HEADACHE RESEARCH

KING'S College LONDON

Pathophysiology of Primary Headaches

The Headache Centre

Guy's & St Thomas's NHS Foundation Trust &

Wolfson SPaRC, King's College London

Headache Centre

Guy's and St Thomas' NHS Foundation Trust

KING'S HEALTH PARTNERS

Disclosures

Potential COI	Organisation
Advisory/ Scientific Boards	Eli Lilly, Neuresta, Zenith Scientific
Speaker / Speakers Boards	Eli Lilly, AbbVie, Pfizer, TEVA
Grant support for research or education	AbbVie, Pfizer, Medical Research Foundation, Brain Research UK, Migraine Trust, Medical Research Council, National Institute of Health, Ipsen
Editorial Board	Cephalgia, Journal of Headache and Pain, Journal of Clinical Medicine, Frontiers in Neurology, Toxins
Author royalties	None
Other	Trustee of the International Headache Society, Chair of Headache SIG of British Pain Society, Lead of National Audit for Headache Disorders/National Audit for Migraine- UK

International Classification of Headache Disorders

International Headache Society, 3rd Edition , 2018

	IHS code	Classification
Primary headaches	1.	Migraine
	2.	Tension-type headache
	3.	Trigeminal autonomic cephalalgias
	4.	Other primary headache disorders
Secondary headaches	5.	Headache attributed to trauma or injury to the head and/or neck
	6.	Headache attributed to cranial or cervical vascular disorder
	7.	Headache attributed to non-vascular intracranial disorder
	8.	Headache attributed to a substance or its withdrawal
	9.	Headache attributed to infection
	10.	Headache attributed to disorder of homoeostasis
	11.	Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structures
	12.	Headache attributed to psychiatric disorder
Painful cranial neuropathies, other facial pains and other headaches	13.	Painful lesions of the cranial nerves and other facial pain
	14.	Other headache disorders

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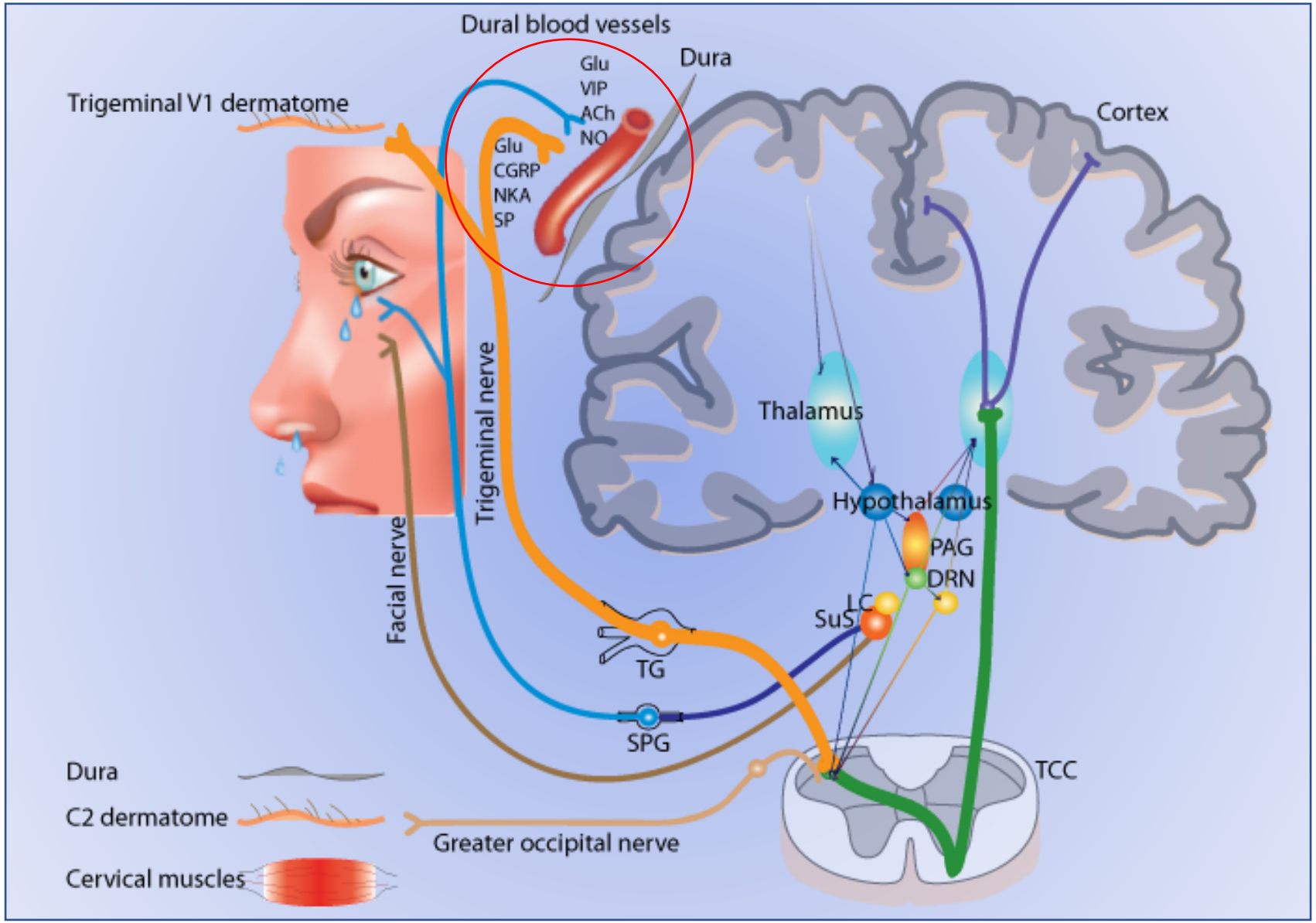
Ascending Trigeminothalamic Pathway – Sensory Information from the Region of Head and Neck



Adopted from Andreou et al., Expert Rev Neuroth, 2010;10(3):389-411

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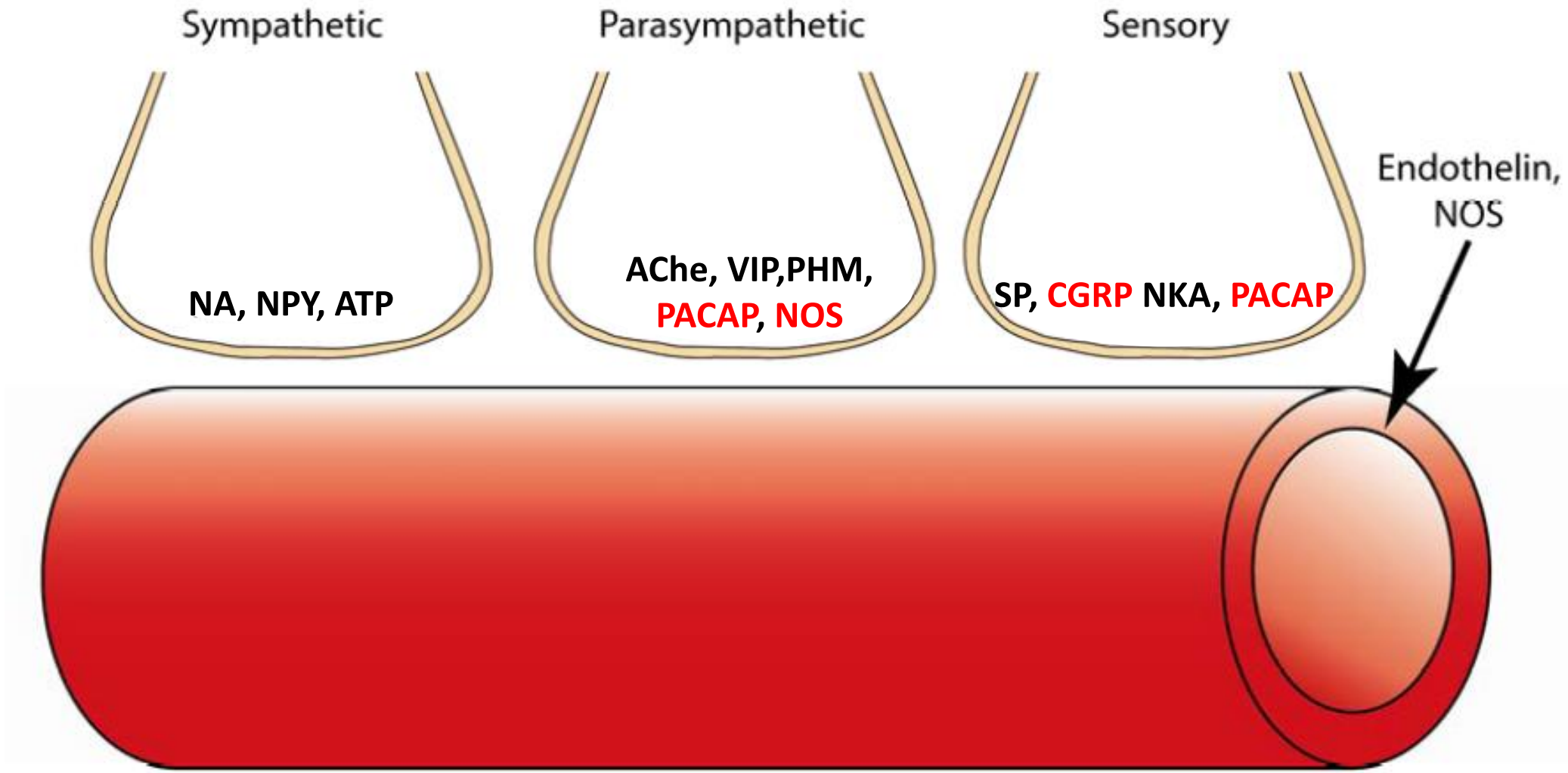
Nerve fibres innervating the cranial circulation – Neuropeptides and Trigeminovascular activation



Ache, acetylcholinesterase; ATP, Adenosine triphosphate; CGRP, Calcitonin gene-related peptide; NPY, Neuropeptide Y; NA, noradrenaline ; NKA, neurokinin A; NOS, Nitric oxide synthase; PACAP, Pituitary Adenylate Cyclase-Activating Polypeptide; PHM, Peptide histidine methionine SP, substance P; VIP, Vasoactive intestinal peptide

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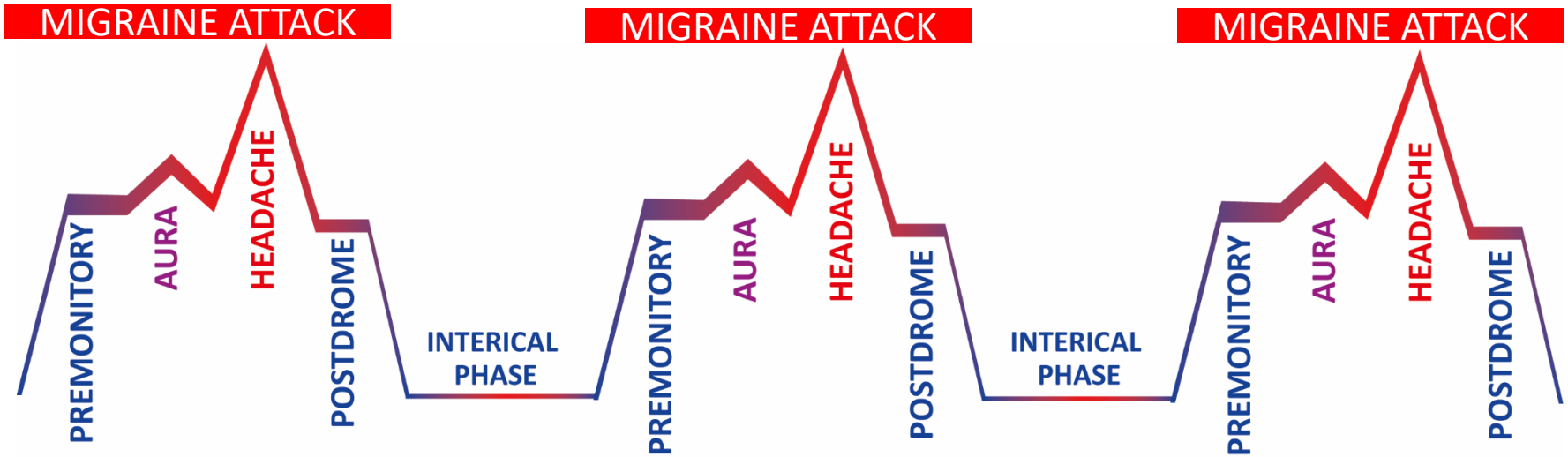
Migraine – A Cycling Disorder

A clinical syndrome characterized by episodic attacks of head pain and associated symptoms, such as nausea, sensitivity to light, sound, or intolerance to head movement

Episodic migraine



Migraine Attach - More than a headache

Characterised by different phases, including a headache phase, with specific features and associated symptoms[1]

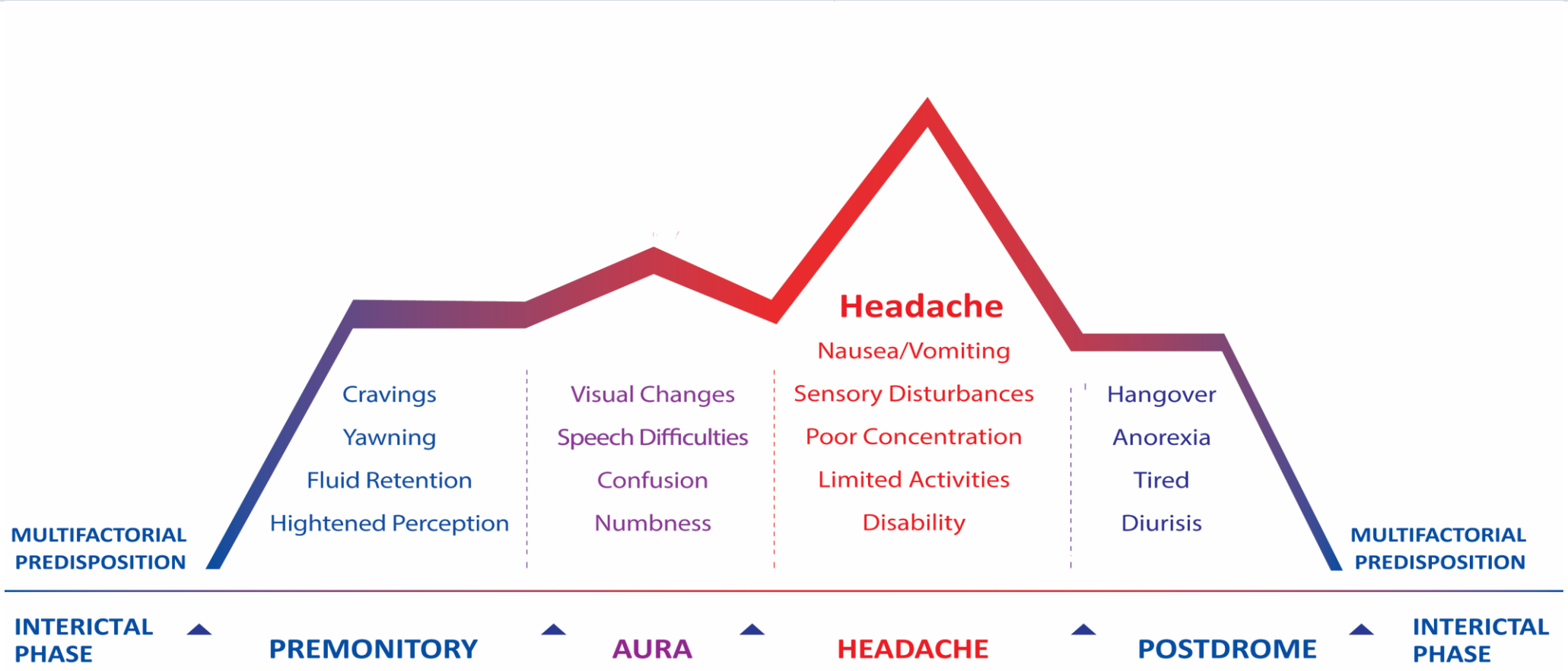


Figure adapted from Andreou AP and Edvinsson L. 2019.[2]

