



SESSIONE 4

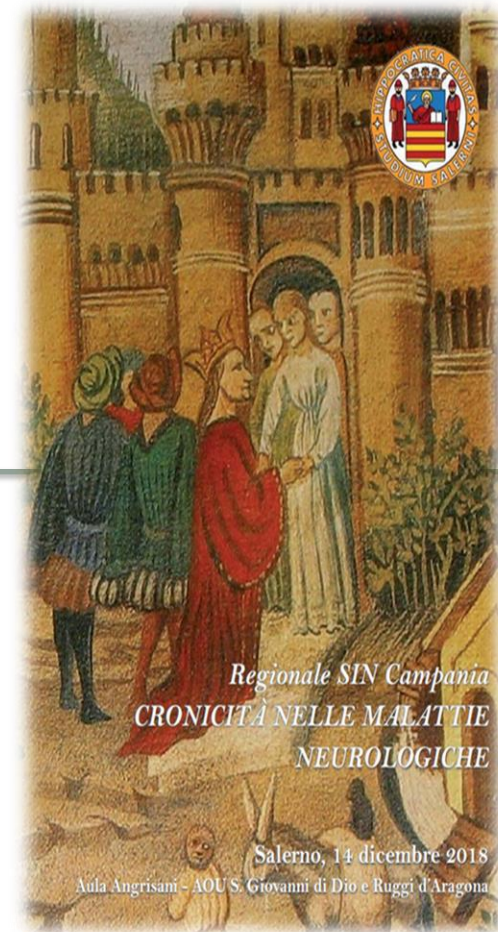
UPDATE SUL DOLORE

Functional imaging nell'emicrania

Gioacchino Tedeschi

Università degli Studi della Campania "Luigi Vanvitelli"

Napoli

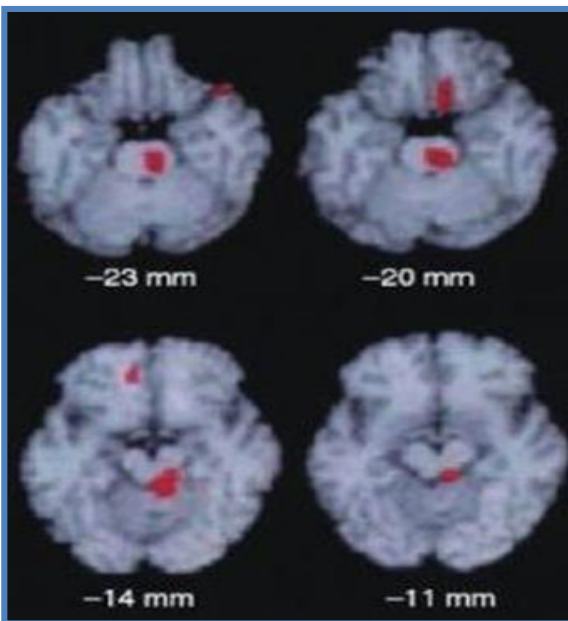




Historical notes

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..."

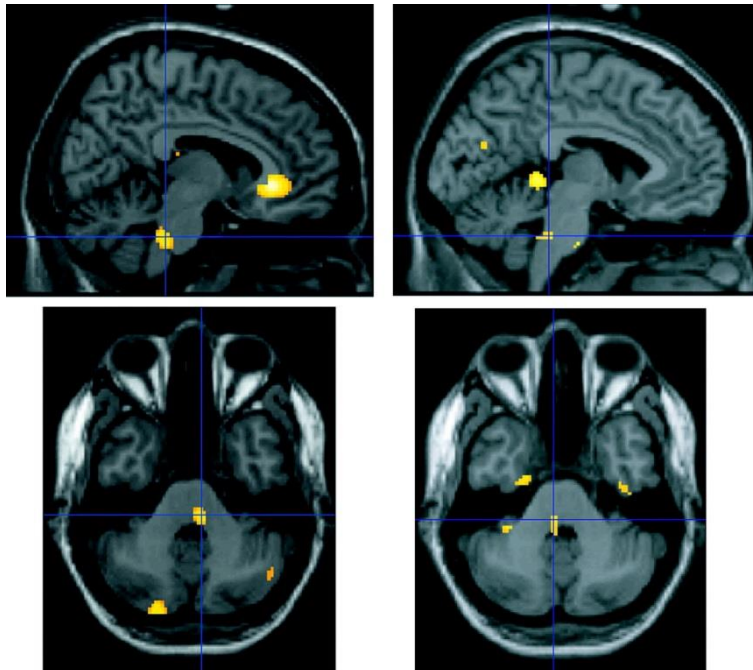


BRAIN A JOURNAL OF NEUROLOGY

(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



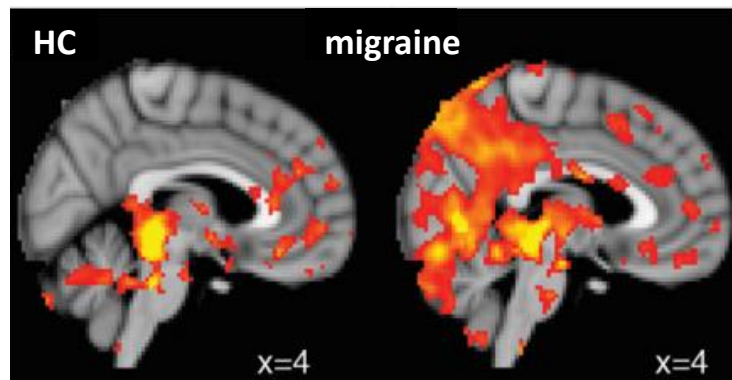
Pons is not the only one in the Brainstem !

Annals of
NEUROLOGY

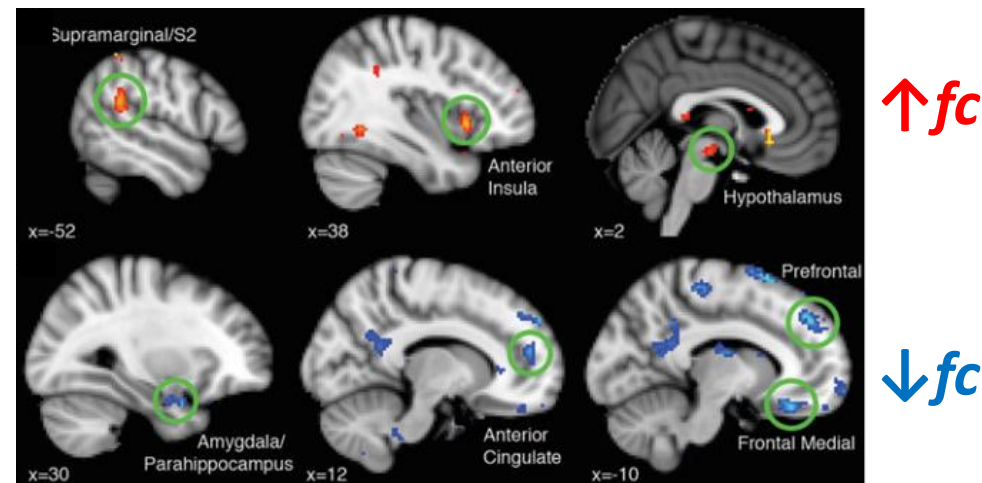
Altered functional MRI resting-state connectivity in periaqueductal gray networks in migraine

