, David Borsook^{1,2,3}
 April 2014 Volume 9 Issue 4



Increased hypothalamic FC with brain regions involved in regulation of **hypothalamic-mediated autonomic symptoms that accompany migraine attacks**

- ✓ locus coeruleus
 - ✓ caudate
 - ✓ parahippocampal gyrus
 - ✓ Cerebellum
 - ✓ temporal pole
- } wakefulness
- } responses to stress
- } regulation of emotion





doi:10.1093/brain/aww097

BRAIN 2016; 139; 1987-1993 | 1987

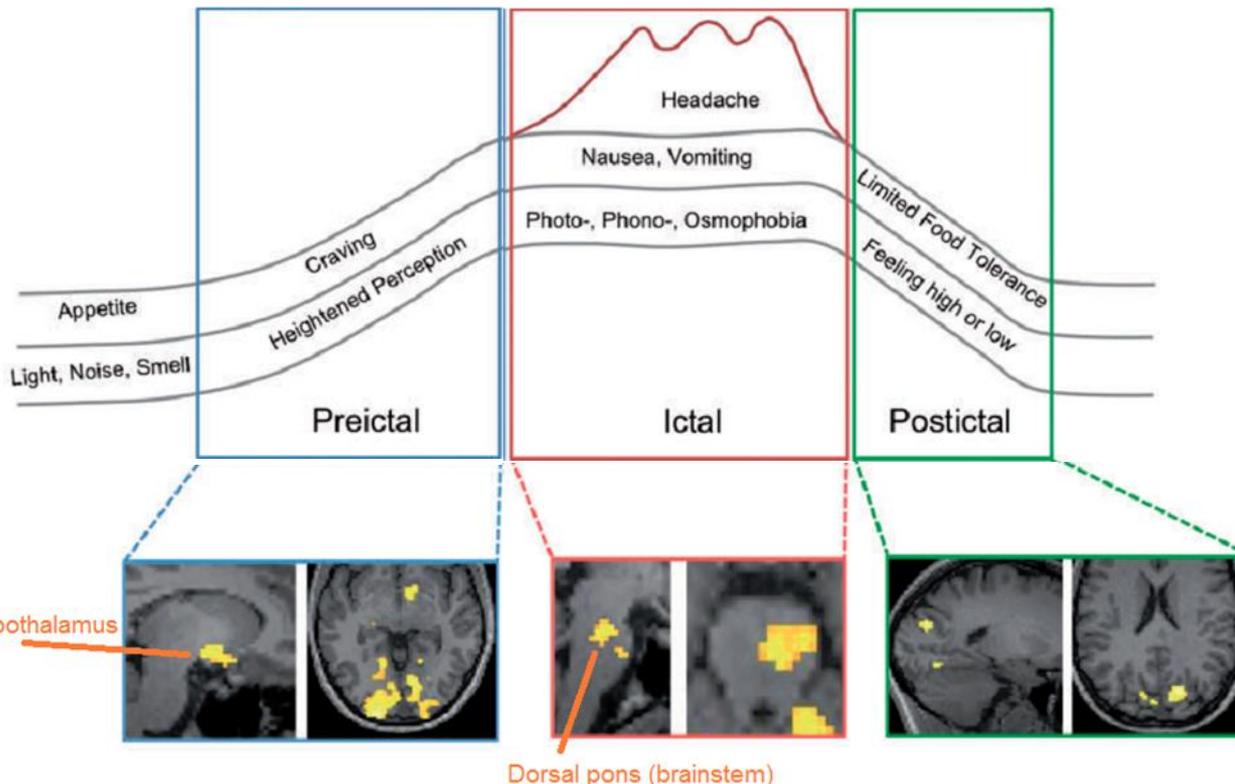
BRAIN

A JOURNAL OF NEUROLOGY

The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks

Laura H. Schulte and Arne May

A migraine patient had MRI every day for 30 days using gaseous to cover a whole month and three complete migraine attacks



Within 24 hours preceding the onset of migraine pain:

hypothalamus activity shows functional coupling with the *spinal trigeminal nuclei*

During the ictal state: the **hypothalamus** is functionally coupled with the *dorsal rostral pons*

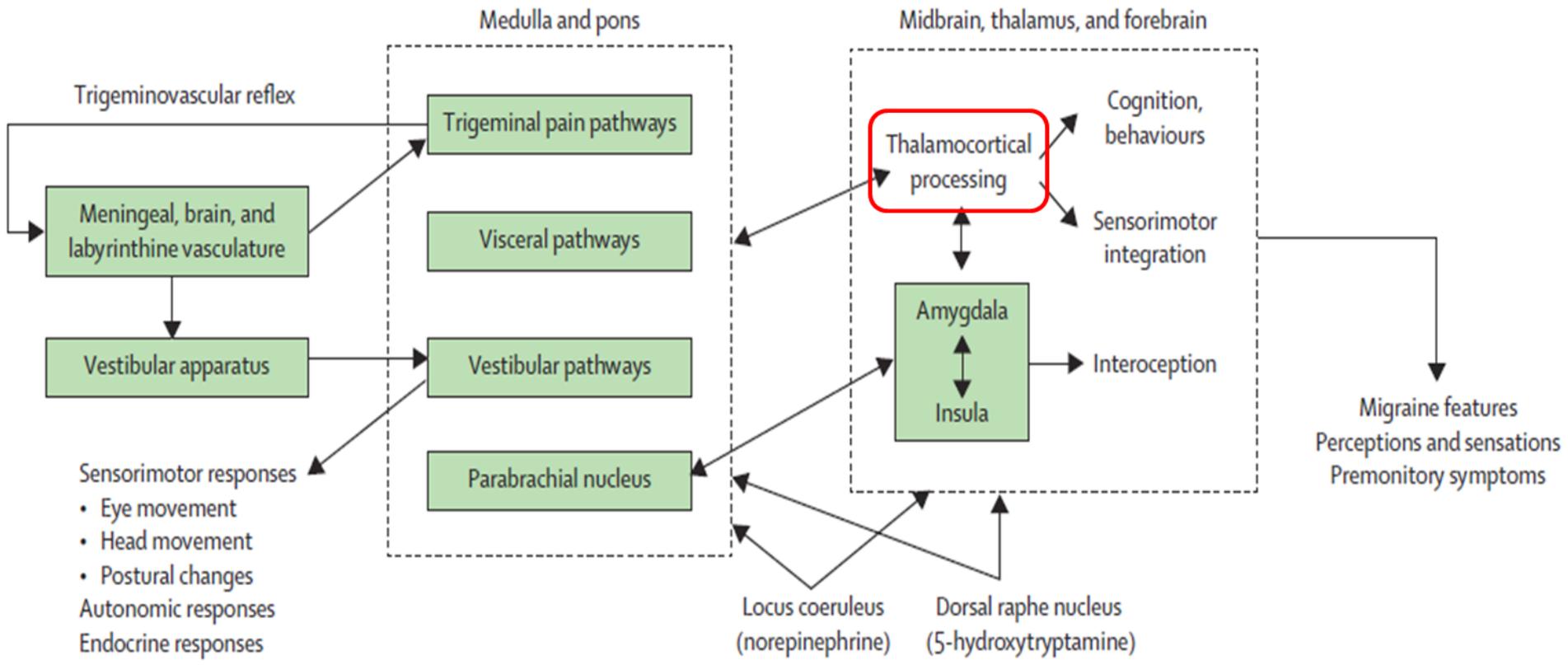
During post-dromal phase: Posterior (occipital) brain areas