1. Blau JN. *Lancet.* 1992;339(8803):1202–1207; 2. Andreou AP and Edvinsson L. *J Headache Pain*. 2019;20(1):117.

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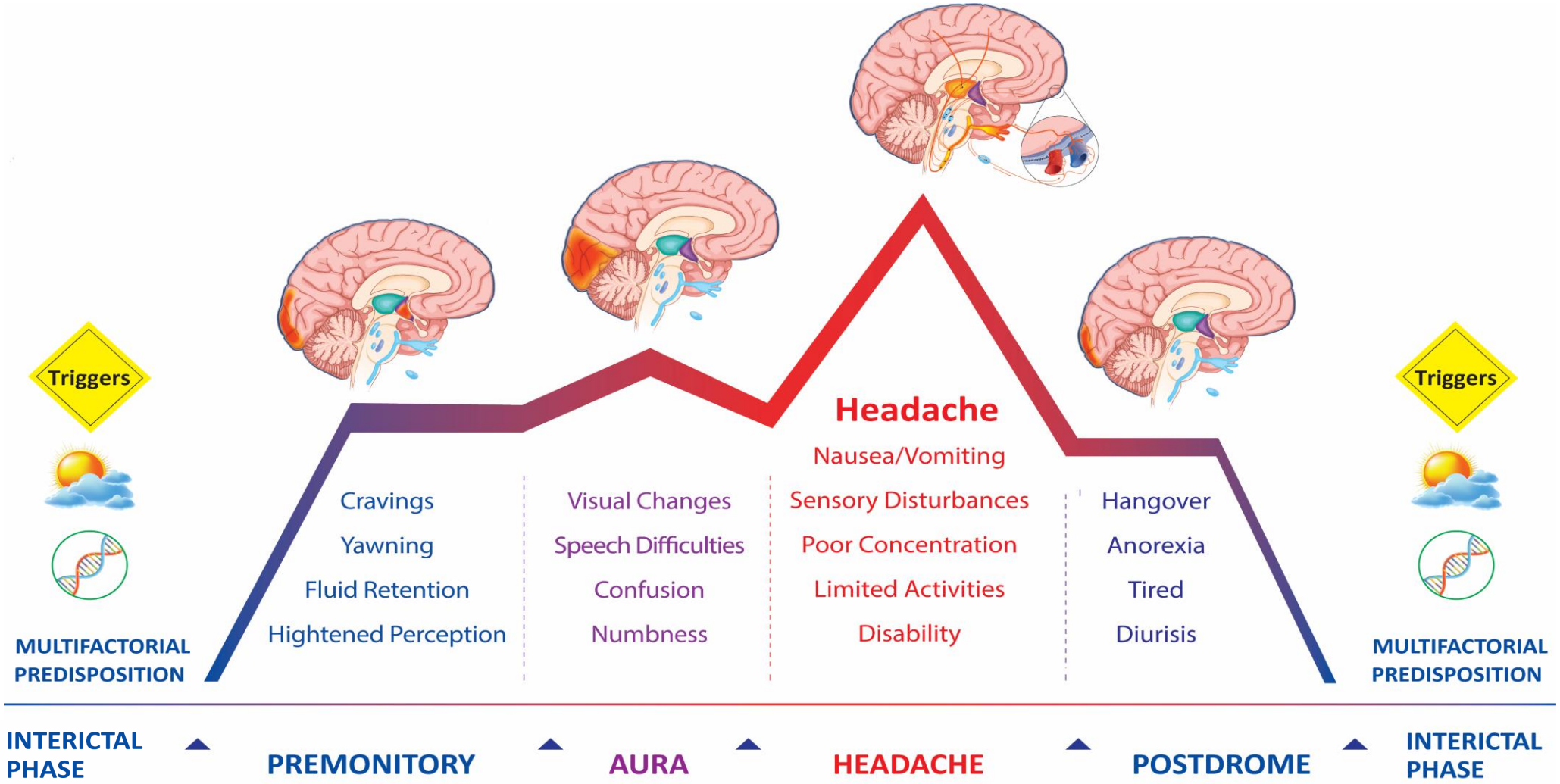
Migraine: Pathophysiology



Andreou AP and Edvinsson L. *J Headache Pain*. 2019;20(1):117.

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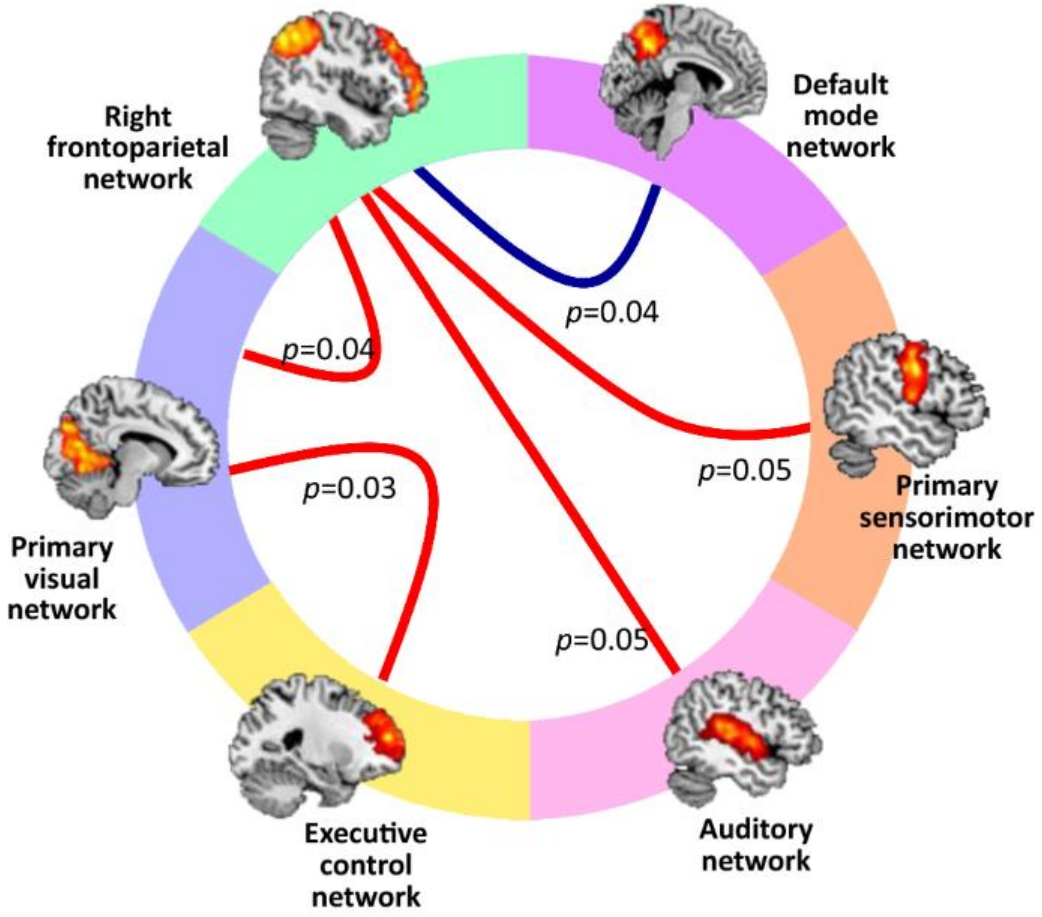
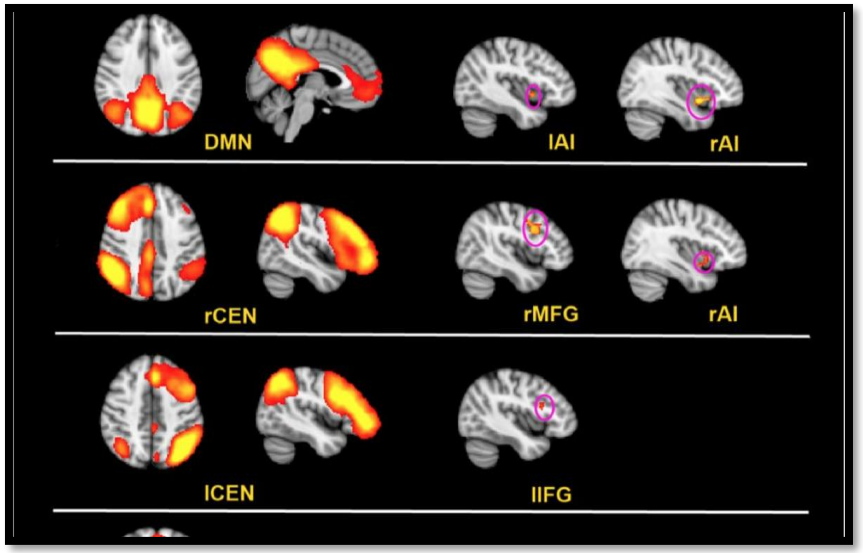
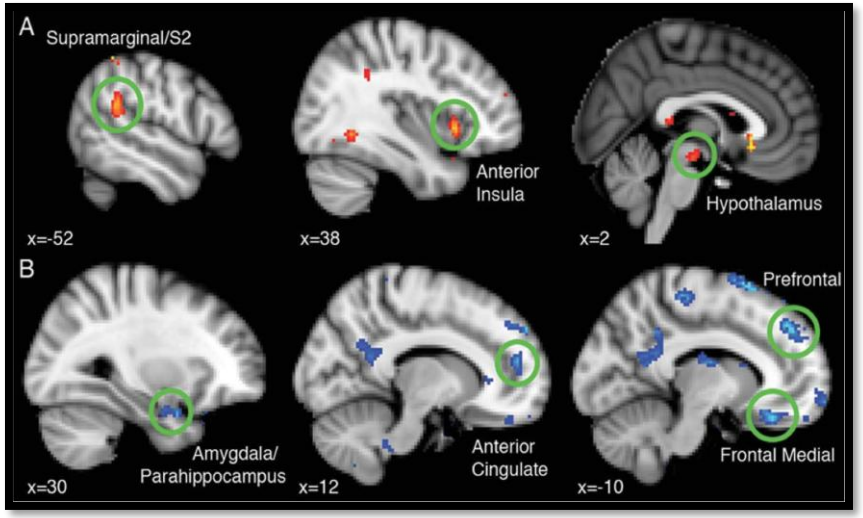
Migraine: Pathophysiology



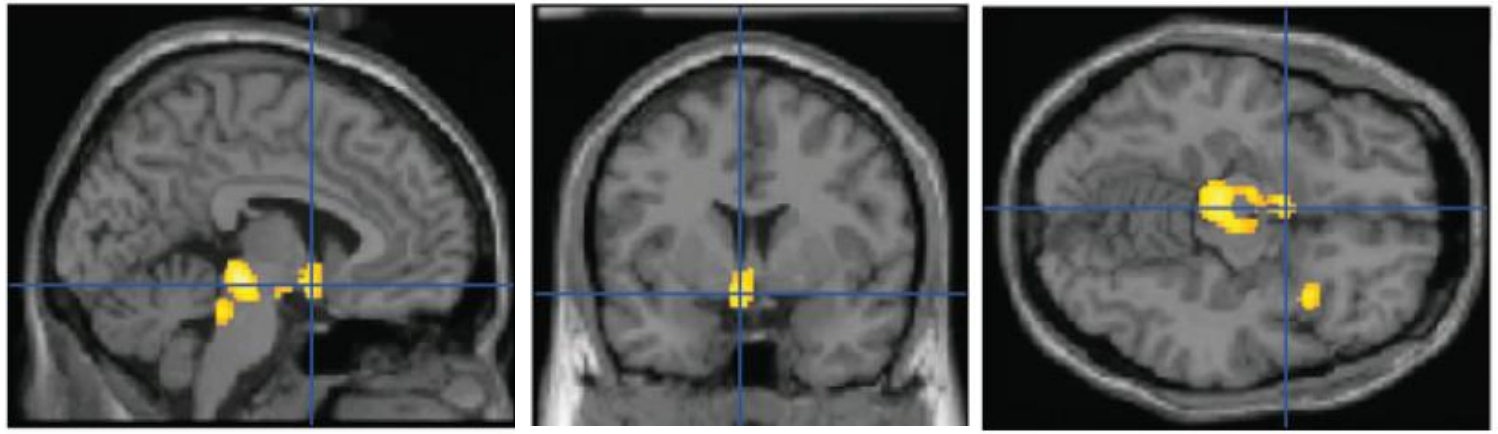




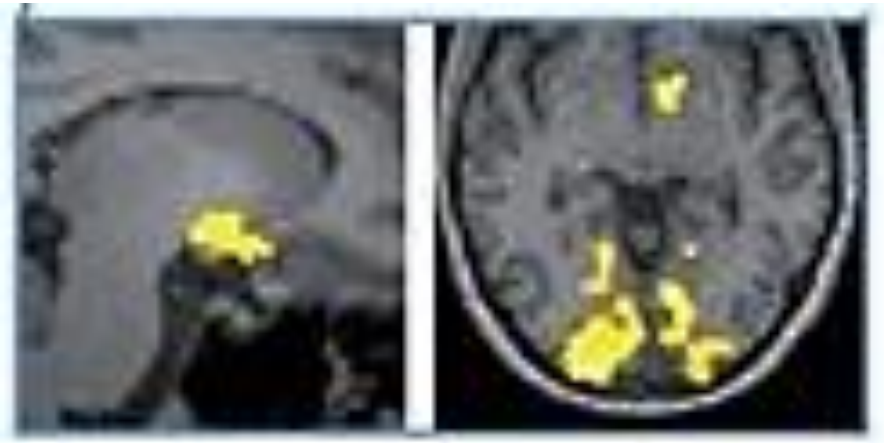
Messina et al., *J Neurology* 2020, 267:60–769; Skorobogatykh et al., *J Headache and Pain, 2019, 20: 108*

Premonitory Phase – Hypothalamic and Cortical Activation

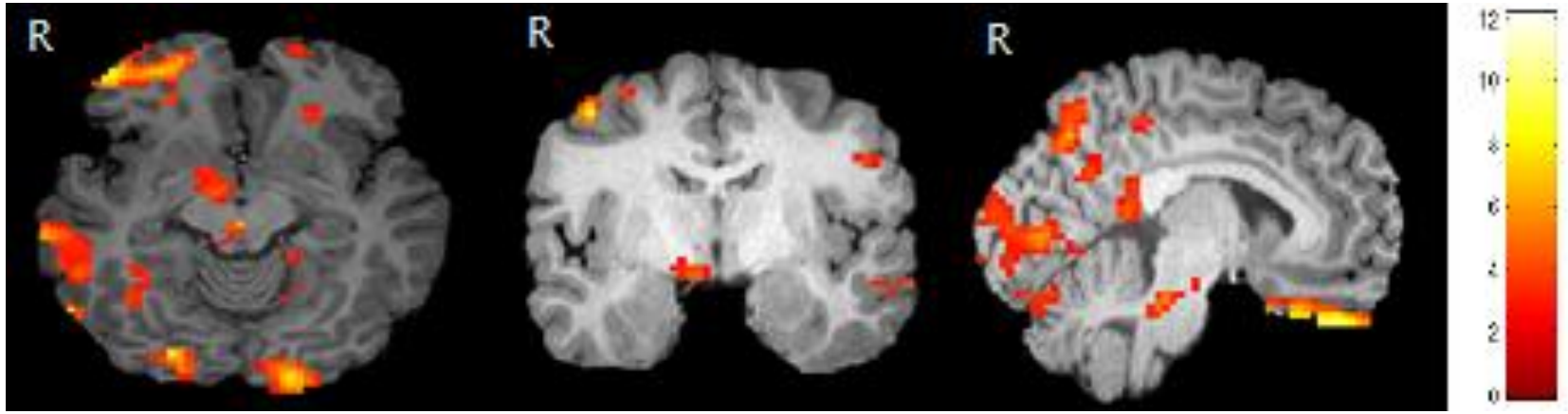
Spontaneous Attacks (PET imaging)



Spontaneous Attacks (fMRI imaging)



GTN-induced Attacks (PET imaging)



Denuelle M. et al. Headache, 2007: 47:1418-1426; Maniyar F. et al. *Brain*, 2016 , 137(1): 232–241; Schulte and May, *Brain*, 2016, 139:7(1987–1993)

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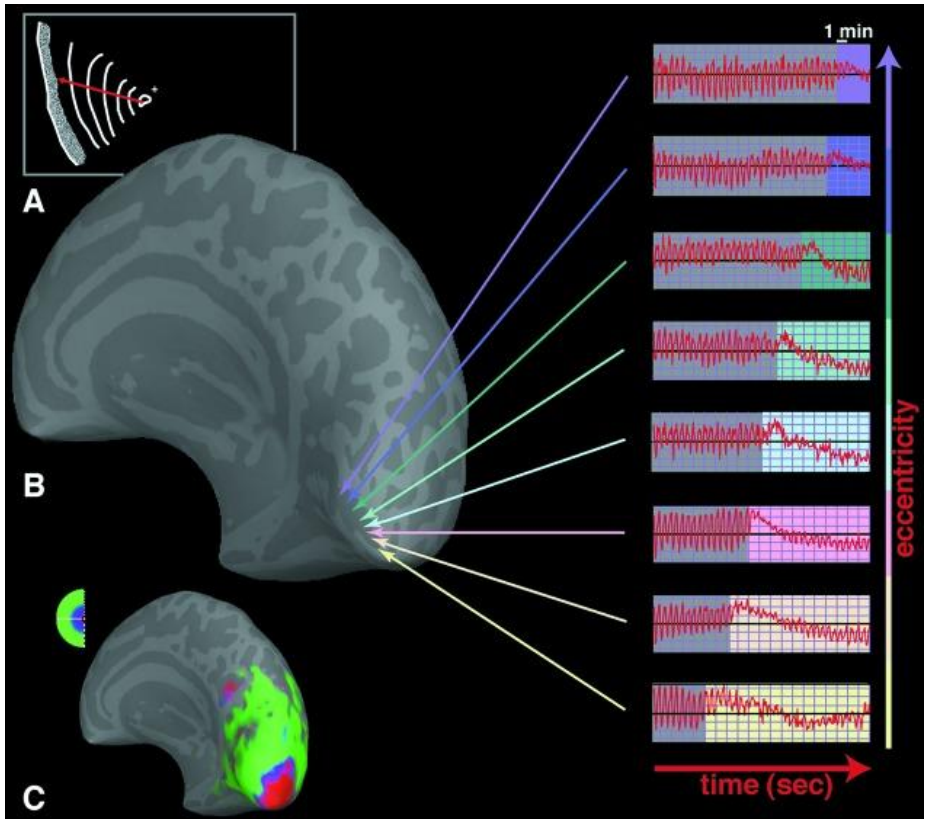
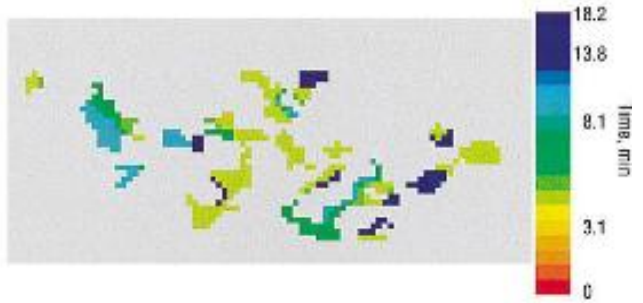
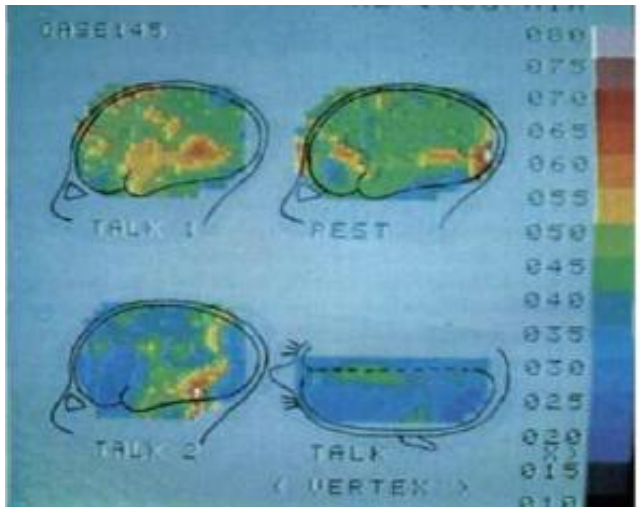
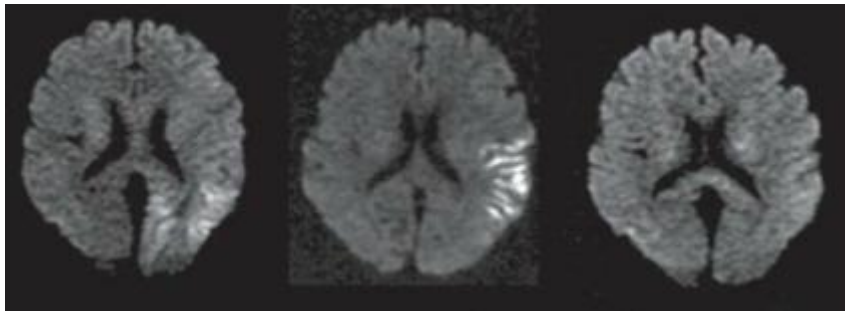
Migraine Aura–
Cortical Spreading Depression