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



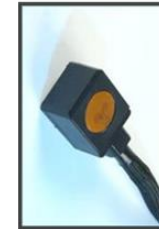
RS-fc with the PAG
correlates with the frequency of migraine attacks



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



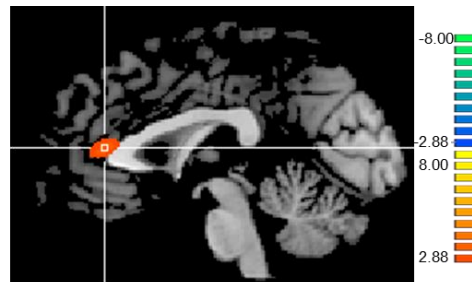
41°C

51°C

53°C

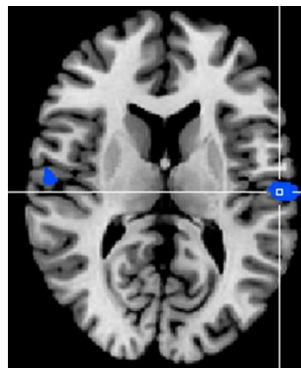
R
A
N
D
O
M

51°C



Patients > Controls

53°C



Controls > Patients

This **adaptive**
responses may
become
progressively less
efficient over
time

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"



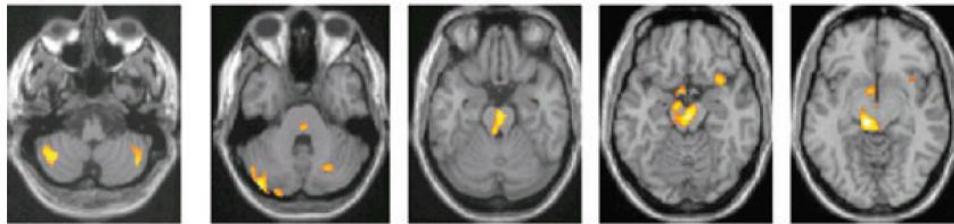
Brainstem is not the only one !

Headache
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Journal compilation © 2007 American Headache Society

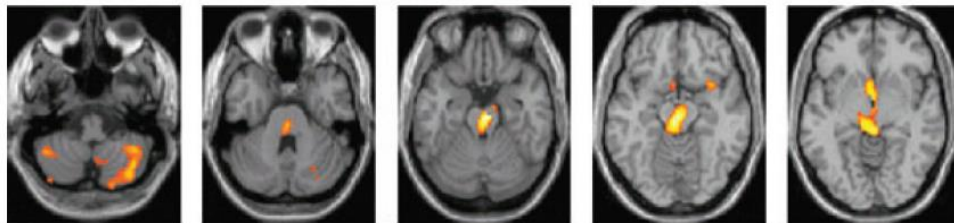
Hypothalamic Activation in Spontaneous Migraine Attacks

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

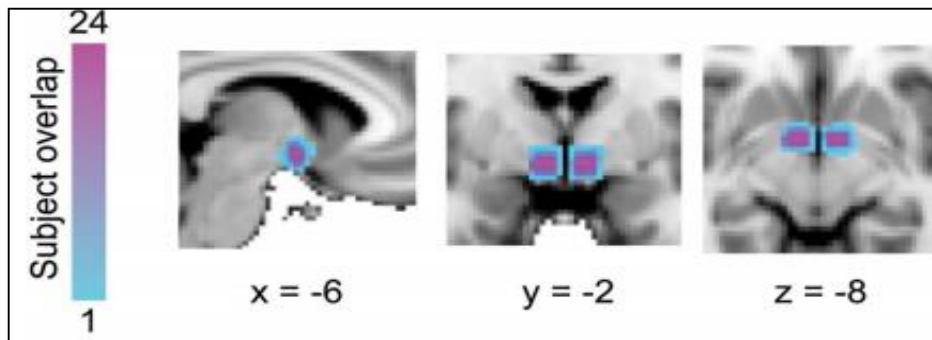
Again... the hypothalamus is not simply related to *headache (pain phase of a migraine attack)* but to the whole migraine phenomenon !!!



Altered Hypothalamic Functional Connectivity with Autonomic Circuits and the Locus Coeruleus in Migraine

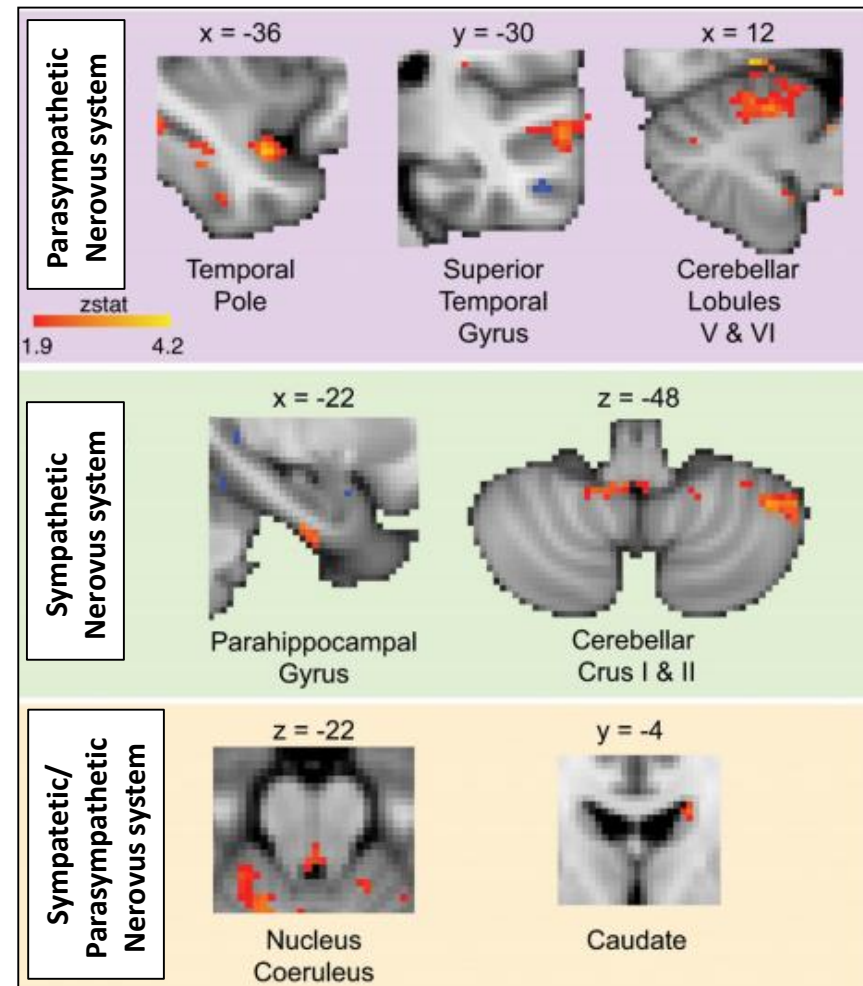
Eric A. Moulton^{1*}, Lino Becerra^{1,2}, Adriana Johnson¹, Rami Burstein⁴, David Borsook^{1,2,3}