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 Fabrizio Esposito, PhD
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Abnormal thalamic function in patients with vestibular migraine

Neurology 2014 Jun 10;82(23):2120-6.





Neurology, 2016

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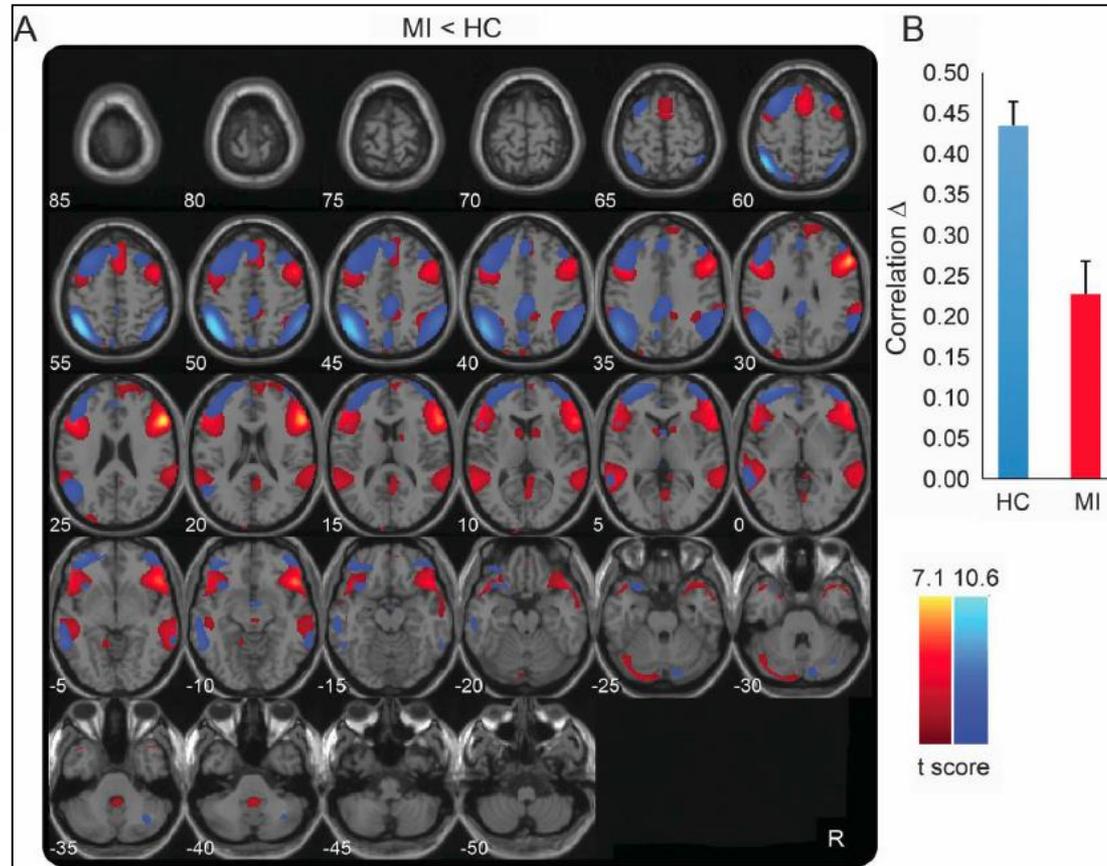
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Thalamo-cortical network activity during spontaneous migraine attacks



- ✓ Decreased Rs-FC during migraine attack between higher-order functions networks (**executive network** and the **dorsal and ventral attention system**)
- ✓ Negative correlation between executive network FC and migraine frequency



Brain networks and migraine

Tessitore et al. *The Journal of Headache and Pain* 2013, 14:89
<http://www.thejournalofheadacheandpain.com/content/14/1/89>

The Journal of Headache and Pain
 a SpringerOpen Journal

Disrupted default mode network connectivity in migraine without aura

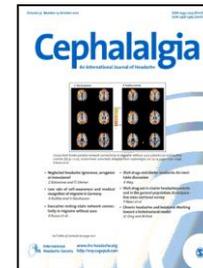
Alessandro Tessitore^{1*}, Antonio Russo^{1,2†}, Alfonso Giordano^{1,2}, Francesca Conte¹, Daniele Corbo¹, Manuela De Stefano¹, Sossio Cirillo³, Mario Cirillo³, Fabrizio Esposito^{4,5} and Gioacchino Tedeschi^{1,2}