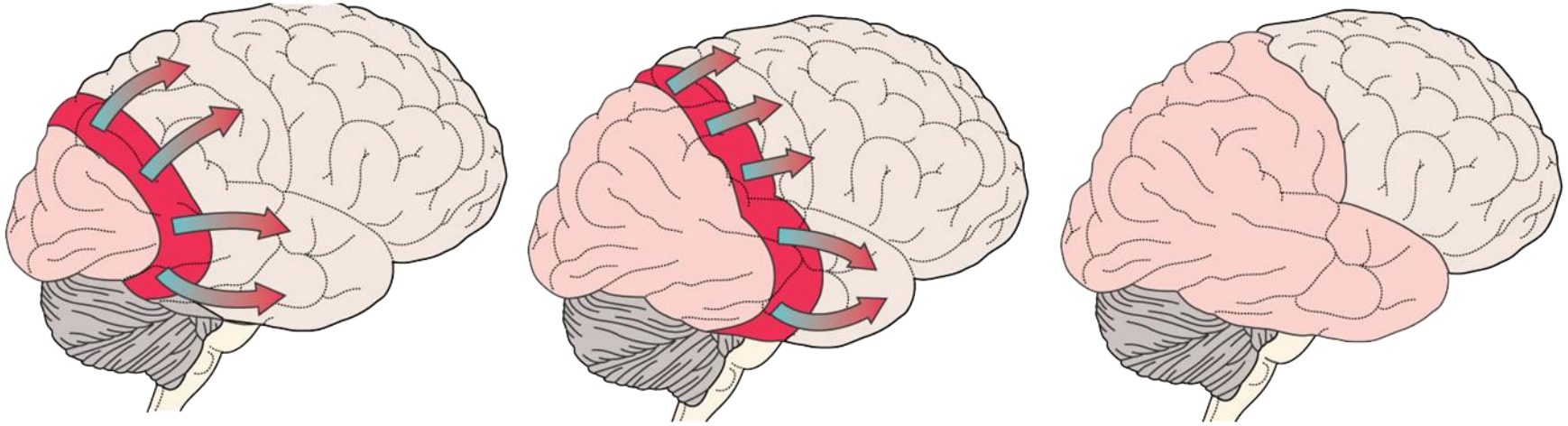






Hadjikhani et al., PNAS (2001), 98, 84687-4692; Olesen et al., The Lancet, 2009, 8(7): 679-690; Cao et al., *Arch Neurol.* 1999;56(5):548-554; Bereczki et al., Headache 2008, 48(8):1226-9;Olesen et al., Ann Neurol, 1981 Apr;9(4):344-52

Migraine Aura–
Cortical Spreading Depression



- Slow, self-propagating wave of depolarization of neurons and glia activation
- Results in an initial hyperaemic phase followed by an oligaemic phase
- Does not cross cerebral hemispheres or spreads to deeper brain structures

Olesen et al., The Lancet, 2009, 8(7): 679-690

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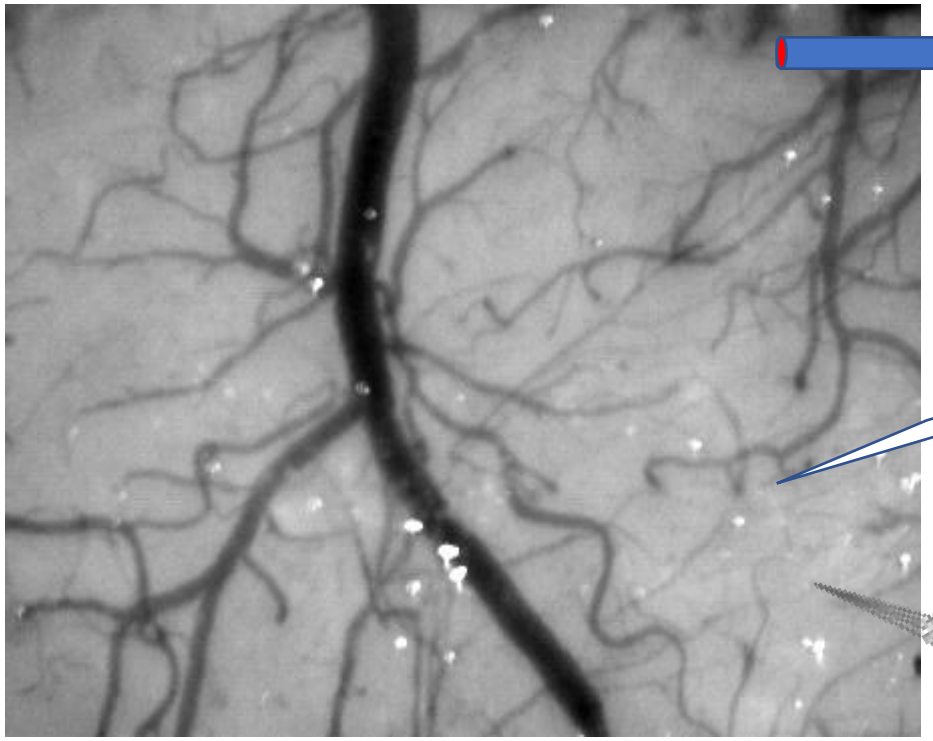
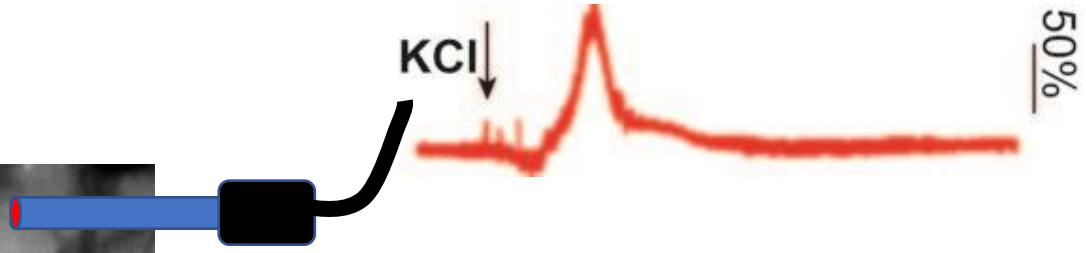
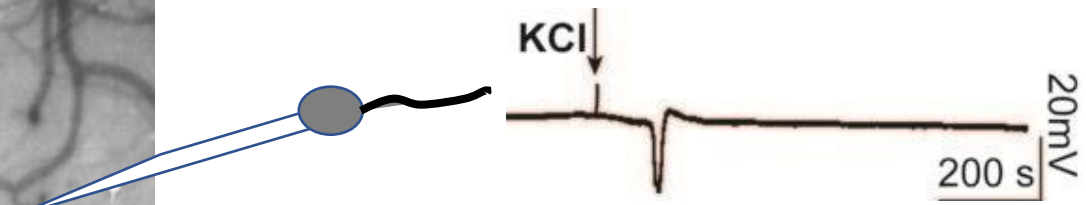
Migraine Aura– Cortical Spreading Depression

Laser Doppler: Cerebral blood flow measurements

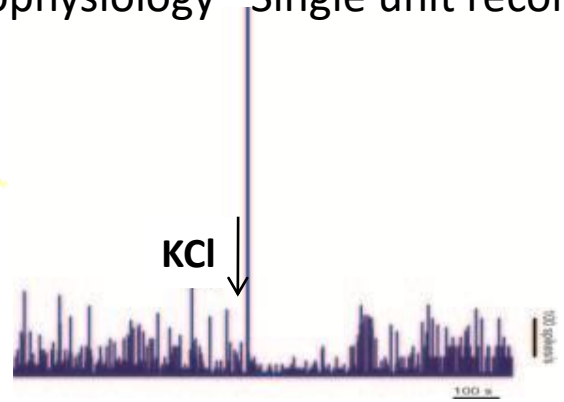




Electrophysiology– Ag/AgCl recordings:
Field potential/ DC-shift



Electrophysiology– Single unit recordings: Spikes/s



Andreou Lab

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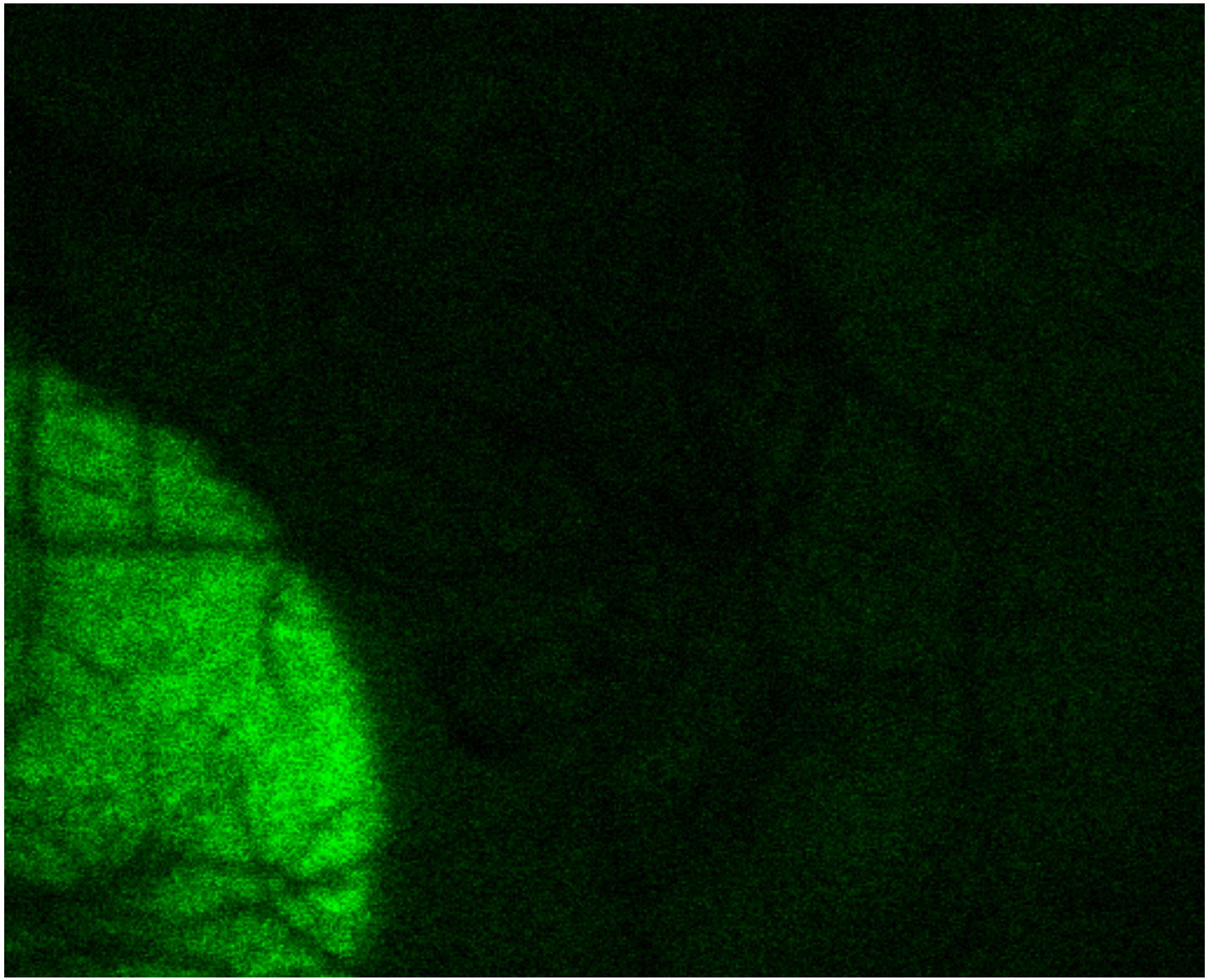
Migraine Aura–
Cortical Spreading Depression



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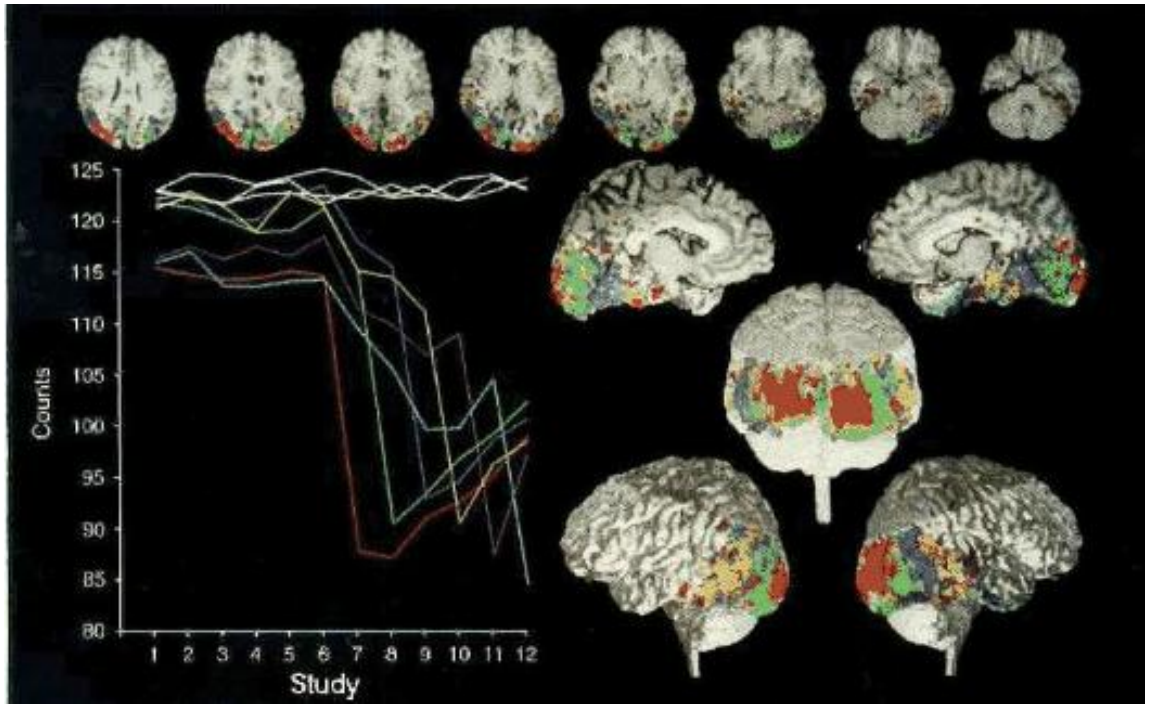
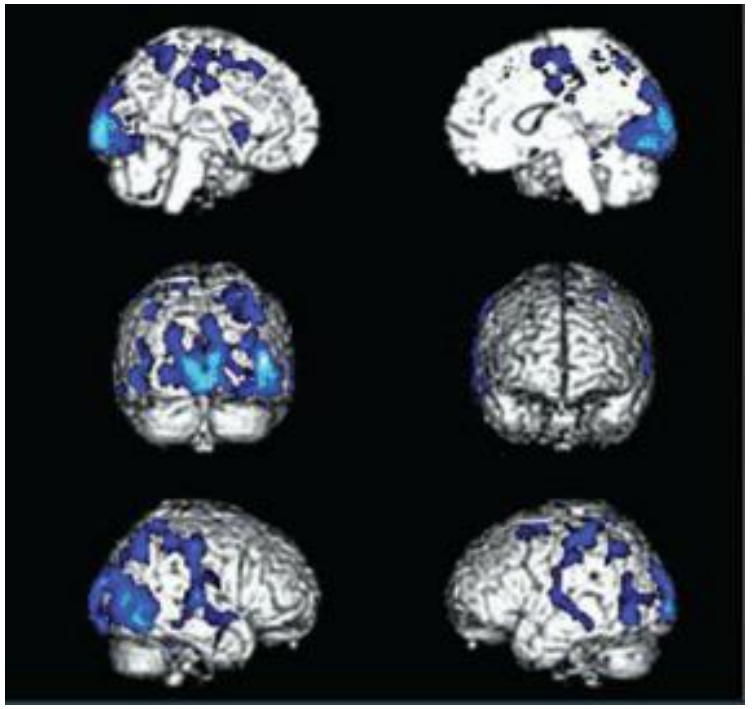
Cortical “Waves” in Migraine *Without* Aura – Cortical Hypoperfusion