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

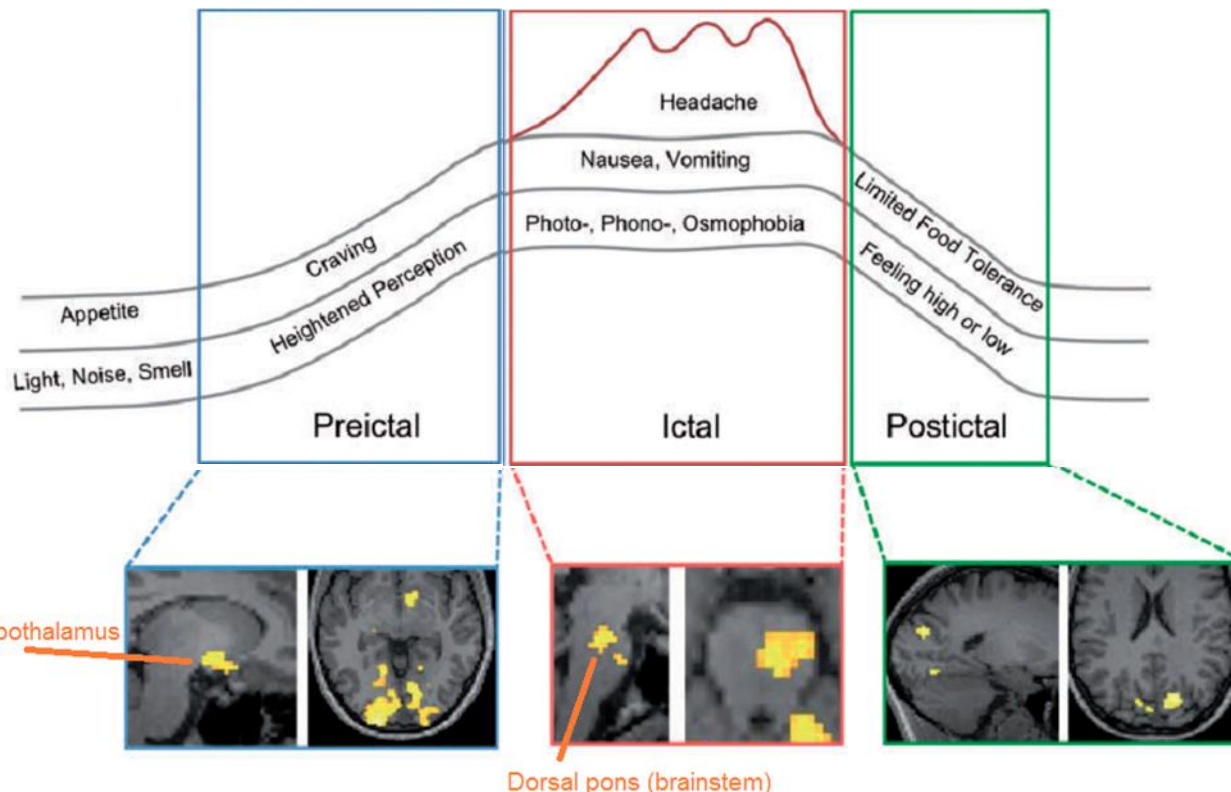
BRAIN

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*

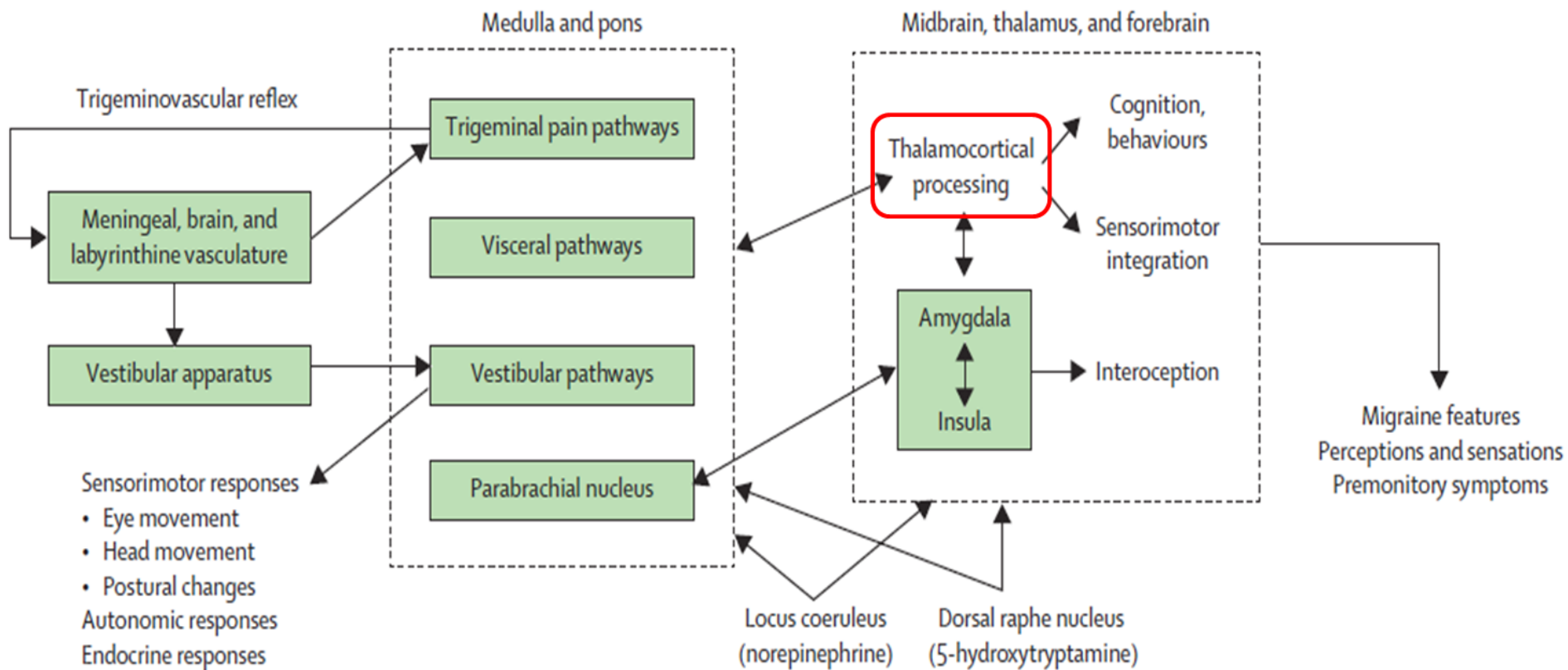
During post-dromal phase: Posterior (occipital) brain areas