Cephalalgia International Headache Society
 An International Journal of Headache

Cephalalgia
 32(14) 1041–1048

Executive resting-state network connectivity in migraine without aura

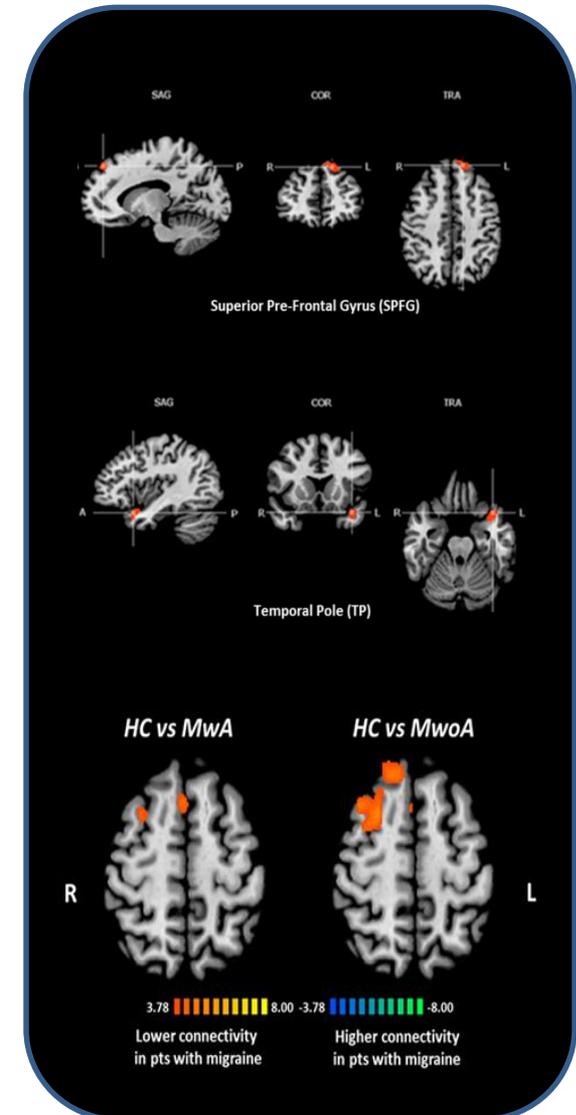
Antonio Russo^{1,2,*}, Alessandro Tessitore^{1,*}, Alfonso Giordano^{1,2}, Daniele Corbo¹, Laura Marcuccio¹, Manuela De Stefano¹, Fabrizio Salemi¹, Renata Conforti², Fabrizio Esposito^{2,3} and Gioacchino Tedeschi^{1,2}



Headache
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Research Submissions

Abnormal Connectivity Within Executive Resting-State Network in Migraine With Aura

Alessandro Tessitore, PhD*; Antonio Russo, PhD*; Francesca Conte, MD; Alfonso Giordano, PhD; Manuela De Stefano, PhD; Luigi Lavorgna, PhD; Daniele Corbo, PhD; Giuseppina Caiazza, PhD; Fabrizio Esposito, PhD; Gioacchino Tedeschi, MD



No neuropsychological abnormalities in migraine patients



The Journal of Headache and Pain

RESEARCH ARTICLE

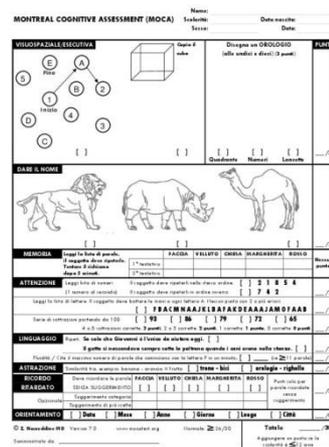
2016

Open Access



Cognitive dysfunctions and psychological symptoms in migraine without aura: a cross-sectional study

Gabriella Santangelo^{1,3*}, Antonio Russo^{2,3†}, Luigi Trojano^{1,4*}, Fabrizia Falco¹, Laura Marcuccio^{2,3}, Mattia Siciliano^{1,3}, Francesca Conte^{2,3}, Federica Garramone¹, Alessandro Tessitore^{2,3} and Gioacchino Tedeschi^{2,3*}



MoCA: Montral Cognitive Assessment

The abnormalities in executive functions are related to migraine disability (MIDAS)