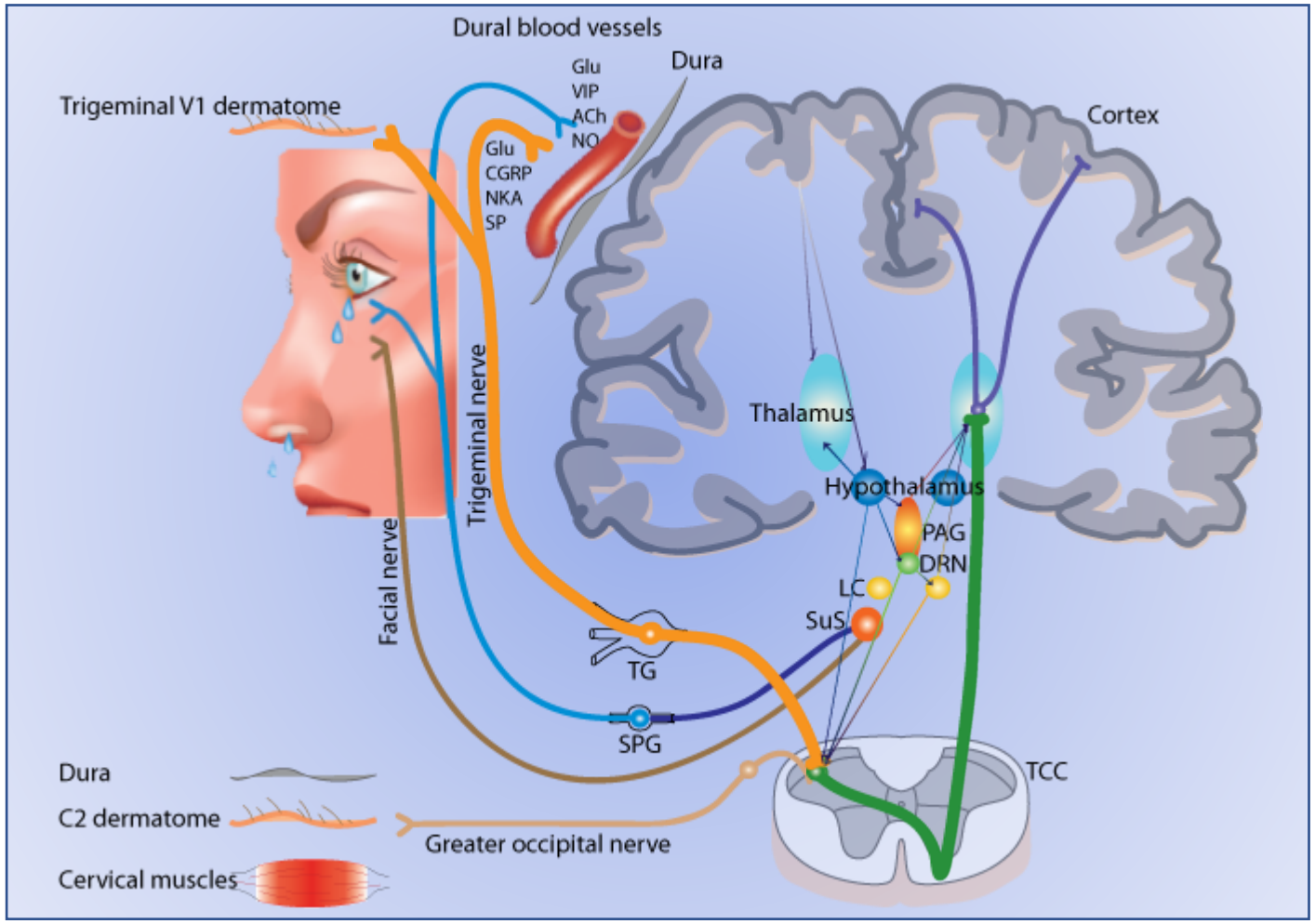




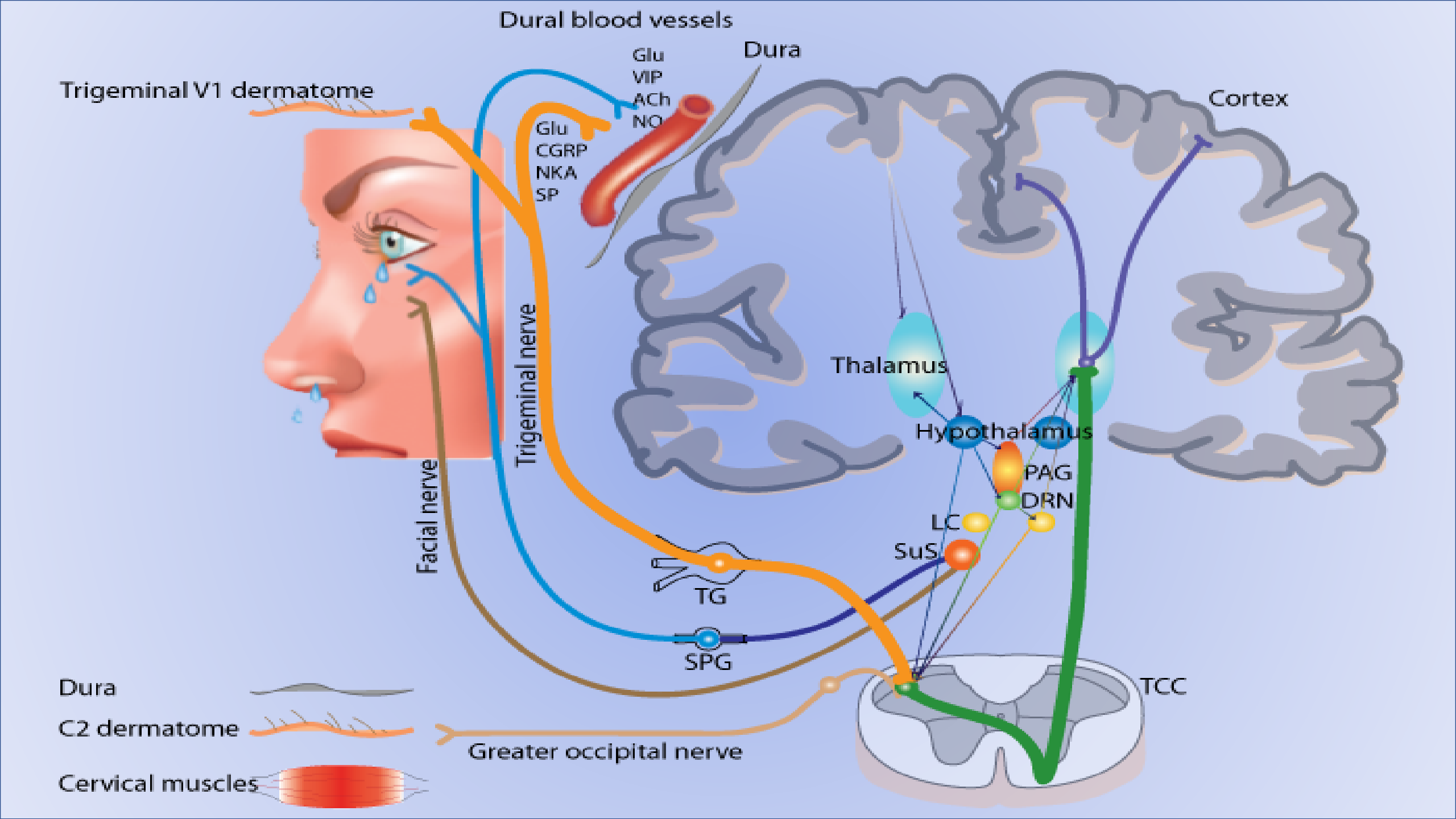
? Cortical activation of a lower threshold than the one required to develop cortical spreading depression (*silent aura*)**?**

Woods et al., N Engl J Med 1994; 331:1689-1692; Denuelle et al., Cephalalgia 2008 Aug;28(8):856-62

Ascending Trigeminothalamic Pathway Sensory – Information from the Region of Head and Neck



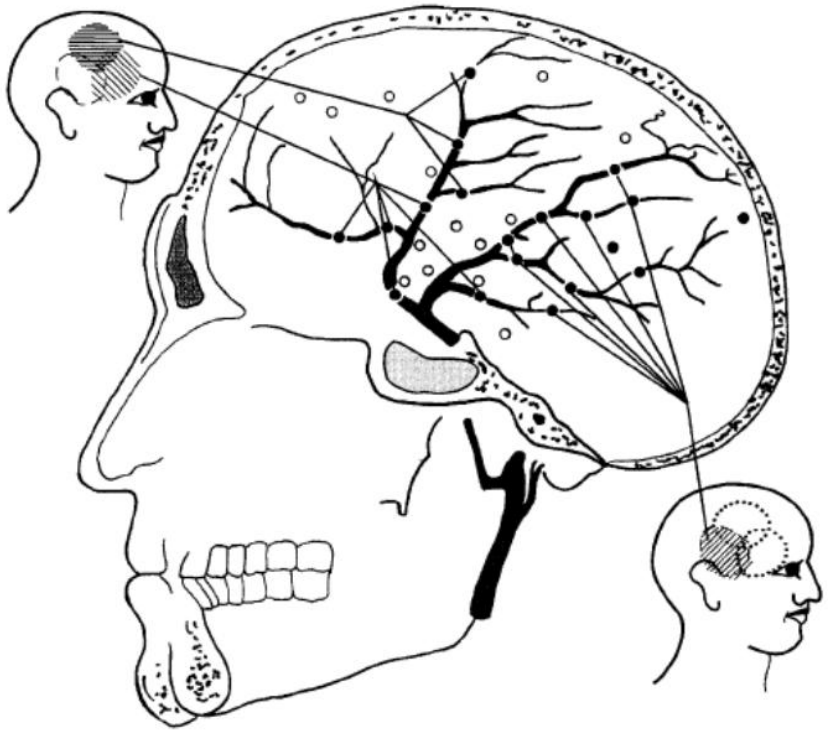
Andreou et al., Expert Rev Neuroth, 2010;10(3):389-411


Dural blood vessels
Dura
Glu
VIP
ACh
NO
Trigeminal V1 dermatome
Glu
CGRP
NKA
SP
Cortex
Trigeminal nerve
Thalamus
Hypothalamus
PAG
DRN
LC
SuS
Facial nerve
TG
SPG
TCC
Dura
C2 dermatome
Greater occipital nerve
Cervical muscles

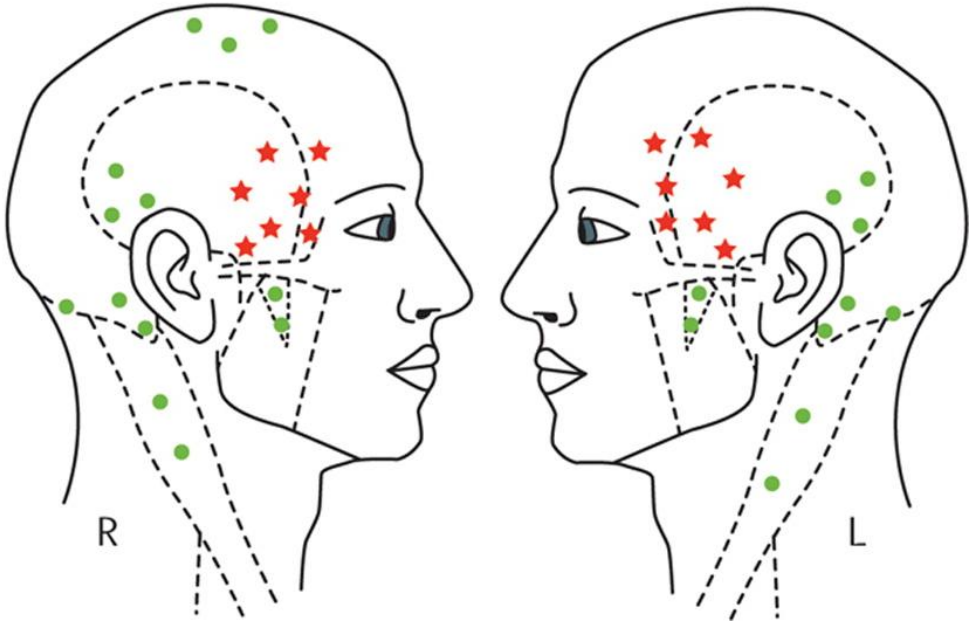
The Role of the Trigeminal System

- The referred pain patterns of migraine headache are similar to the locations of referred pain after stimulation of cerebral arteries

Wolff's Headache – Stimulation of Meningeal Structures Produces Headache-like Pain



Sensitive structures of the meninges and areas of referred pain



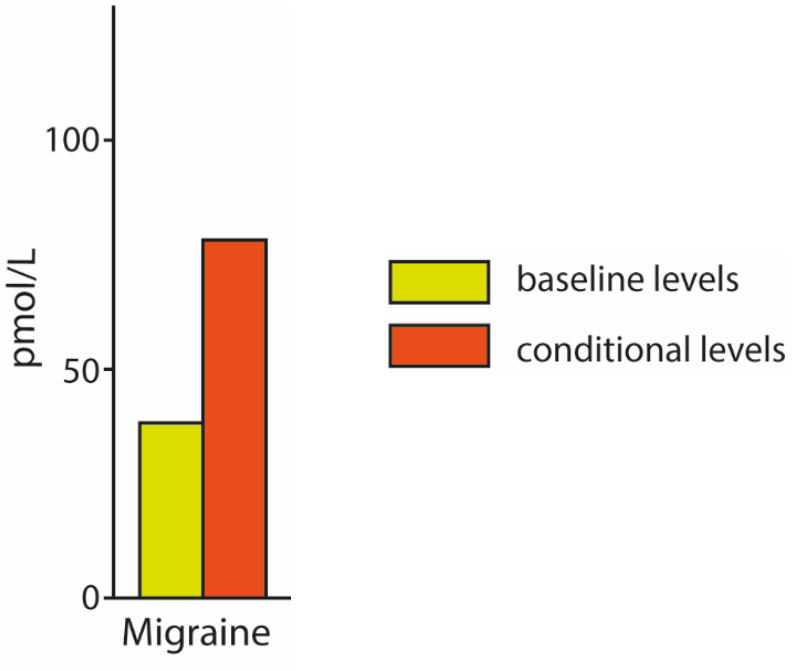
Correlation of pain and tenderness during attacks of migraine (★ pain, ● tenderness)

Penfield WA. Assoc Res Nerv Ment Dis. 1935; 15:399-416
Ray BS, Wolff HG. Arch Surg. 1940; 41:813-856
Olesen et al., Lancet Neurol 2009; 8: 679–90

The Role of the Trigeminal System

- The referred pain patterns of migraine headache are similar to the locations of referred pain after stimulation of cerebral arteries

- CGRP levels are increased during a migraine attack



Goadsby et al., Ann Neurol. 1990 Aug;28(2):183-7
Zagami et al., Neuropeptides. 1990 Jun;16(2):69-75
Goadsby et al., Ann Neurol. 1988 Feb;23(2):193-6