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Abnormal thalamic function in patients with vestibular migraine

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





Neurology, 2016

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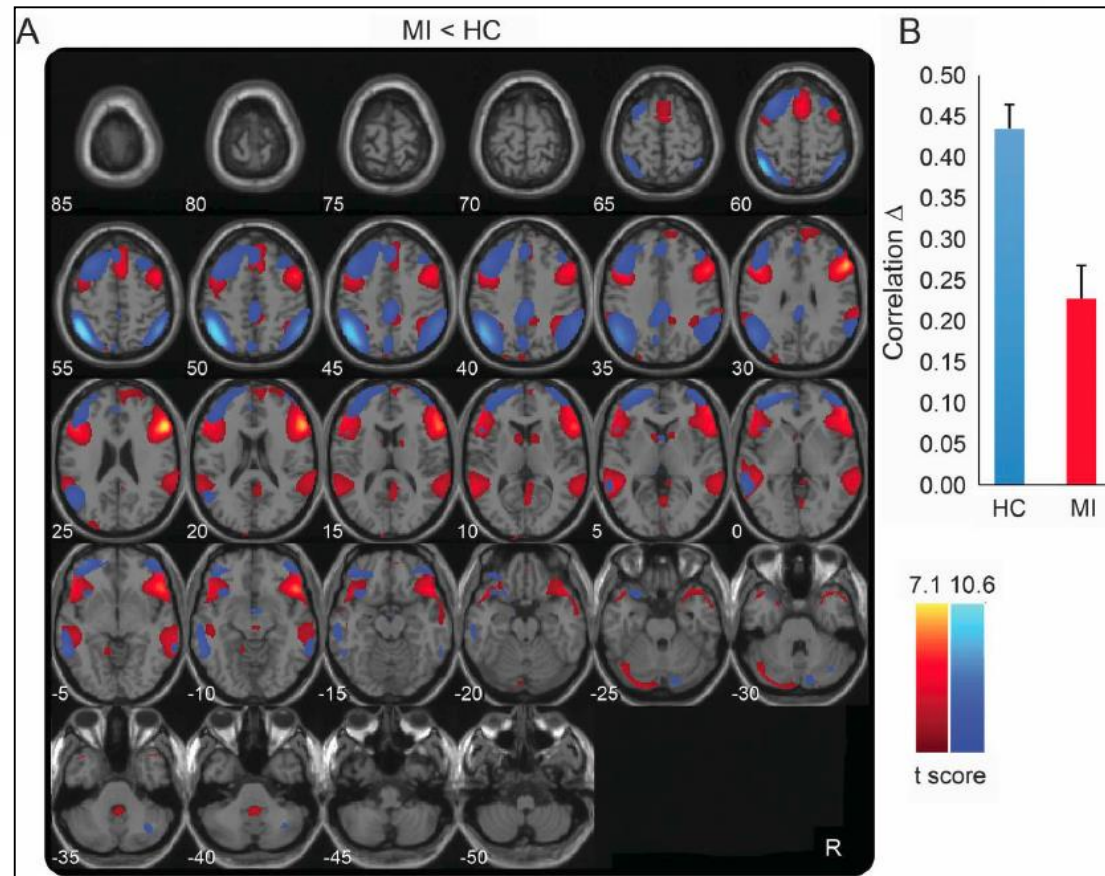
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Thalamo-cortical network activity during spontaneous migraine attacks



- ✓ 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

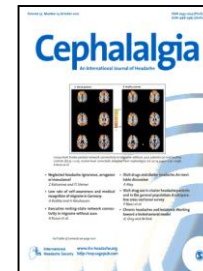
Alessandro Tessitore^{1*}, Antonio Russo^{1,2†}, Alfonso Giordano^{1,2}, Francesca Conte¹, Daniele Corbo¹, Manuela De Stefano¹, Sossio Cirillo³, Mario Cirillo³, Fabrizio Esposito^{4,5} and Gioacchino Tedeschi^{1,2}

Cephalalgia International Headache Society
An international journal of headache

Cephalalgia
32(14) 1041–1048

Executive resting-state network connectivity in migraine without aura

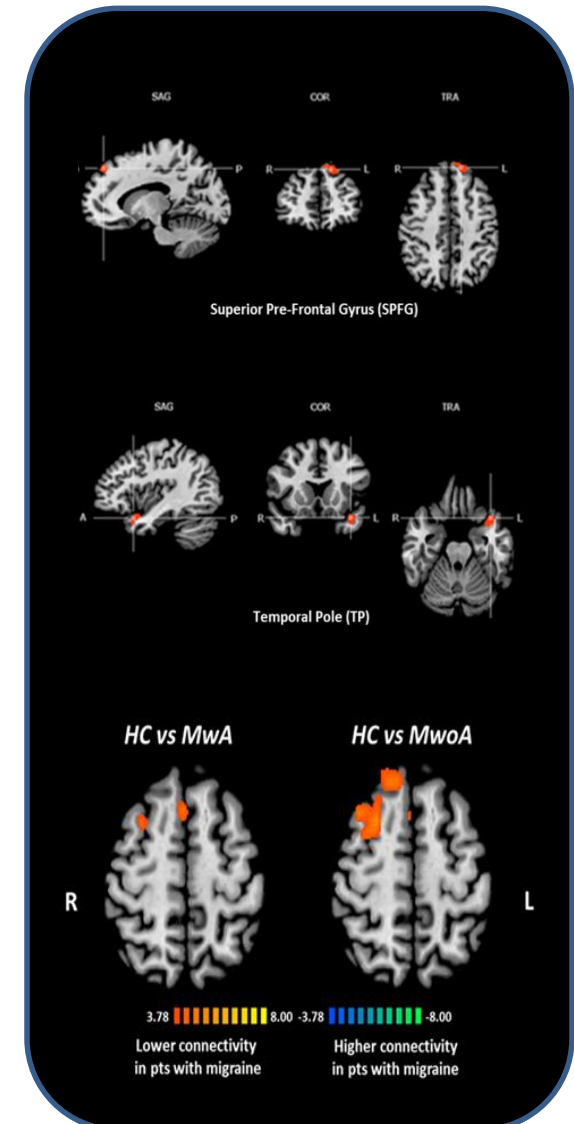
Antonio Russo^{1,2,*}, Alessandro Tessitore^{1,*},
Alfonso Giordano^{1,2}, Daniele Corbo¹, Laura Marcuccio¹,
Manuela De Stefano¹, Fabrizio Salemi¹, Renata Conforti²,
Fabrizio Esposito^{2,3} and Gioacchino Tedeschi^{1,2}