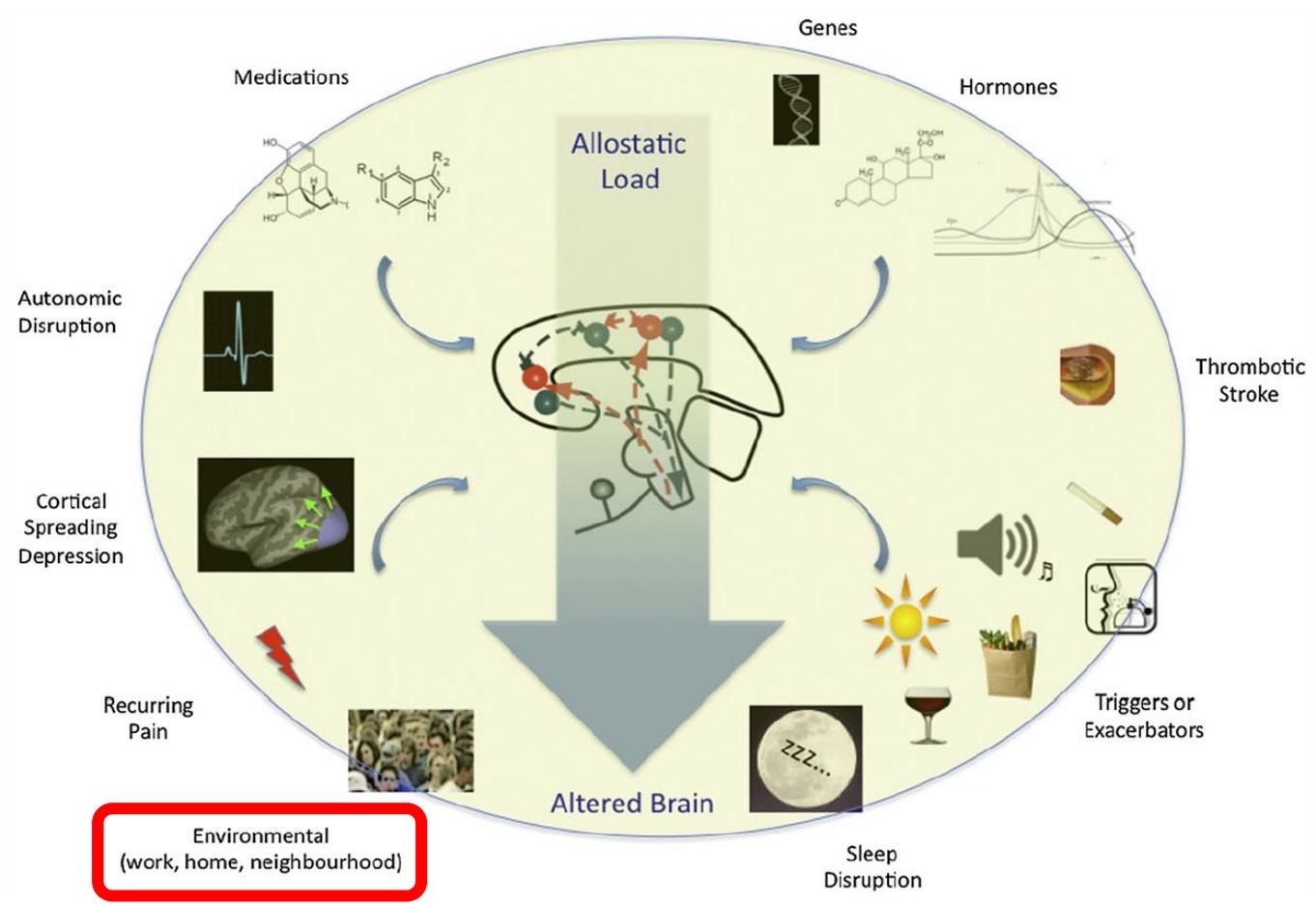
	Disease duration	Attacks per month	MIDAS	HIT-6	VAS
Cognitive domains	rho (p value)	rho (p value)	rho (p value)	rho (p value)	rho (p value)
Visuospatial	-0.117 (0.342)	0.139 (0.252)	0.067 (0.589)	0.177 (0.149)	0.113 (0.359)
Executive	0.177 (0.149)	-0.307 (0.010)	-0.341 (0.004)	-0.092 (0.455)	0.098 (0.427)
Attention	0.099 (0.421)	-0.011 (0.931)	0.043 (0.729)	0.221 (0.070)	0.041 (0.742)
Language	0.061 (0.620)	-0.128 (0.290)	-0.248 (0.041)	-0.079 (0.524)	0.116 (0.348)
Memory	-0.205 (0.094)	-0.008 (0.950)	-0.112 (0.361)	-0.151 (0.218)	0.196 (0.109)
Orientation	0.197 (0.108)	0.111 (0.359)	0.088 (0.477)	0.187 (0.126)	0.055 (0.654)
MoCA total score	-0.021 (0.865)	-0.006 (0.963)	-0.093 (0.453)	0.160 (0.192)	0.317 (0.008)
BDI-II	0.134 (0.275)	0.031 (0.799)	0.254 (0.037)	0.141 (0.251)	-0.065 (0.601)
AES-S Behaviour	0.056 (0.648)	0.232 (0.053)	0.061 (0.623)	0.110 (0.372)	0.029 (0.817)
AES-S-Cognitive	0.007 (0.957)	0.187 (0.121)	0.210 (0.085)	0.298 (0.014)	-0.037 (0.763)
AES-S-Emotive	0.059 (0.632)	0.022 (0.855)	-0.011 (0.930)	-0.057 (0.645)	-0.147 (0.231)
AES-S-Others	-0.030 (0.809)	-0.078 (0.521)	-0.017 (0.894)	0.010 (0.936)	-0.261 (0.031)
AES-S-Total	0.059 (0.634)	0.197 (0.102)	0.180 (0.141)	0.207 (0.090)	-0.115 (0.352)
STAI-Y-1	0.041 (0.742)	0.015 (0.900)	0.076 (0.535)	-0.091 (0.462)	-0.200 (0.102)
STAI-Y-2	0.126 (0.307)	0.070 (0.563)	0.156 (0.205)	-0.060 (0.626)	-0.009 (0.944)

* in bold are reported significant differences after Bonferroni correction



Understanding Migraine through the Lens of Maladaptive Stress Responses: A Model Disease of Allostatic Load

David Borsook,^{1,*} Nasim Maleki,¹ Lino Becerra,¹ and Bruce McEwen²
Neuron 73, January 26, 2012





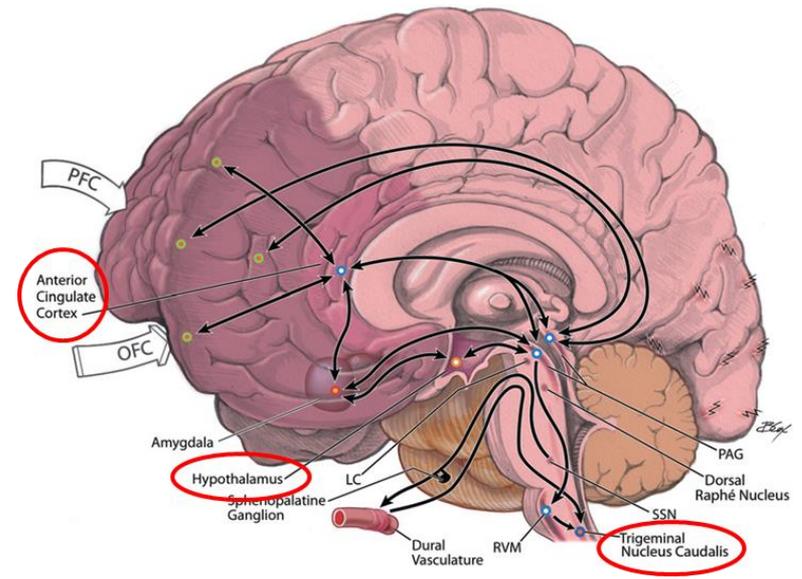
Headache
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View and Perspective

Beyond Neurovascular: Migraine as a Dysfunctional Neurolimbic Pain Network

Morris Maizels, MD; Sheena Aurora, MD; Mary Heinricher, PhD

- The neurolimbic model expands the model of migraine as a dysfunction of brainstem nuclei.
- The influence between brainstem and cortical centers is bidirectional, reflecting the bidirectional interaction of *pain, mood and emotions*.