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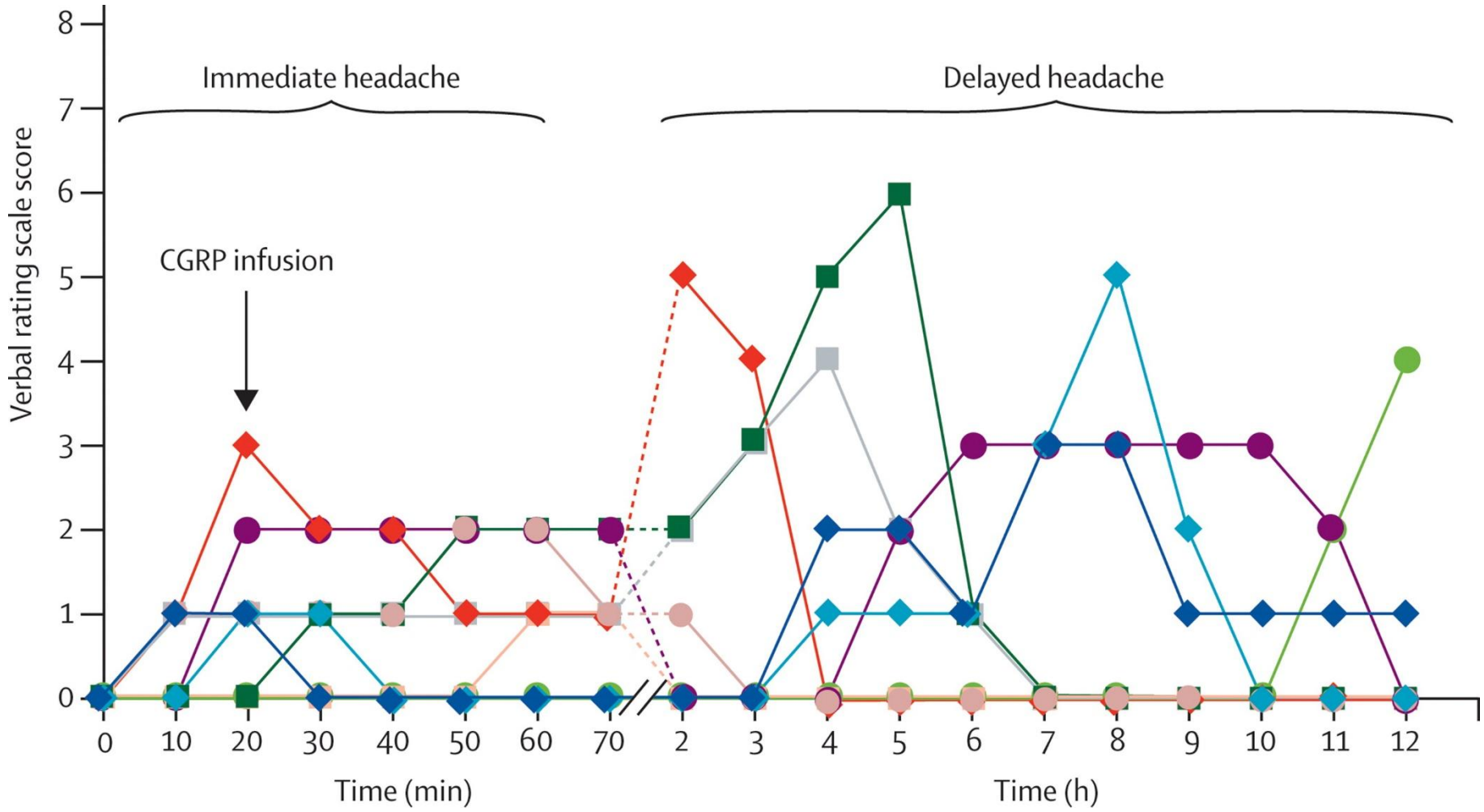
The Role of the Trigeminal System

- The referred pain patterns of migraine headache are similar to the locations of referred pain after stimulation of cerebral arteries
- CGRP levels are increased during a migraine attack
- Chemicals that do not cross the blood-brain barrier can trigger a migraine attack in sufferers (e.g. CGRP, Histamine)

Example: Systemic Administration of CGRP Can Induce Migraine Attacks



Lassen et al., Cephalalgia (2002), 22:54-61

The Role of the Trigeminal System

- The referred pain patterns of migraine headache are similar to the locations of referred pain after stimulation of cerebral arteries
- CGRP levels are increased during a migraine attack
- Chemicals that do not cross the blood-brain barrier can trigger a migraine attack in sufferers (CGRP, Histamine)
- Effective migraine treatments do not cross the blood-brain barrier (e.g. Triptans, Botulinum toxin A, CGRP mAbs)

Example: BOTOX® in the Treatment of Chronic Migraine

Long-term significant reduction of headache days by BOTOX® – a peripherally acting treatment[1–3]

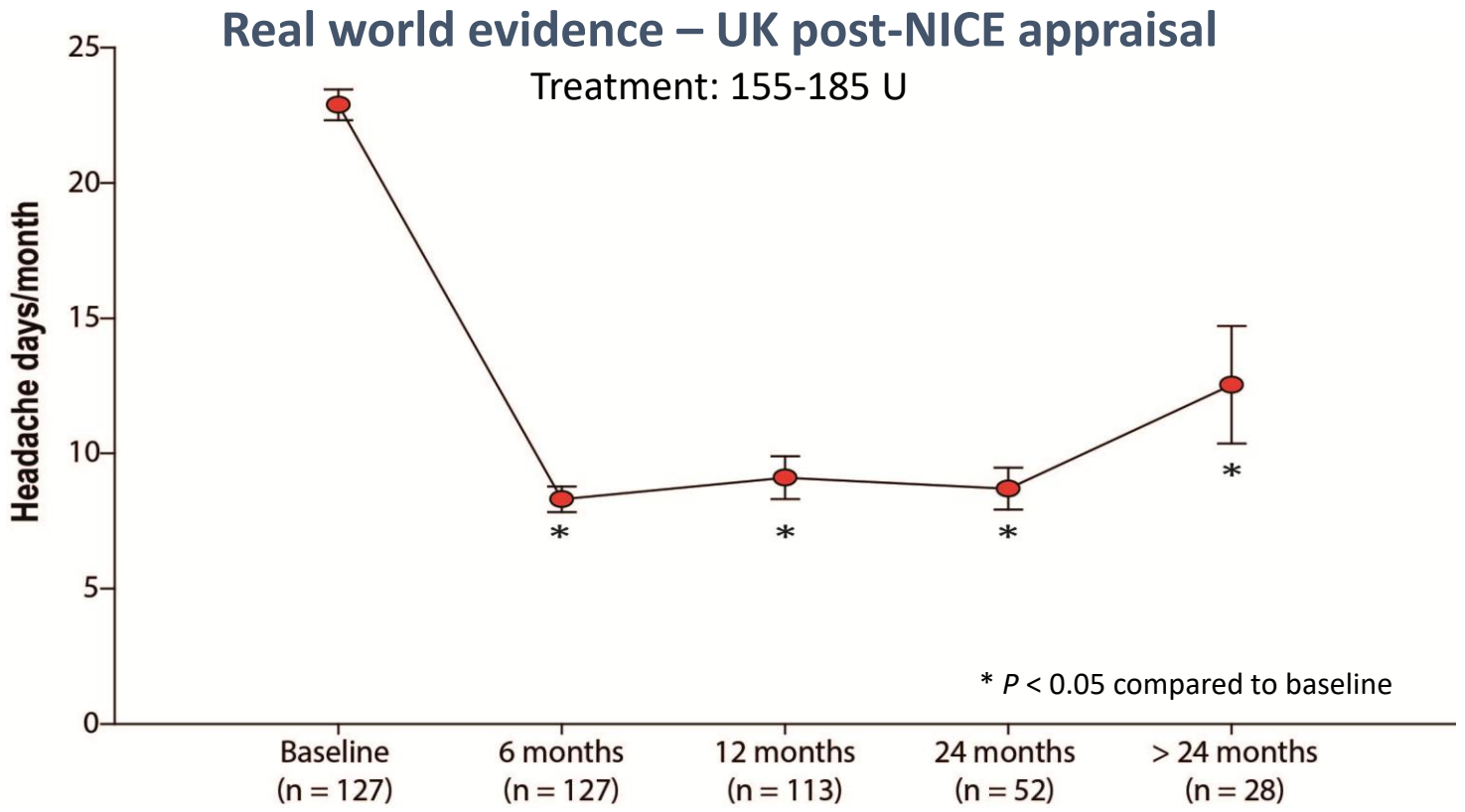
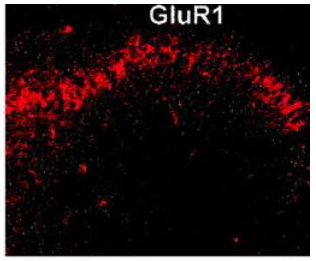


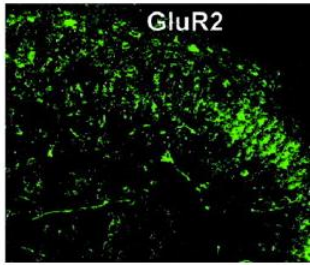
Figure adapted from Andreou AP, *et al*. 2018.

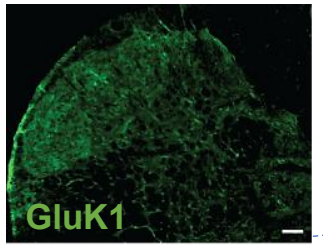
NICE, National Institute for Health and Care Excellence.

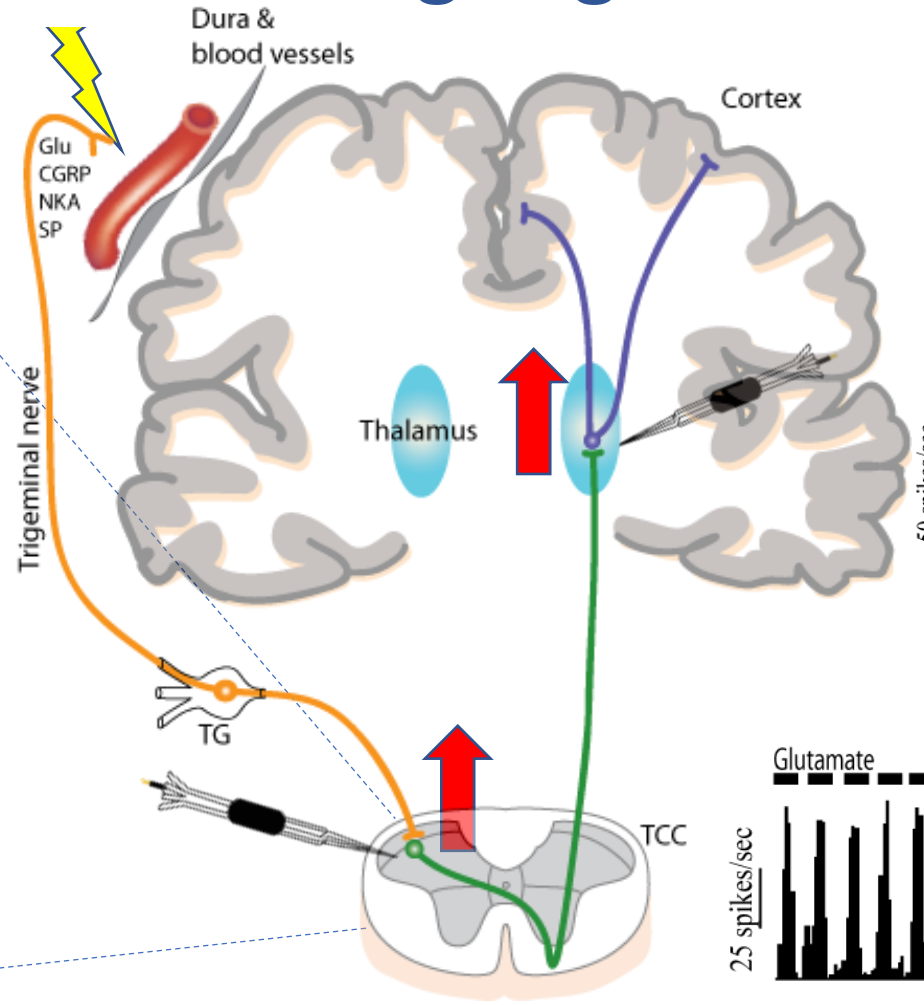
1. Andreou AP, *et al. Eur J Neurol*. 2018;25(8):1069-e83; 2. Aurora SK, *et al. Headache*. 2011;51(9):1358–1373;
3. Aurora SK, *et al*. *Acta Neurol Scand*. 2014;129(1):61–70.

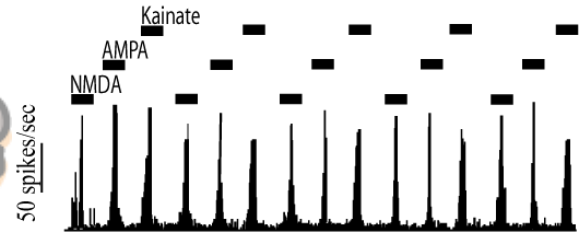
Glutamate– The Excitatory Neurotransmitter in the Ascending Trigeminal Pathway

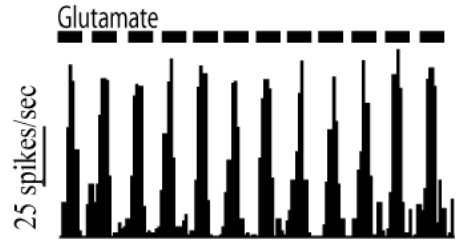












Adapted from Andreou AP et al*, Expert Rev. Neurother. 2010*, 10(3): 389-411; Andreou A. *Discovery.ucl.* 2009. eprint/15783; Engelman et al., *J Neurosc*. T1999, 19(6):2081–2089

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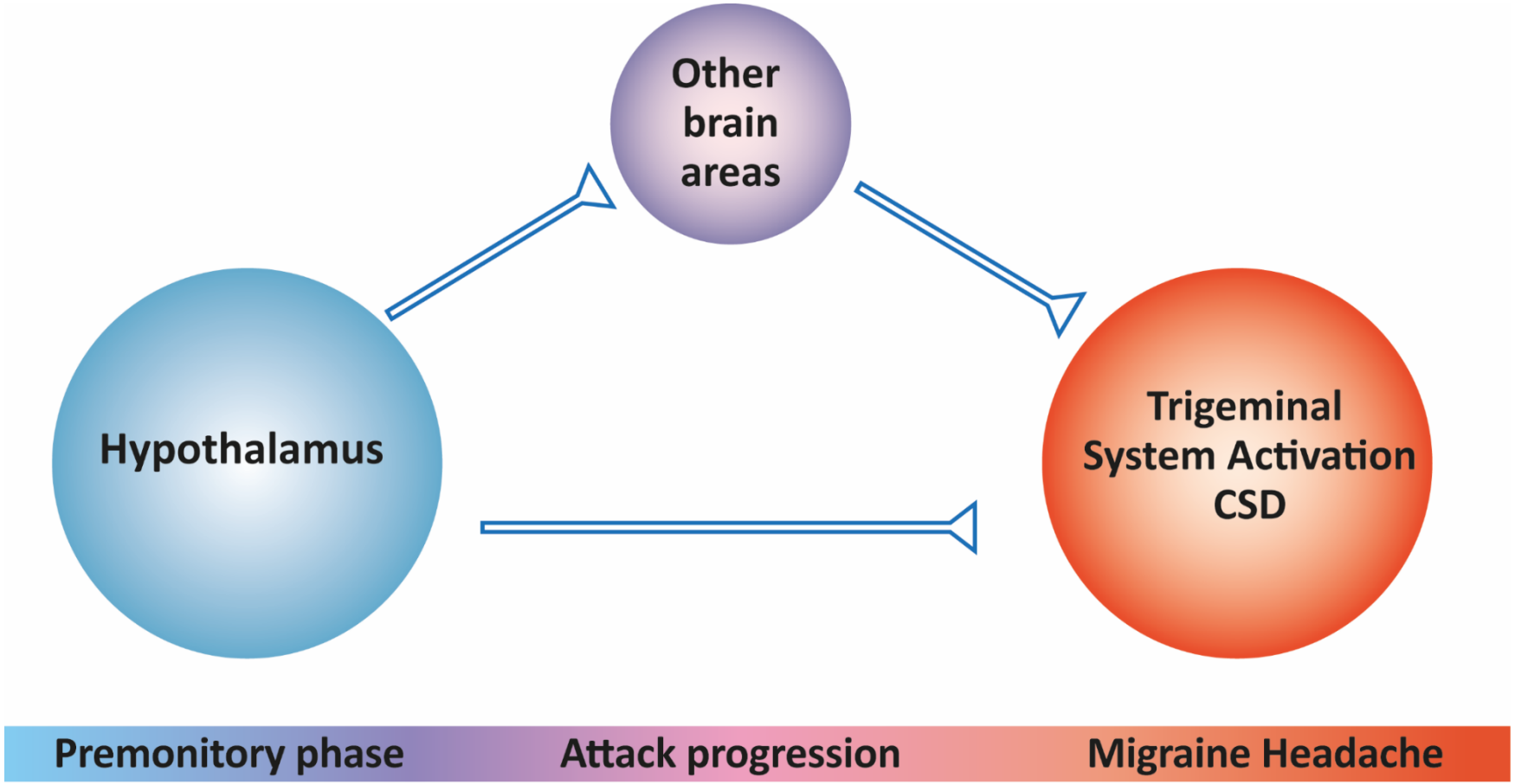
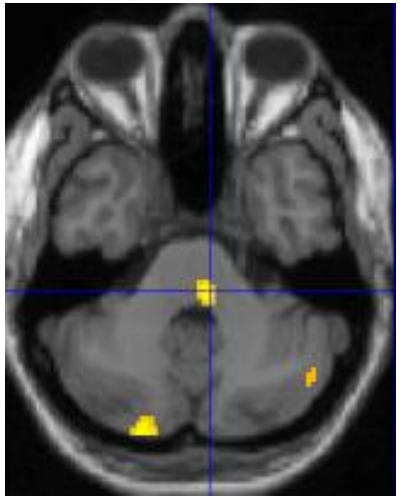
How is Migraine Headache Generated Following Hypothalamic Activation?