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 Caiazzo, 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)

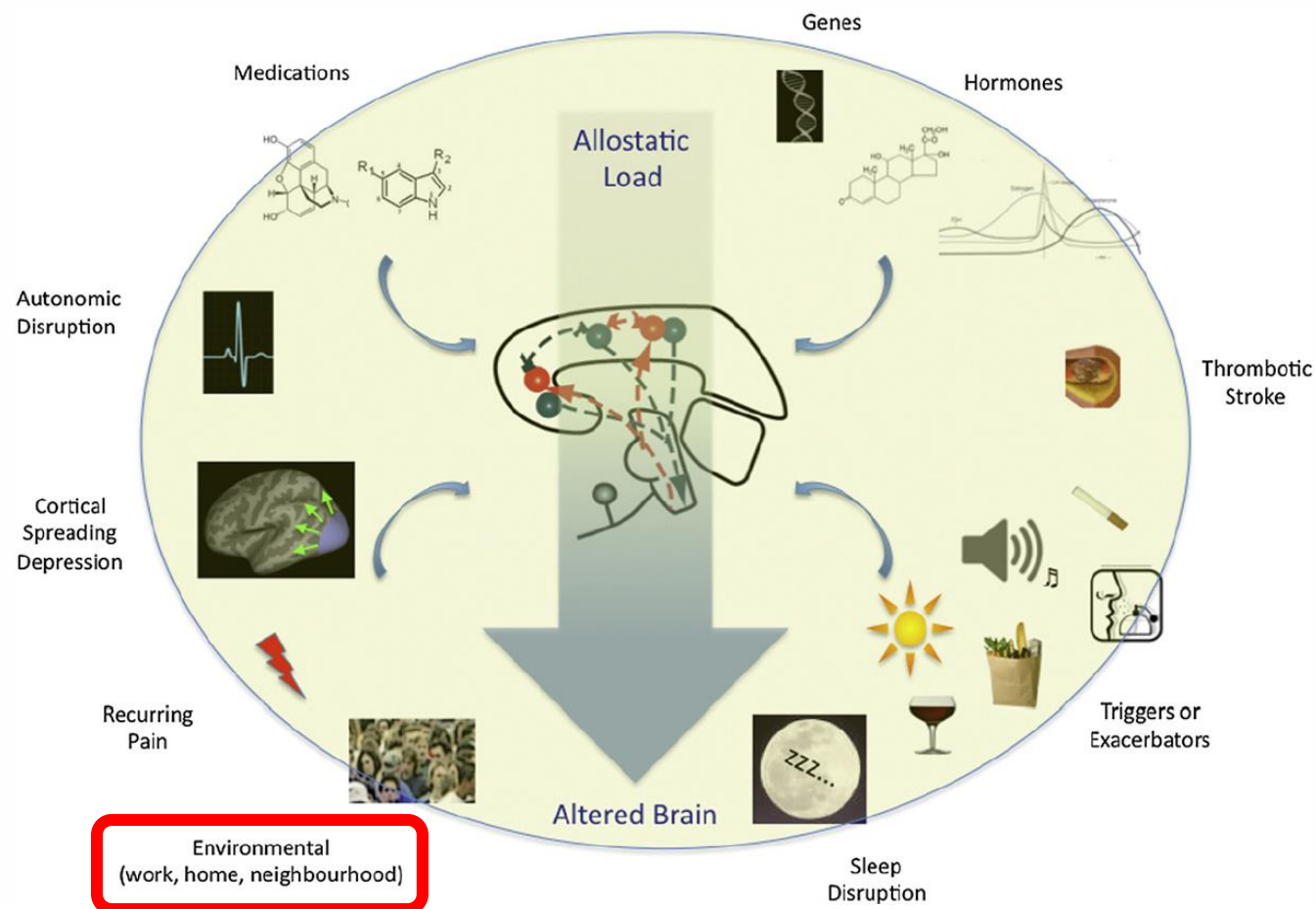
In bold are reported significant differences after Bonferroni correction



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





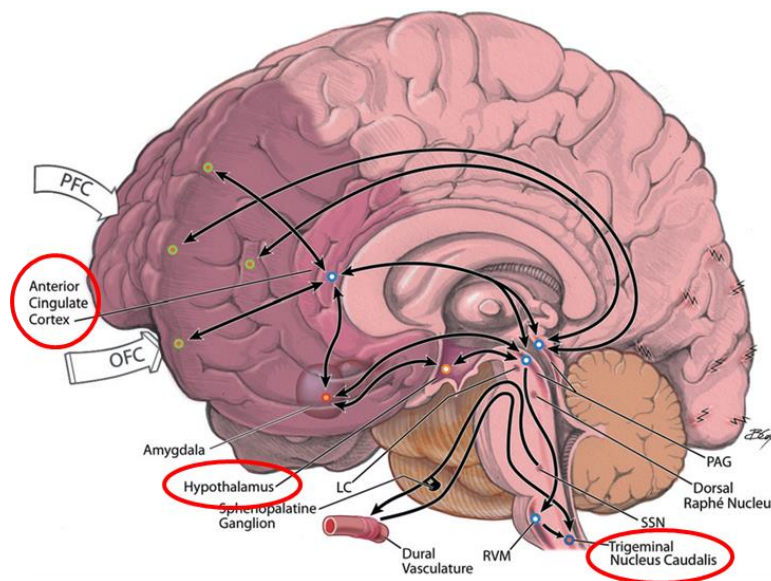
Headache
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View and Perspective