Cingulate Cortex

- Noxious intensity encoding
- Subjective pain sensation
- Affective reaction to pain
- Cognitive-attentional response
- Anticipation of pain

MFC

- Processing of pain
- Maintenance of chronic pain
- Affective dimension of pain («pain catastrophizing»)

Somatosensorial cortex

- Painful stimuli
- Innocuous somatic stimuli

Brainstem

- nociceptive relays related to arousing activity
- set-up of descending pain controls

Amygdala

- Nociceptive integration
- Pain memory
- Affective components of pain
- Emotional pain behaviour

LPFC

- Pain intensity and unpleasantness
- Pain control by modulating cortico-subcortical pathways

Insula

- **Anterior**
Anticipation of pain
- **Posterior**
Actual experience of pain

PFC

- Chronic pain modulation

Thalamus

- Discriminative sensory response
- Attentional sensory response



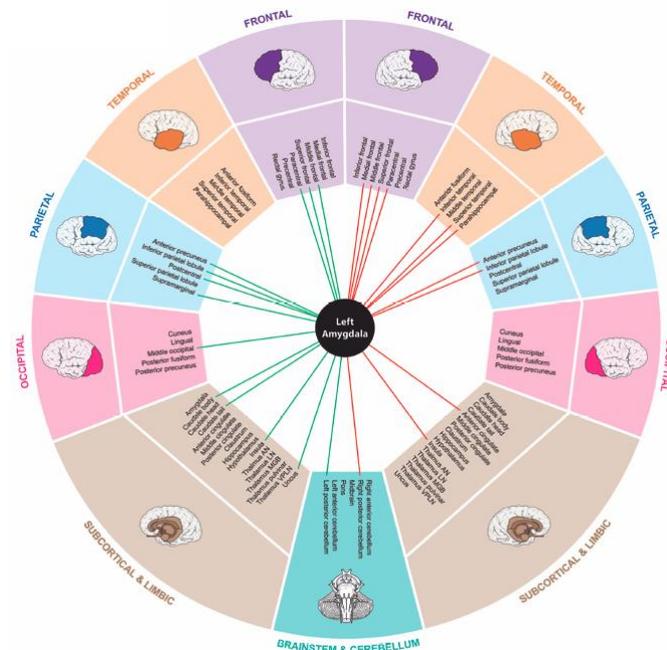
Brain discriminative areas in migraine

Cephalalgia
An International Journal of Headache

Migraine classification using magnetic resonance imaging resting-state functional connectivity data

Catherine D Chong¹, Nathan Gaw², Yinlin Fu², Jing Li²,
Teresa Wu² and Todd J Schwedt¹

- ✓ Machine-learning techniques to develop discriminative brain-connectivity biomarkers from rs-fMRI data that distinguish between individual migraine patients and healthy controls.
- ✓ Regions best discriminated migraine brain from that of a healthy control (accuracy 86.1%)
 - ✓ right middle temporal gyrus
 - ✓ posterior insula
 - ✓ middle cingulate cortex
 - ✓ left ventromedial prefrontal gyrus
 - ✓ bilateral amygdala



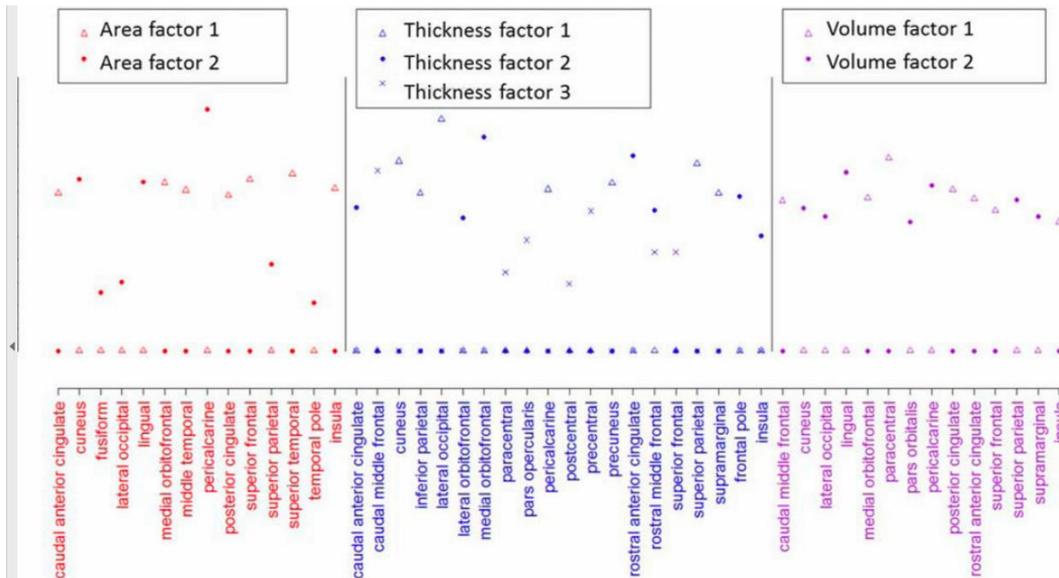


Brain discriminative areas in migraine

Headache. 2017 July ; 57(7): 1051–1064. doi:10.1111/head.13121.