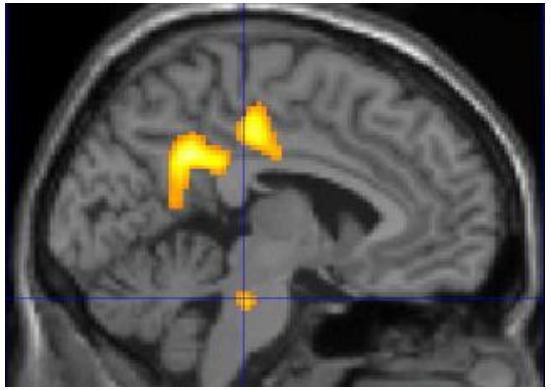


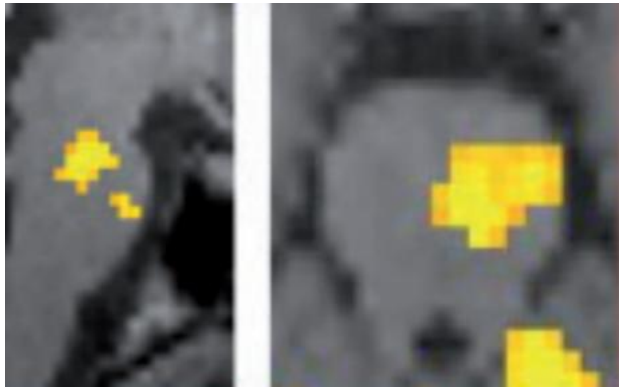
Andreou & Edvinsson, J Headache Pain. 2019 Dec 23;20(1):117

Brainstem Activation During the Headache Phase

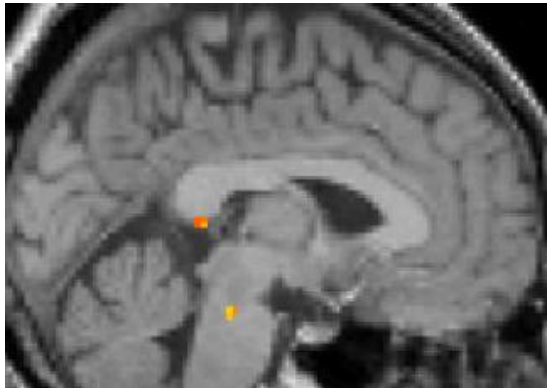
Spontaneous Migraine Attacks







GTN-Triggered Migraine Attacks

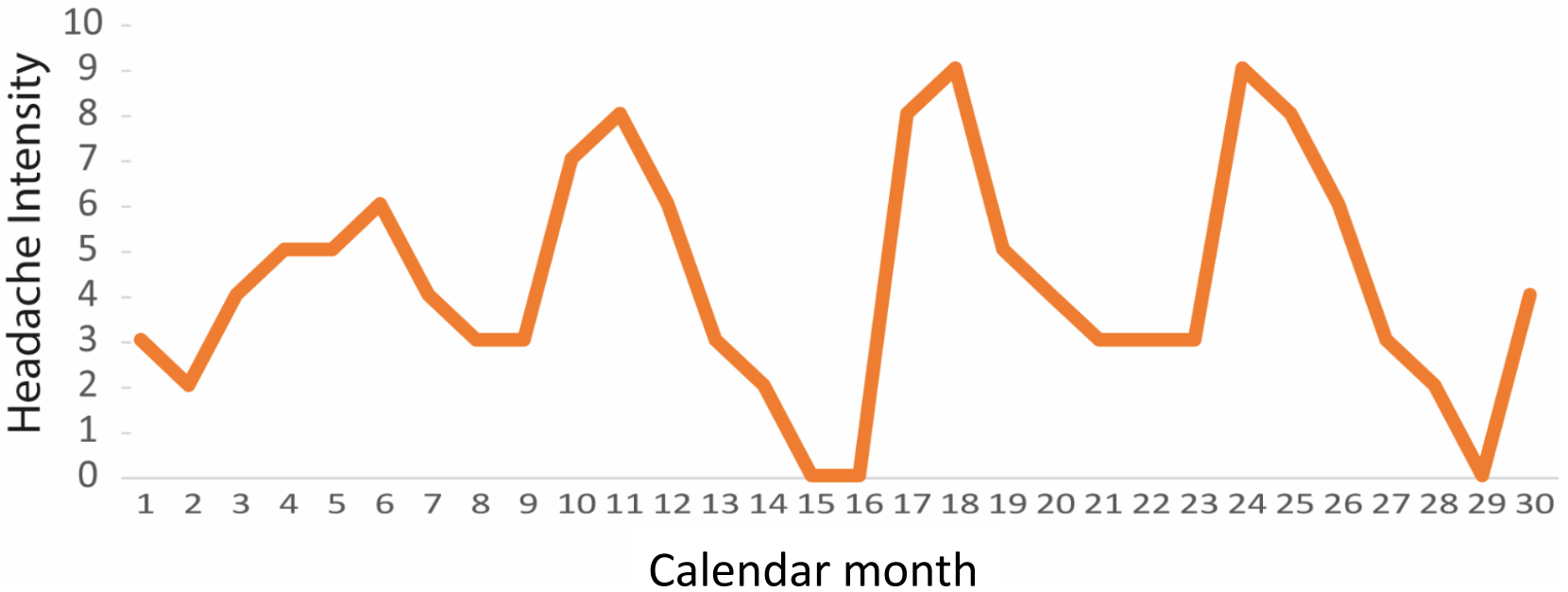


Afridi et al., Brain 2005;128:932-9; Afridi S.et al., Arch Neurol 2005;62:1270-75
Bahra et al., Lancet 2001;357:1016-17; Schulte & May. *Brain,* 2016: 139; 1987–1993

HEADACHE RESEARCH

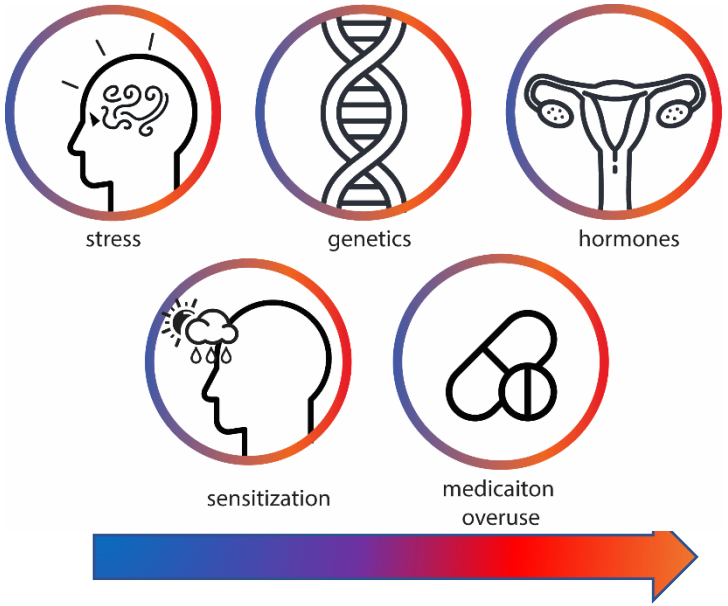
Chronic Migraine

- Headache occurring on ≥ 15 or more days/month for more than three months
- At least 8 days per month, have the features of migraine headache (photophobia, phonophobia, worsen by movement, nausea, aura…)

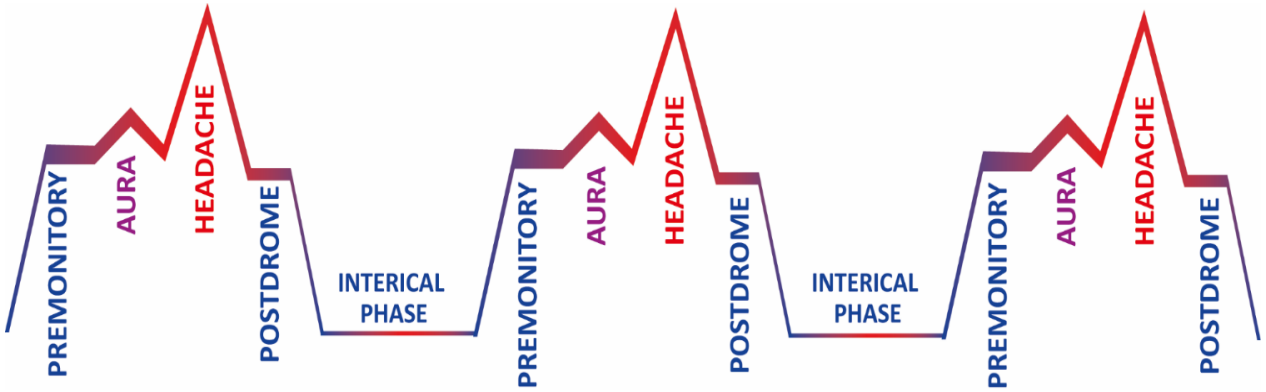


The International Classification of Headache Disorders 3rd edition

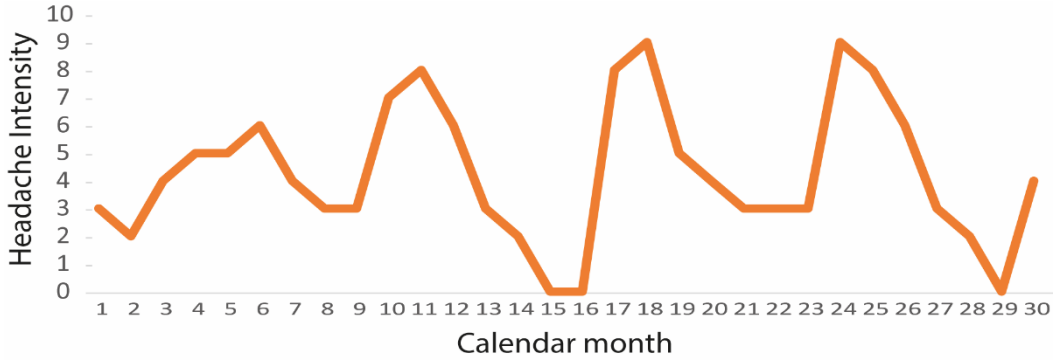
Migraine – A Cycling Disorder with Evolutive Characteristics



Episodic migraine



Chronic migraine



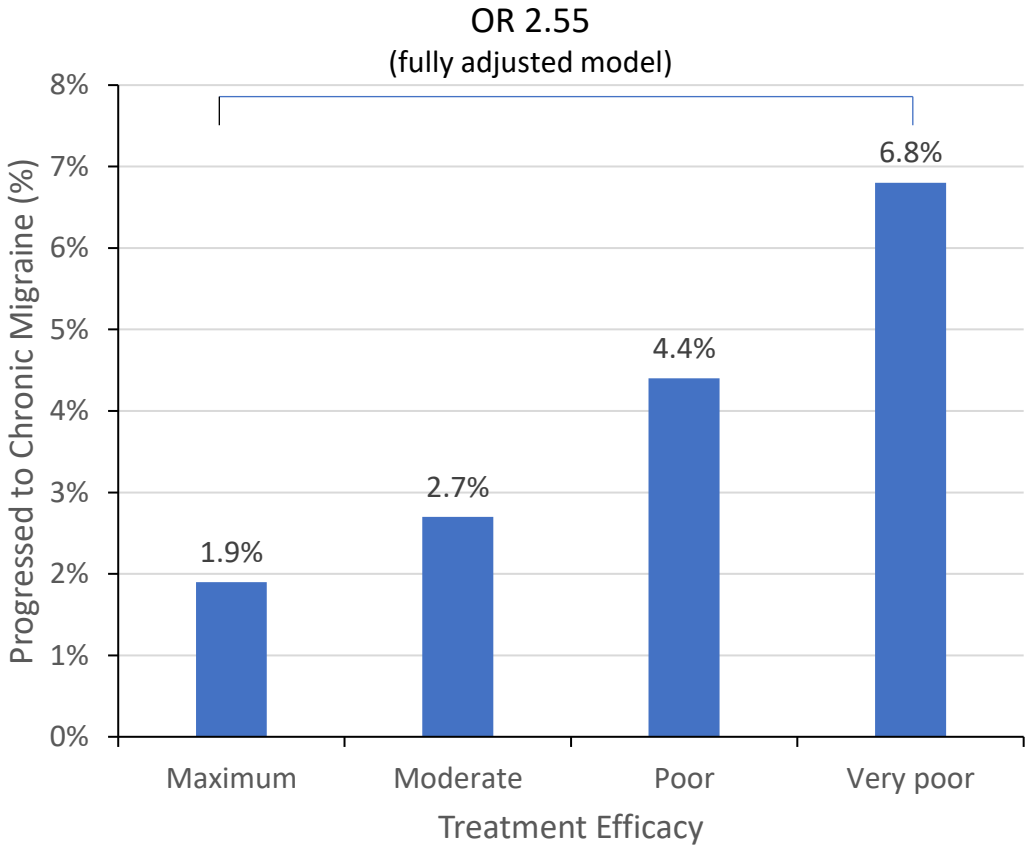
Poor Acute Treatment Associated with Chronic Migraine Risk

American Migraine Prevalence and Prevention Study

- N=5,681 with EM in 2006 → 3.1% progressed to CM

Conclusion:

- Inadequate acute treatment efficacy was associated with an increased risk of new onset CM over the course of 1 year
- Optimal acute treatment might prevent migraine progression

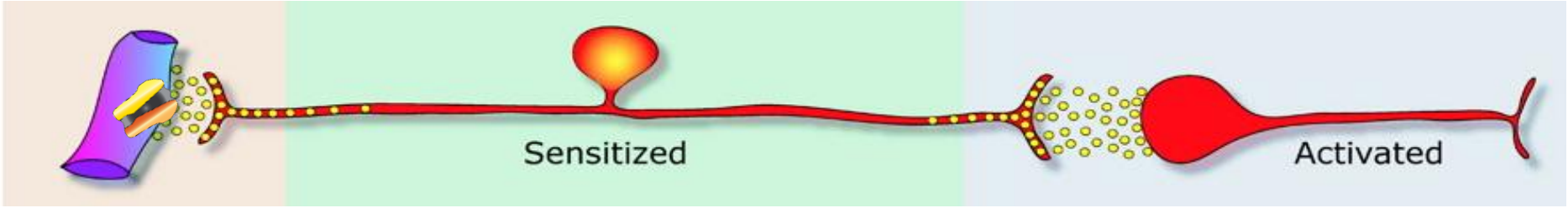


CM, chronic migraine; EM, episodic migraine

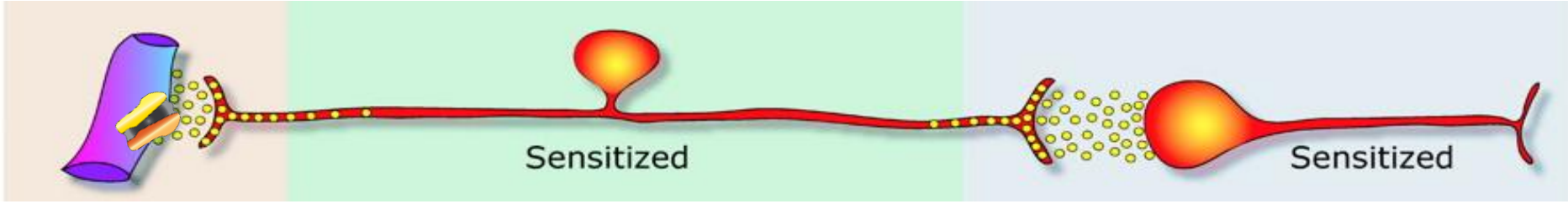
Lipton RB, et al. *Neurology*. 2015;84:688-695.

Peripheral Sensory Inputs are Important in Sustaining Central Drive in Pain

Peripheral sensitisation



Central sensitisation



Pericranial tissue Peripheral first-order neuron Central second-order neuron

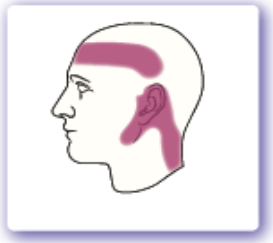
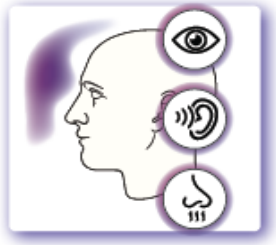
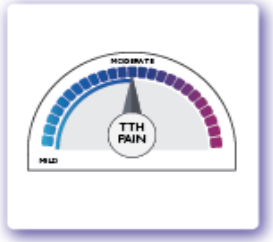
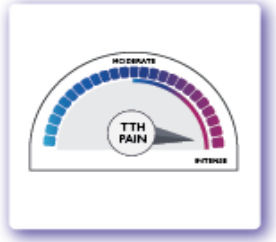
Figure adapted from Levy D, *et al*. 2004.

Levy D, *et al. Proc Natl Acad Sci U S A*. 2004;101(12):4274–4279.

Tension-Type Headache

HEADACHE RESEARCH

Tension-type headache vs. Migraine differential diagnosis

TENSION-TYPE HEADACHE	MIGRAINE
 Sensation of pressure or tightness, sometimes spreading into or from the neck	 Sensitivity to light, sound and smell Sometimes aura before onset
 Moderate but steady ache not affected by physical activity	 Moderate to severe pain aggravated by physical activity
 Bilateral pain often described like a band around the head	 Pounding or throbbing pain, often on one side of the head

Pathophysiology of TTH

Unknown

- Presence of pericranial and cervical muscle tenderness in TTH patients during attacks compared to controls
- Mechanical trigger points- Is excess pericranial muscle activity involved in the pathophysiology of TTH?