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

LPFC

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

Insula

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

PFC

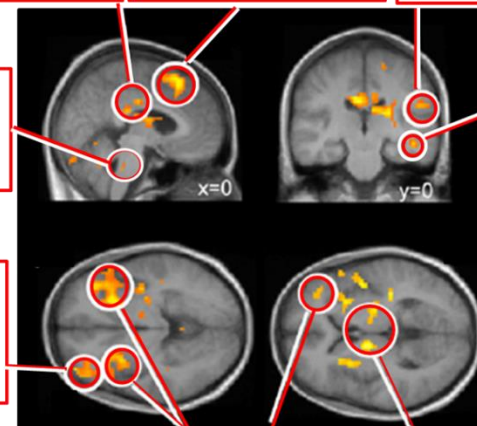
- Chronic pain modulation

Thalamus

- Discriminative sensory response
- Attentional sensory response

Amygdala

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





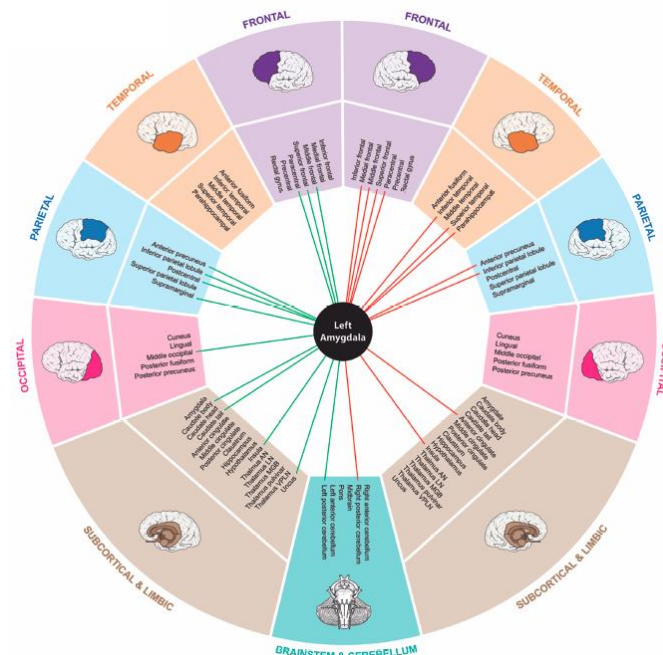
Brain discriminative areas in migraine

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



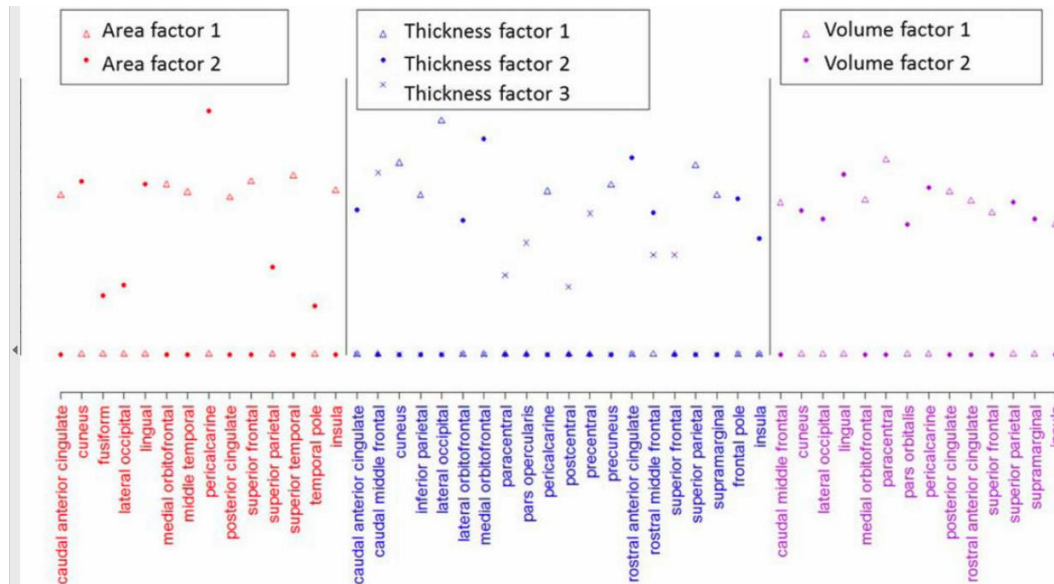


Brain discriminative areas in migraine

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

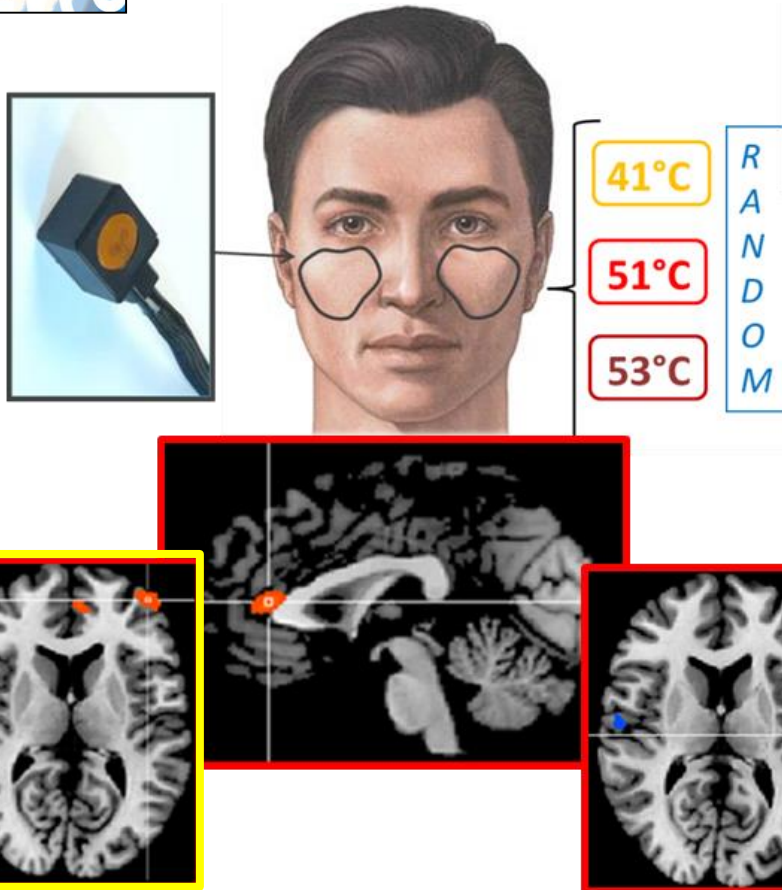


- Accuracy of detection between patient and HC of 86.1%
- Longer the disease duration, higher was the accuracy (96.7% if > than 14 years)