Migraine sub-classification via a data-driven automated approach using multimodality factor mixture modeling of brain structure measurements

Todd J. Schwedt¹, Bing Si², Jing Li², Teresa Wu², and Catherine D. Chong¹



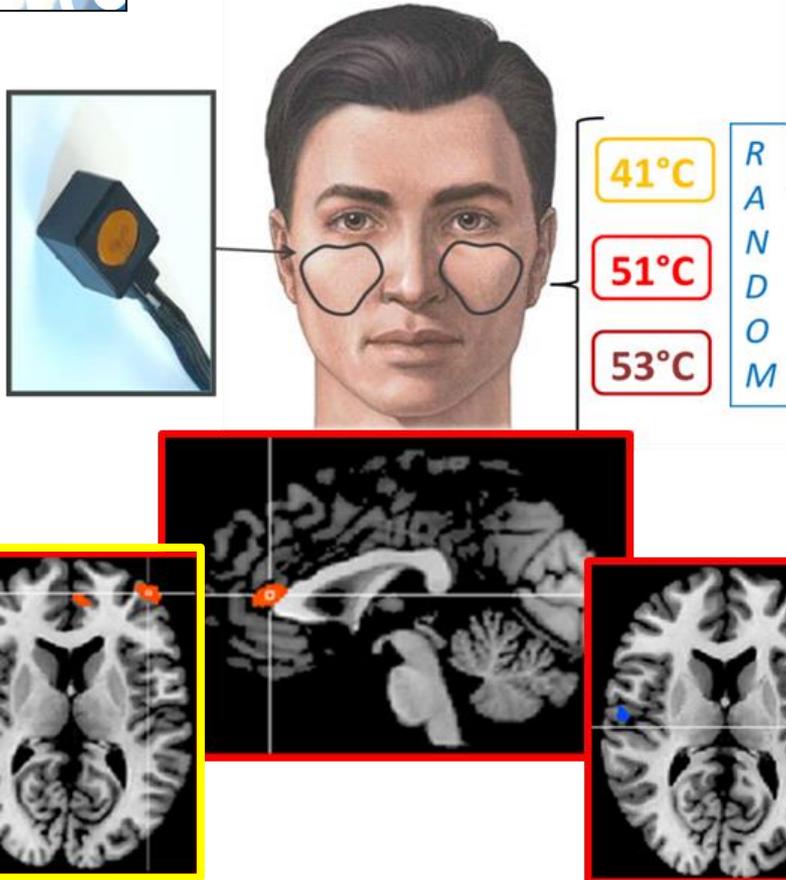
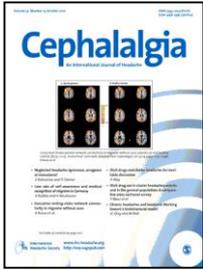
- Accuracy of detection between patient and HC of 86.1%
- Longer the disease duration, higher was the accuracy (96.7% if > than 14 years)

Data-driven sub-classification of brain MRIs identified two sub-groups as for **allodynia**

symptom severity



Higher-order brain areas and allodynia



- CHEPS
- MwoA patients without ictal CA
- MwoA patients with ictal CA
- HC

DLPFC activation **only in MwoA CA+** pts may represent:

- *a recruitment of additional resources to meet analgesic demands and to maintain proficiency*
- *a correlate of pain negative cognitive content (**pain catastrophizing and rumination**) and consequent inadequate **pain coping***