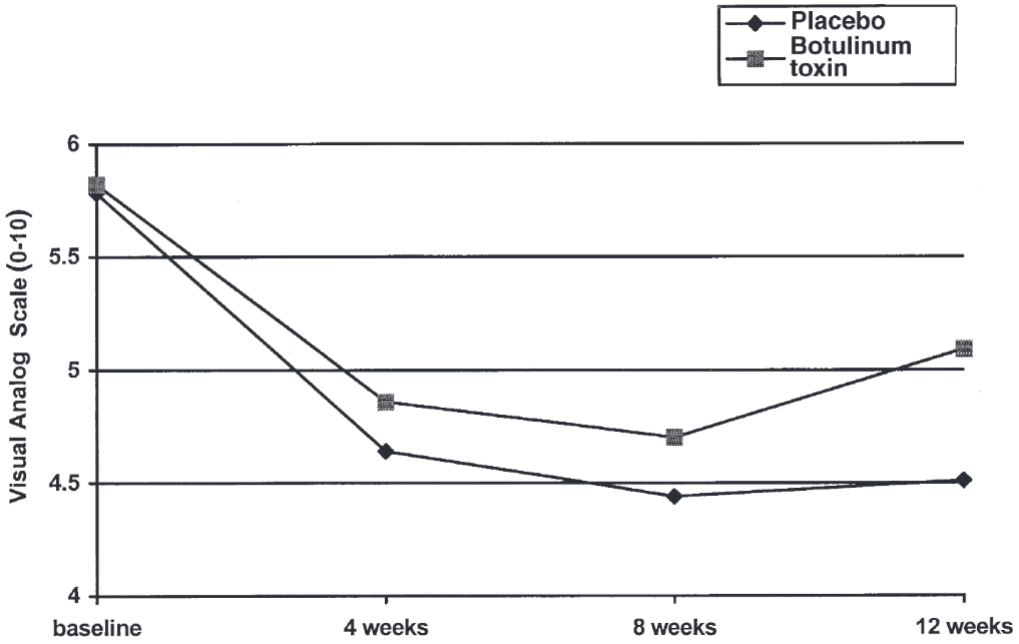
Ashina M. Cephalalgia 2004;24(3):161-172
Bendtsen L, Ferna´ ndez-de-la-Penas C. Curr Pain Headache Rep 2011; 15(6):451-458
Ashina M, Stallknecht B, Bendtsen L, et al. Brain 2002;125(pt 2):320-326
Ashina M, Stallknecht B, Bendtsen L, et al. Cephalalgia 2003;23(2):109-116

HEADACHE RESEARCH

Treatment of Tension-type Headache With Botulinum Toxin Type A: A Double-Blind, Placebo-Controlled Study

Jens D. Rollnik, MD; Oliver Tanneberger; Margot Schubert, MD; Udo Schneider, MD; Reinhard Dengler, MD

(*Headache* 2000;40:300-305)



Results.–After 4, 8, and 12 weeks, no significant differences between placebo and treatment could be observed (with respect to visual analog scale, frequency and duration of headache attacks, consumption of analgesics, pressure pain threshold, total tenderness score, and quality-of-life parameters).

Conclusions.–The findings of our study strongly support the hypothesis that peripheral mechanisms, such as increased muscle tenderness, only play a minor role in the pathogenesis of tension-type headache.

* Botulinum toxin A induces muscle paralysis by cleaving SNAP-25 at the neuromuscular junction

HEADACHE RESEARCH

Pathophysiology of TTH

Unknown

- Pericranial and cervical muscle tenderness compared to controls
- Absence of pericranial muscle activity or inflammation

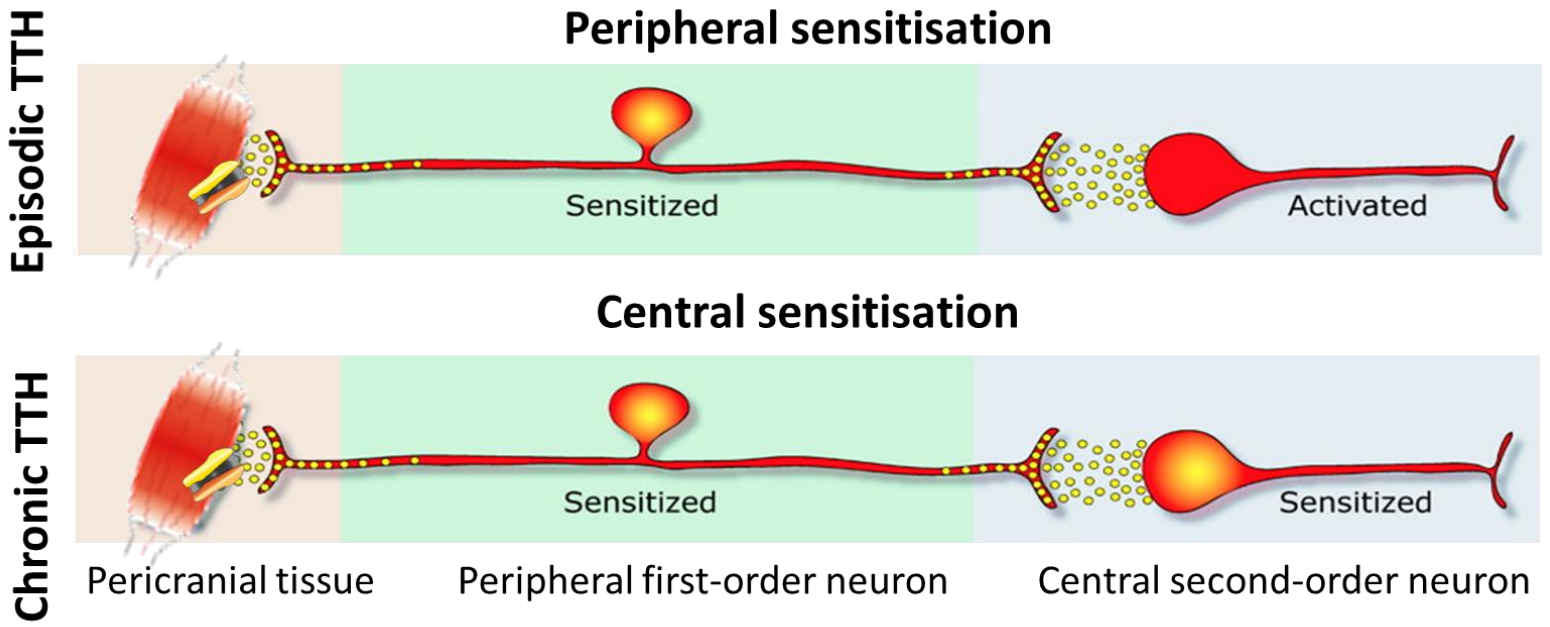


Figure adapted from Levy D, *et al*. 2004.

Ashina M. Cephalalgia 2004;24(3):161-172; Bendtsen et al.,. Curr Pain Headache Rep 2011; 15(6):451-458; Ashina et al. Brain 2002;125(pt 2):320-326

HEADACHE RESEARCH

International Classification of Headache Disorders

International Headache Society, 3rd Edition , 2018

	IHS code	Classification
Primary headaches	1.	Migraine
	2.	Tension-type headache
	3.	Trigeminal autonomic cephalalgias
	4.	Other primary headache disorders
Secondary headaches	5.	Headache attributed to trauma or injury to the head and/or neck
	6.	Headache attributed to cranial or cervical vascular disorder
	7.	Headache attributed to non-vascular intracranial disorder
	8.	Headache attributed to a substance or its withdrawal
	9.	Headache attributed to infection
	10.	Headache attributed to disorder of homoeostasis
	11.	Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structures
	12.	Headache attributed to psychiatric disorder
Painful cranial neuropathies, other facial pains and other headaches	13.	Painful lesions of the cranial nerves and other facial pain
	14.	Other headache disorders

HEADACHE RESEARCH

Trigeminal Autonomic Cephalalgias

HEADACHE RESEARCH

Trigeminal Autonomic Cephalalgias

3.1 Cluster headache
- 3.1.1 Episodic cluster headache
- 3.1.2 Chronic cluster headache

3.2 Paroxysmal hemicrania
- 3.2.1 Episodic paroxysmal hemicrania
- 3.2.2 Chronic paroxysmal hemicrania

3.3 Short-lasting unilateral neuralgiform headache attacks (SUNCT/SUNA)
- 3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
  - 3.3.1.1 Episodic SUNCT
  - 3.3.1.2 Chronic SUNCT
- 3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
  - 3.3.2.1 Episodic SUNA
  - 3.3.2.2 Chronic SUNA

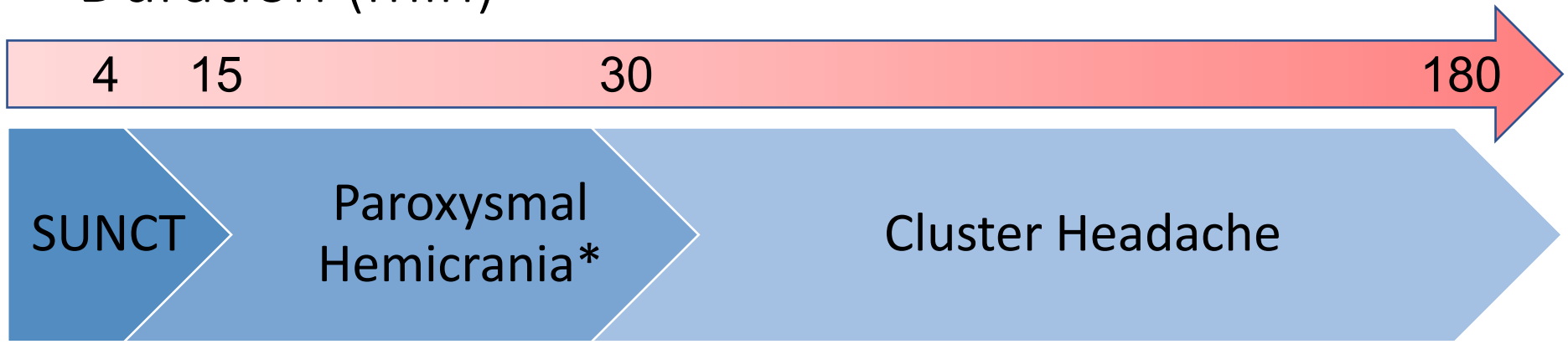
3.4 Hemicrania continua
- 3.4.1 Hemicrania continua, remitting subtype
- 3.4.2 Hemicrania continua, unremitting subtype

3.5 Probable trigeminal autonomic cephalalgia

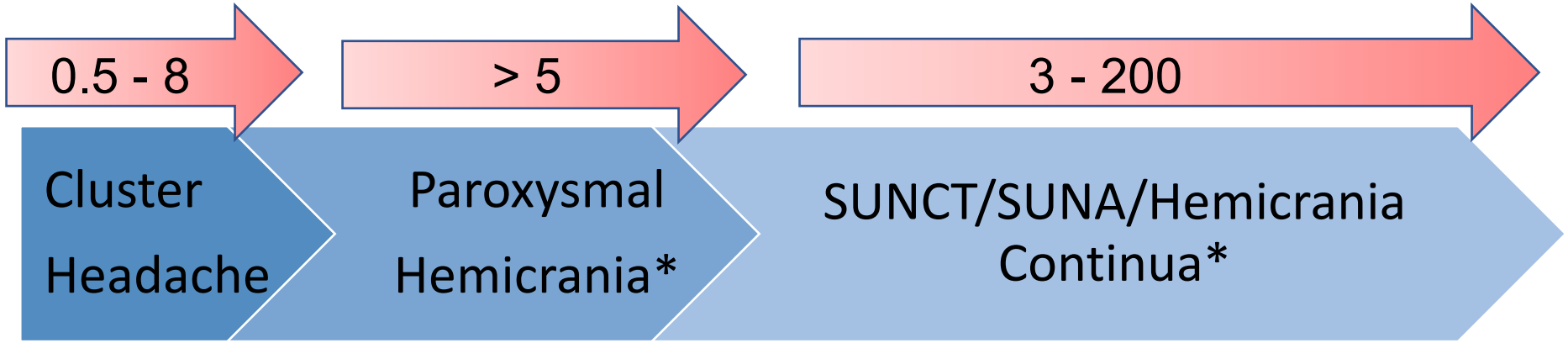
HEADACHE RESEARCH

Trigeminal Autonomic Cephalalgias (TACs)

- Duration (min)



- Frequency (attacks/day)



* Indomethacin responsive headaches

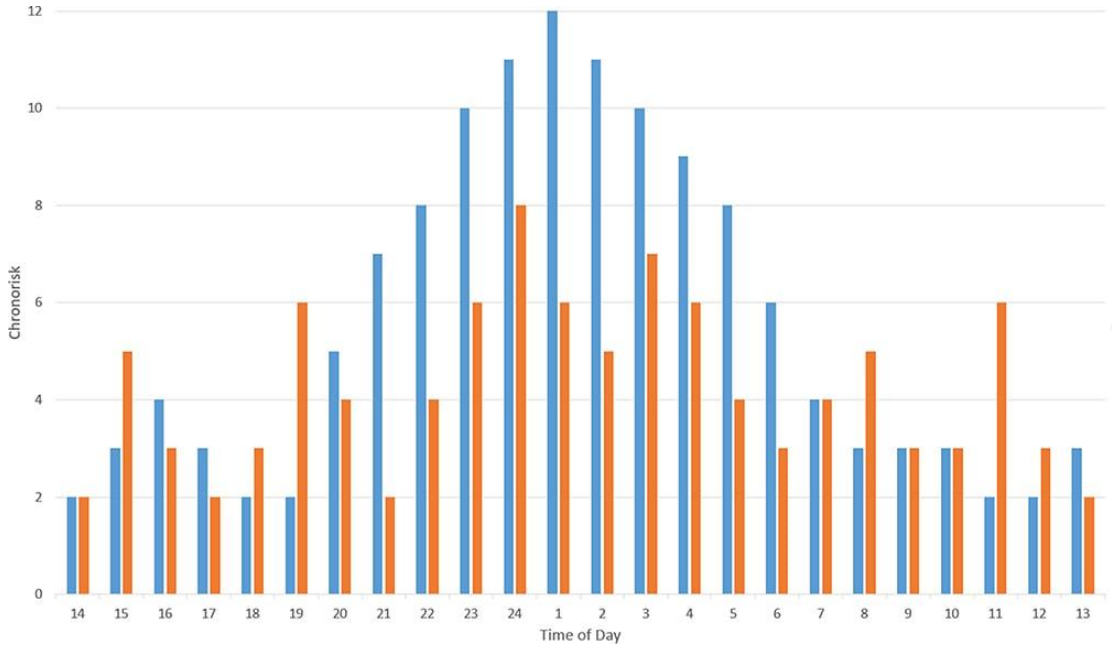
HEADACHE RESEARCH

Trigeminal Autonomic Cephalalgias – Cluster Headache

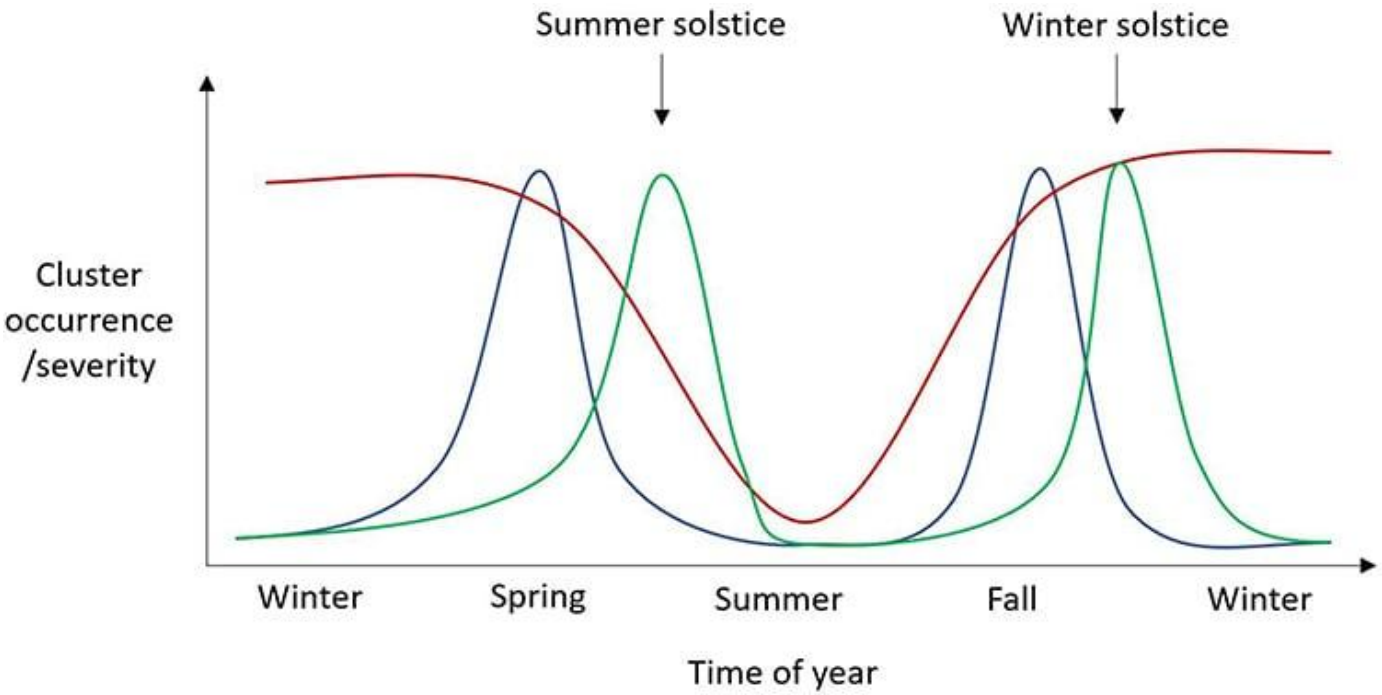
HEADACHE RESEARCH

Cluster Headache (CH) Chronobiology

Circadian rhythmicity



Cirannual rhythmicity



Red line – cluster occurrence/severity improves during the summer months, possibly due to number of daylight hours. Blue line – Clusters occur during the spring and autumn months. Green line – clusters occur around the time of the solstices, possibly due to an inability to synchronize the internal circannual pacemaker.