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



Higher-order brain areas and allodynia



Russo A. et al., Cephalalgia 2016

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

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

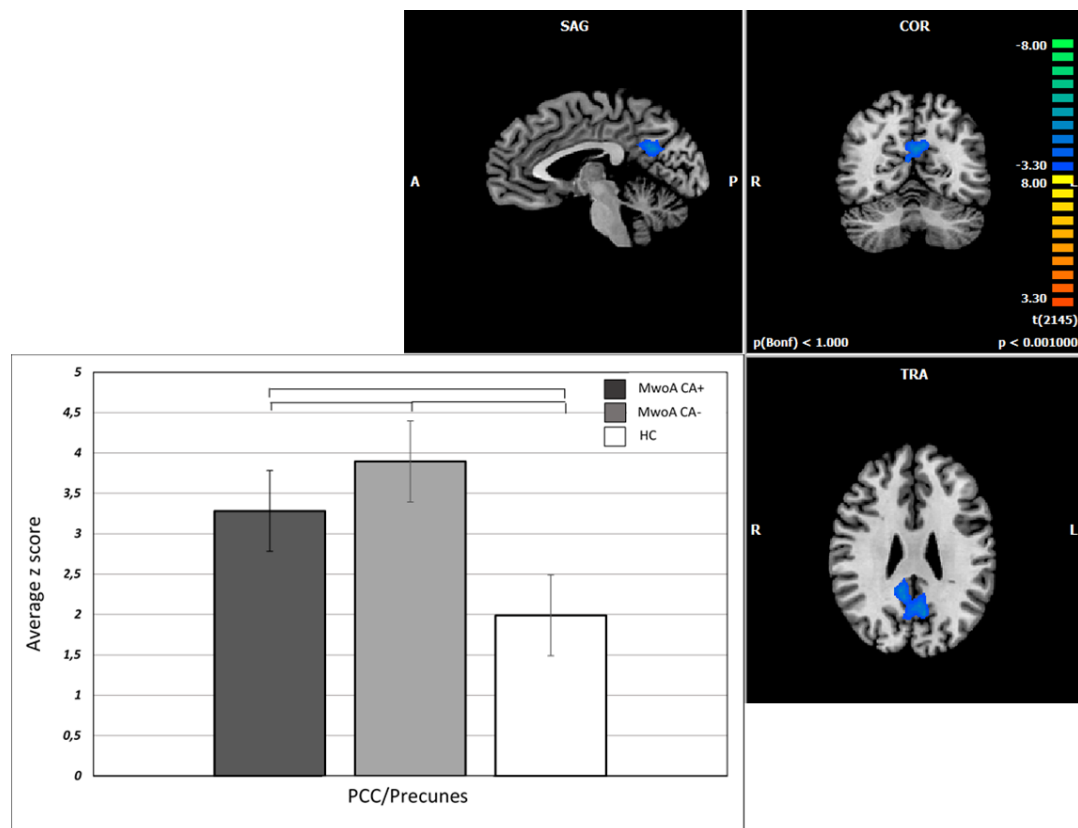
- *a recruitment of additional resources to meet analgesic demands and to maintain proficiency*
- *a correlate of pain negative cognitive content (**pain catastrophizing and rumination**) and consequent inadequate **pain coping***



MwoA CA+ vs MwoA CA- vs HC

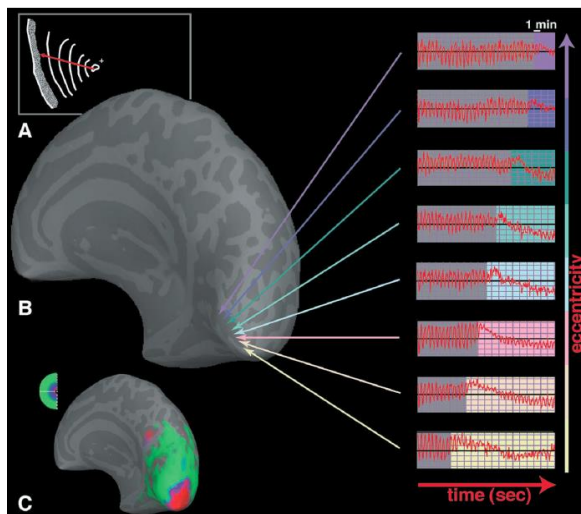
Rs-fMRI 3 y FU

- 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

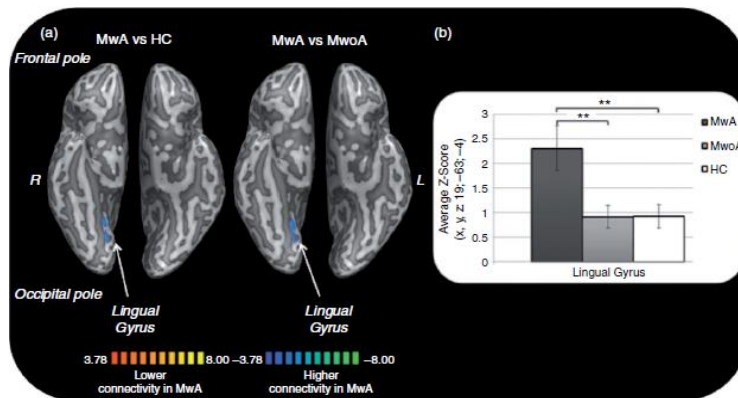


Hadjikhani et al., PNAS 2001

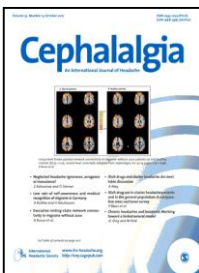
- ✓ The MR perturbations developed earlier in the foveal representation, compared with more eccentric representations of retinotopic visual cortex.