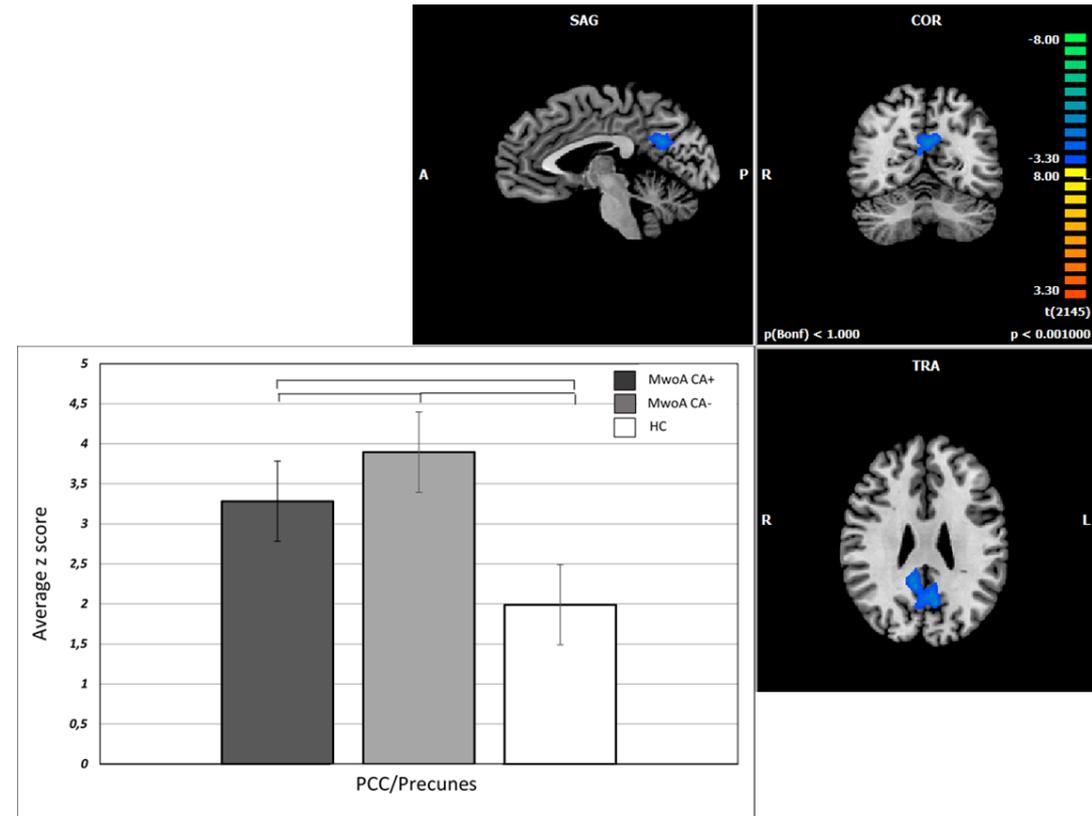
Russo A. et al., Cephalalgia 2016



MwoA CA+ vs MwoA CA- vs HC

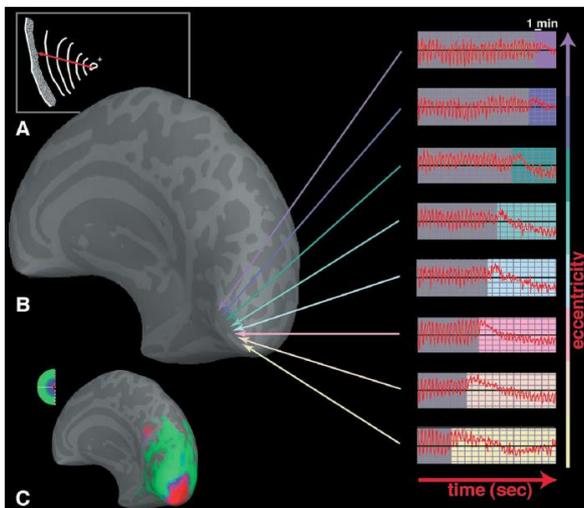
*R*s-fMRI 3 y FU

- Increased PCC-FC could represent an effort of adaptive response to stressful events and repetitive migraine attacks in migraine patients
- Reduced PCC-FC at baseline in migraine patients who will develop CA after 3 years





The role of lingual gyrus in migraine aura

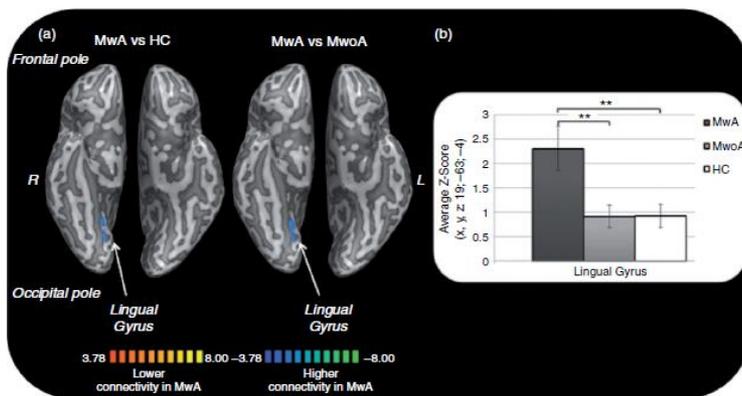


Hadjikhani et al., PNAS 2001

- ✓ The MR perturbations developed earlier in the foveal representation, compared with more eccentric representations of retinotopic visual cortex.

In patients with MWA:

- ✓ Increased functional connectivity in VN (right lingual gyrus)
- ✓ *No correlations with structural or microstructural abnormalities*
- ✓ No correlations with clinical parameters of migraine severity



Tedeschi G. et al., Cephalalgia 2017



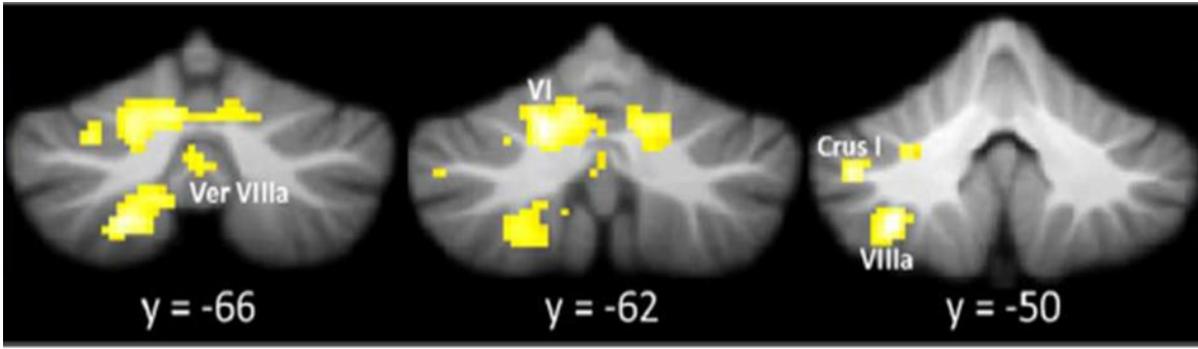
TOP TEN articles



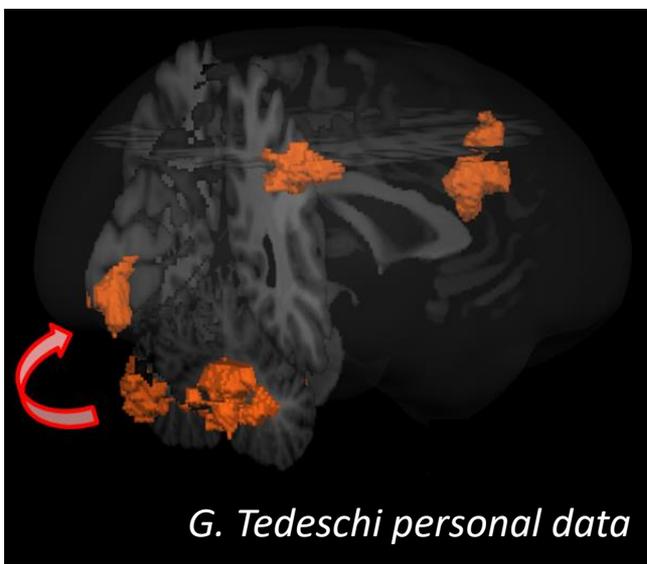
Brain Res Rev. 2010 October 5; 65(1): 14–27. doi:10.1016/j.brainresrev.2010.05.005.

The Cerebellum and Pain: Passive Integrator or Active Participant?