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



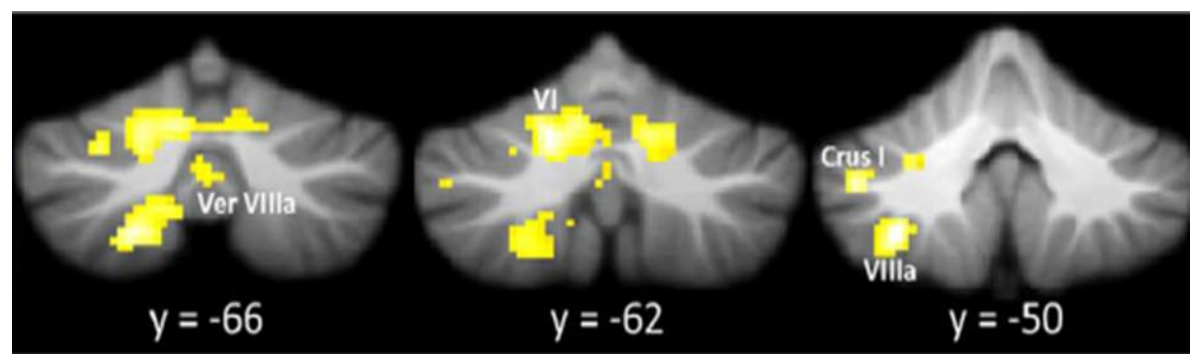
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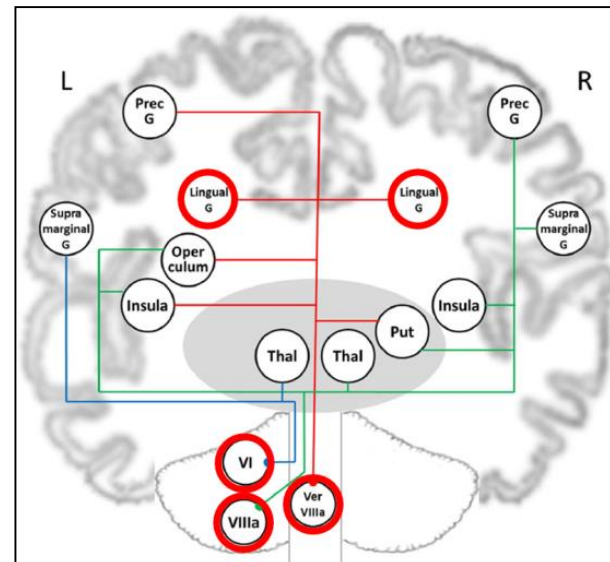
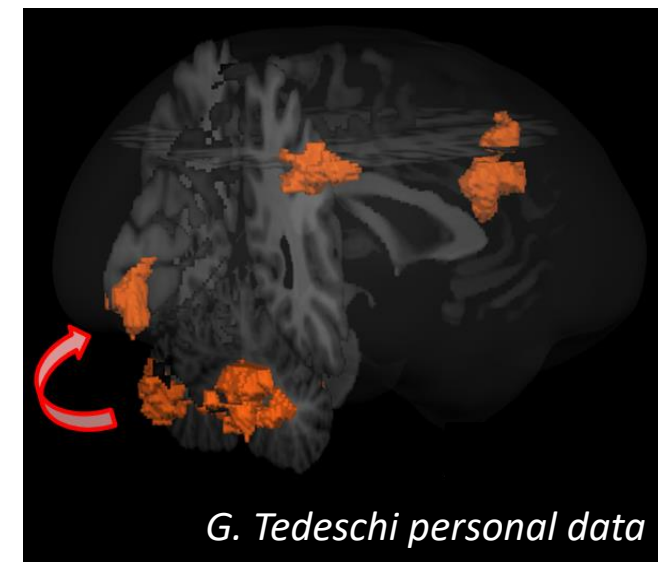
Brain Res Rev. 2010 October 5; 65(1): 14–27. doi:10.1016/j.brainresrev.2010.05.005.

The Cerebellum and Pain: Passive Integrator or Active Participant?

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



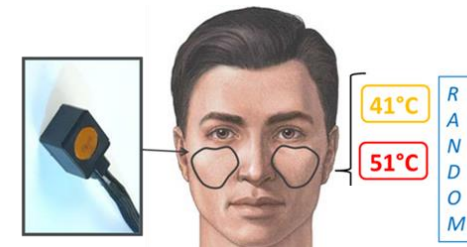
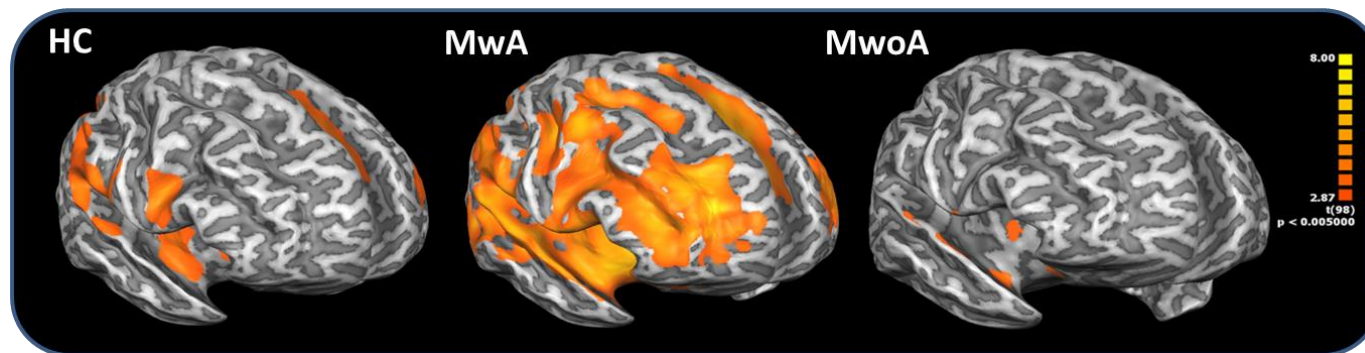
**Cerebellum and brainstem
activation during nociceptive
trigeminal stimulation**



**Functional connectivity
between cerebellum and
lingual gyrus in migraine
patients**



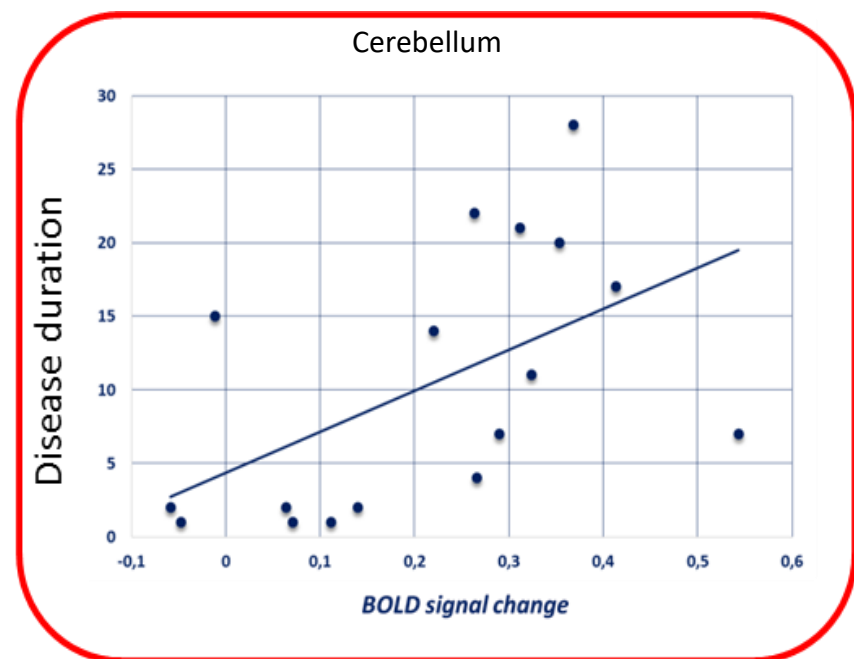
Relationship between pain and aura



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

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fMRI Group

A. Russo

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