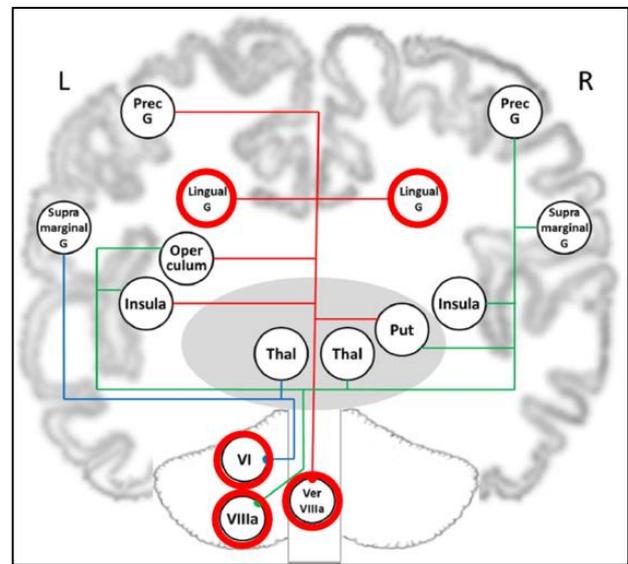
Eric A. Moulton¹, Jeremy D. Schmahmann², Lino Becerra¹, and David Borsook¹



Cerebellum and brainstem activation during nociceptive trigeminal stimulation



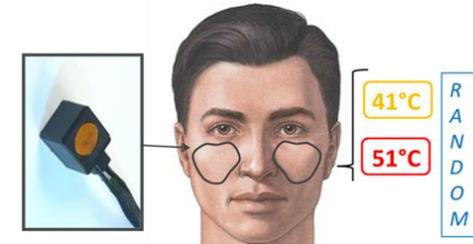
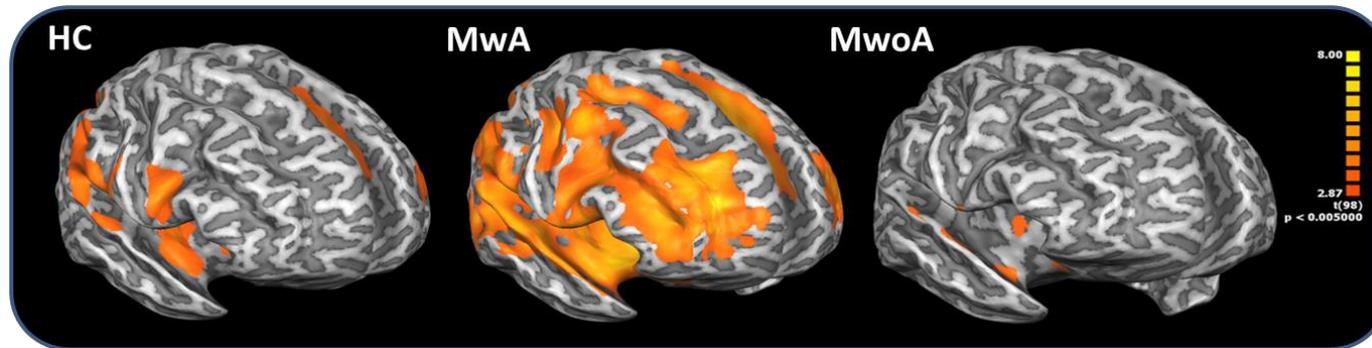
G. Tedeschi personal data



Functional connectivity between cerebellum and lingual gyrus in migraine patients



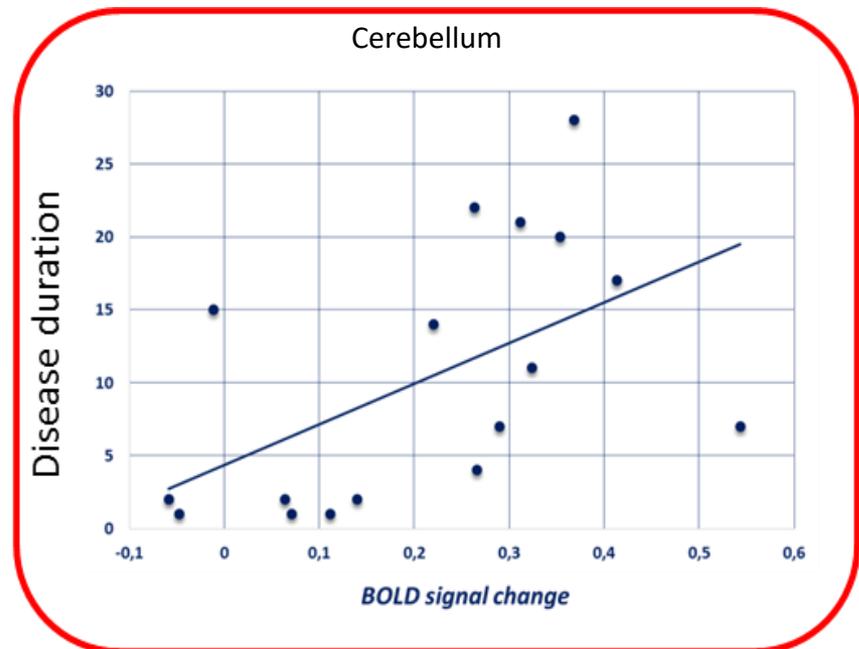
Relationship between pain and aura



Russo A. et al., Cephalalgia – Under Revision

During noxious-stimulus in MwA patients increased activity in:

- Lingual gyrus
- Inferior parietal lobe
- Inferior dorsal frontal lobe
- Superior medial frontal lobe
- Cerebellum



Neurolimbic **visual**-pain network
in migraine with aura ?



Conclusions

Advanced neuroimaging techniques have provided important insights in migraine :

- ✓ Elucidating the role of subcortical structures in migraine pathophysiology
- ✓ Expanding the importance of non pain-related aspects of migraine
- ✓ Defining the concept of neuro-limbic pain network
- ✓ Moving to neuro-limbic-visual-pain network

We believe:

- ✓ that migraine is the result of dysfunctional brain networks that makes the patient more prone to answer with migraine attacks to behavioural (adaptive/maladaptive) stimuli: pathophysiology phenomenon !



Acknowledgments

Headache Group

A. Russo

M. Silvestro

L. Marcuccio

F. Conte

A. Giordano

A. Tessitore

fMRI Group

A. Russo

F. Esposito

R. Conforti

M. Cirillo

A. Paccone

F. Di Nardo

G. Caiazzo

S. Cirillo

A. Tessitore

NPS group

P. Montella

M. De Stefano

M. Siciliano

G. Santangelo

A handwritten signature in blue ink that reads "Grazie" (Thank you) with a large checkmark underneath it. The signature is written on a light blue, slightly textured background.