Barloese M. Current Understanding of the Chronobiology of Cluster Headache and the Role of Sleep in Its Management. Nat Sci Sleep. 2021;13:153-162

HEADACHE RESEARCH

Cluster Headache (CH) Pathophysiology

Fig. 1 Multi-subject GML analysis shows cerebral activation area in the posterior grey hypothalamus, ipsilateral to the pain side ($P < 0.001$ uncorrected for descriptive purposes), superimposed on a T1-weighted anatomical reference MR image in axial (**a**) and coronal (**b**) planes

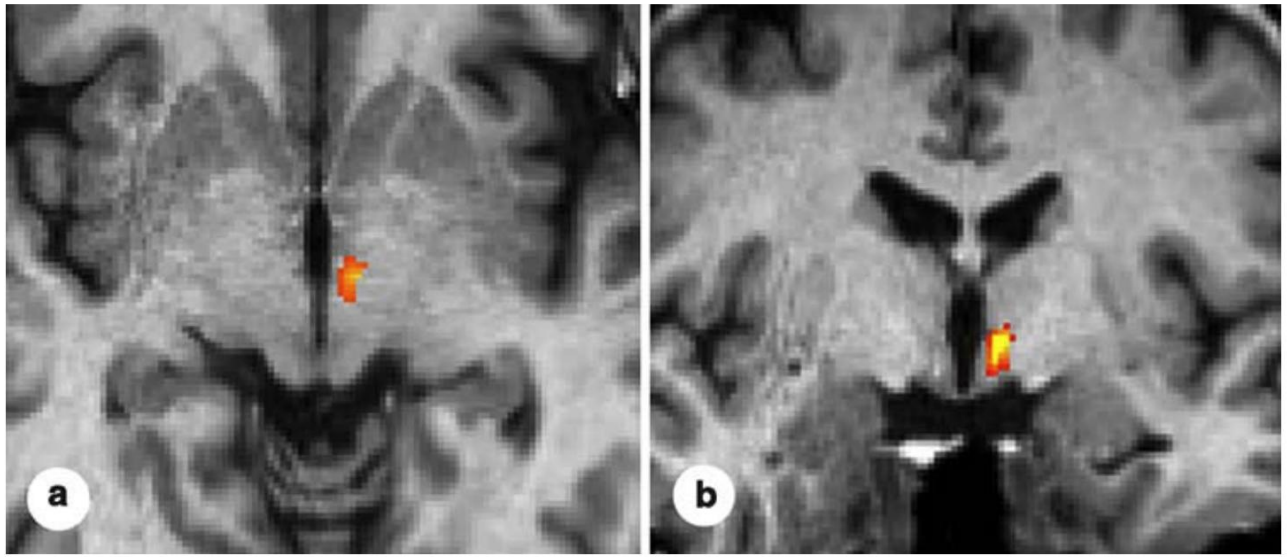
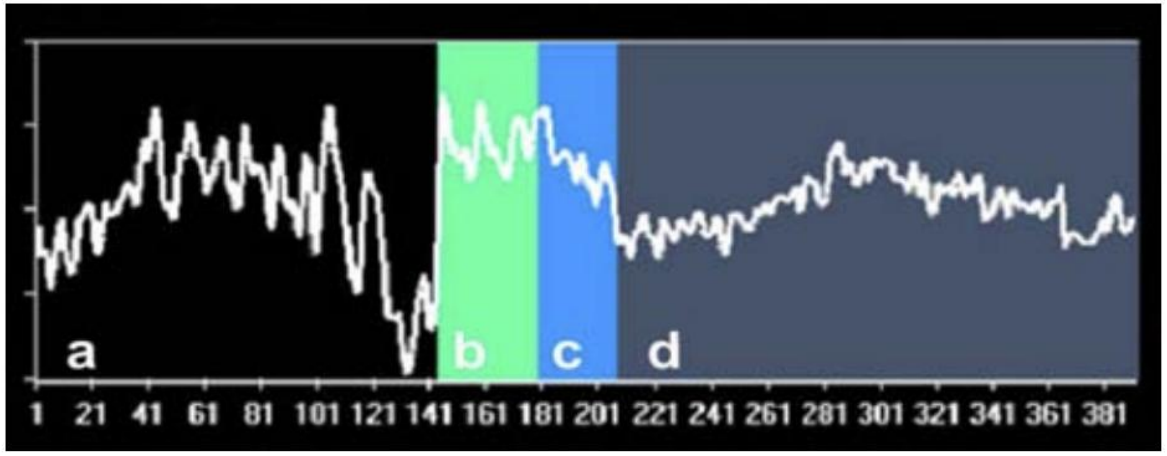
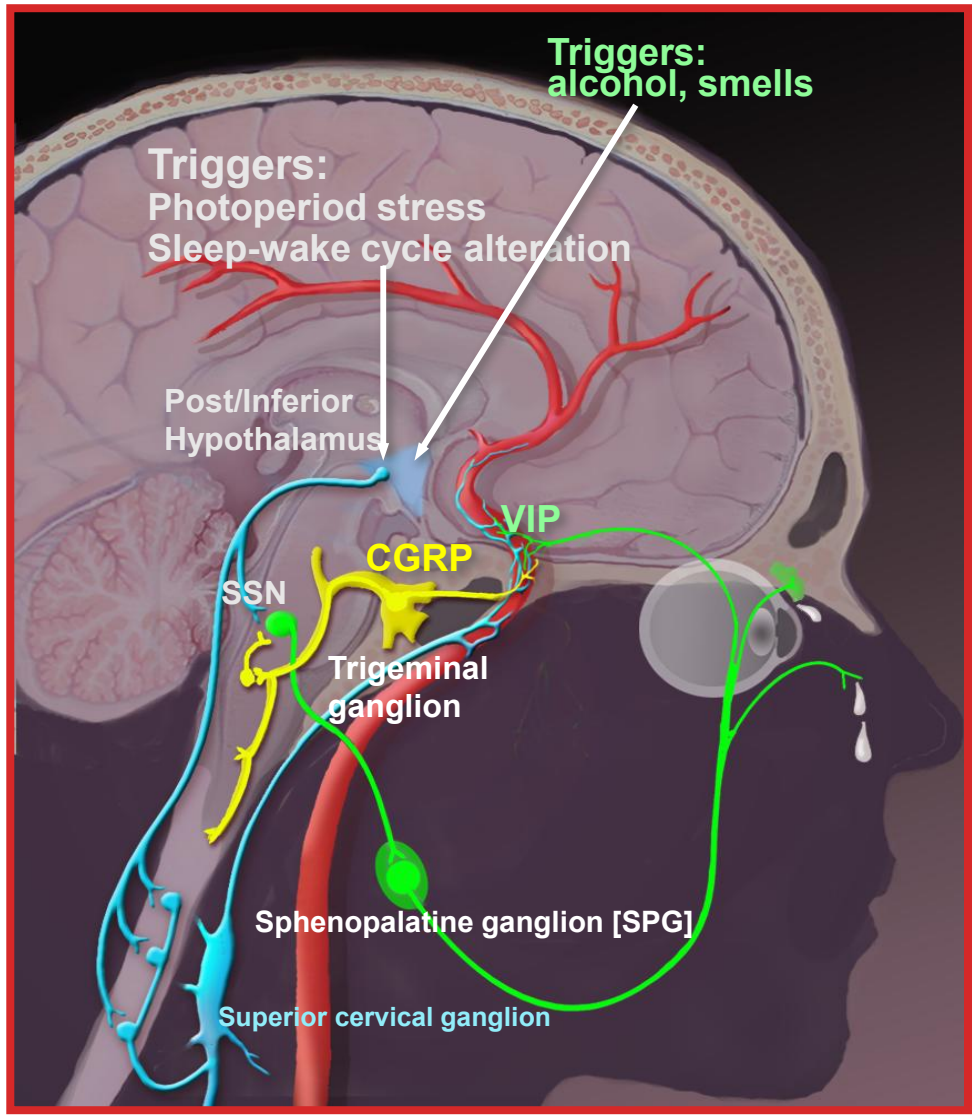


Fig. 2 Temporal course of the BOLD signals in the hypothalamus ipsilaterally to the pain-side in patient 2. Asymptomatic state (**a**). Onset of the headache attack and state of pain (**b**). Administration of sumatriptan (**c**). Pain relief-state (**d**). On the horizontal line the number of the 400 GE-EPI acquisitions, is indicated



Spontaneous attacks: Moelli et al., J Headache Pain (2009) 10:11–14
GTN-induced attacks: May et al., The Lancet (1998), 352 (9124), P275-278

Cluster Headache (CH) Pathophysiology



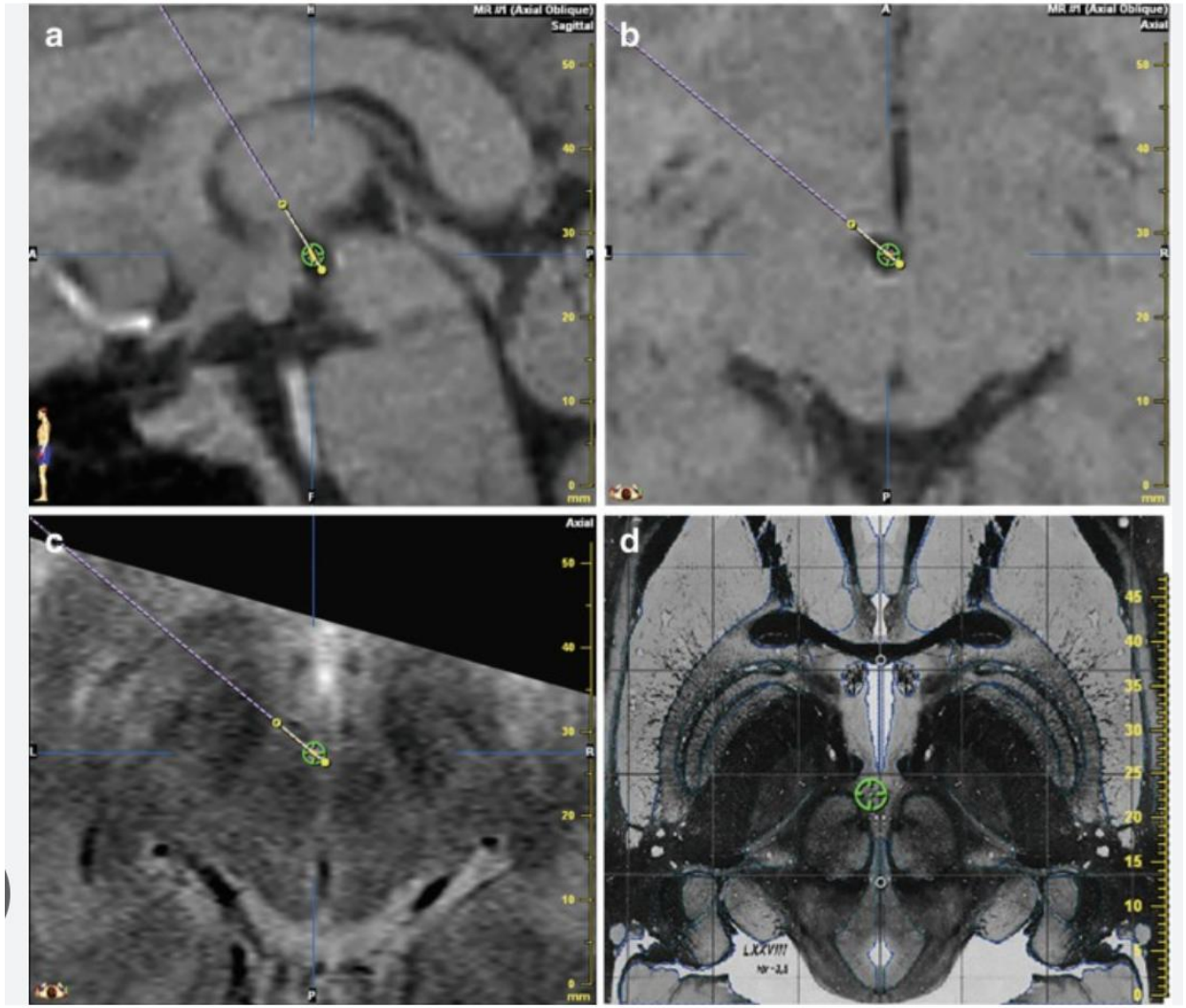
- Posterior hypothalamic activation may modulate signalling through the trigeminocervical complex (TCC)

- Trigeminal fibers activate the parasympathetic system through the superior salivatory nucleus, which in tern activates fibers of the grater petrosal nerve through the sphenopalatine ganglion, activating the trigeminal autonomic reflex and triggering the attack.

May A, et al. *Neurology.* 2000;55(9):1328–1335.

HEADACHE RESEARCH

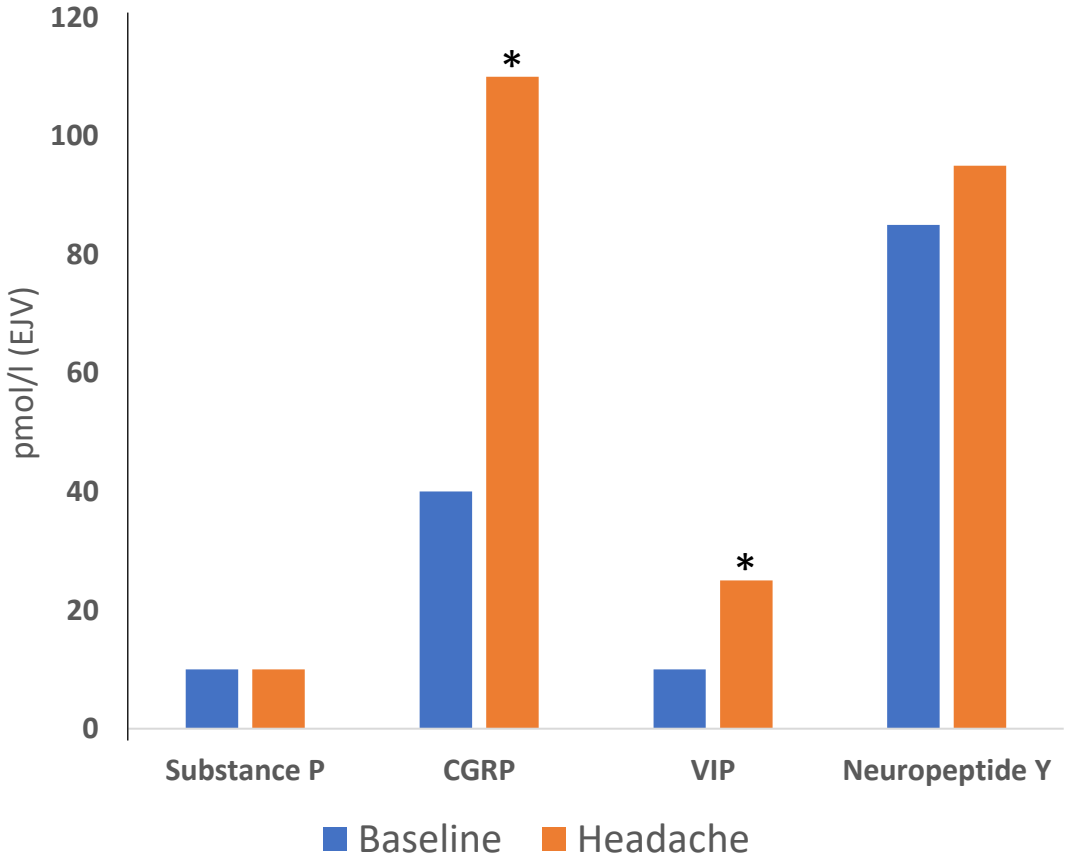
Hypothalamic deep brain stimulation in Cluster Headache

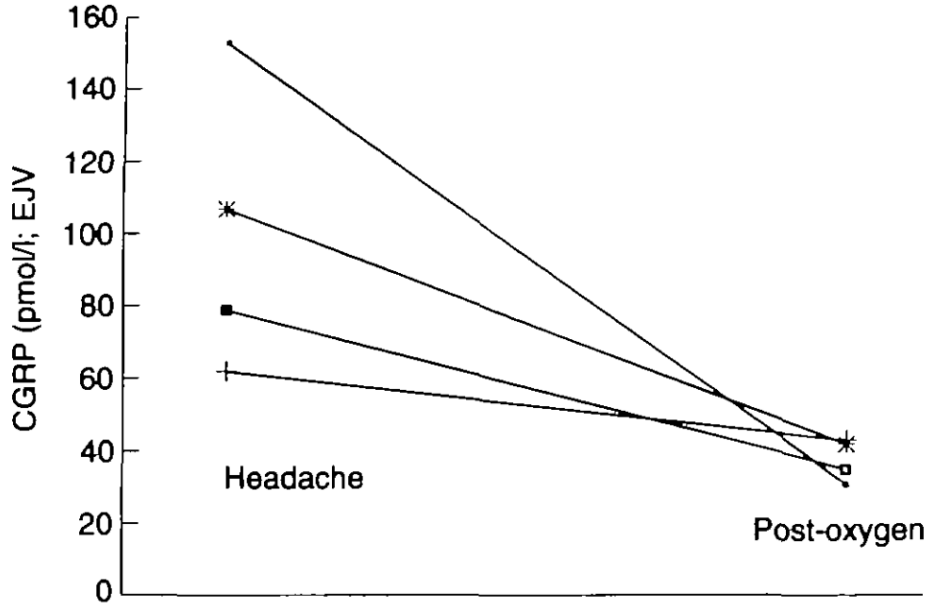


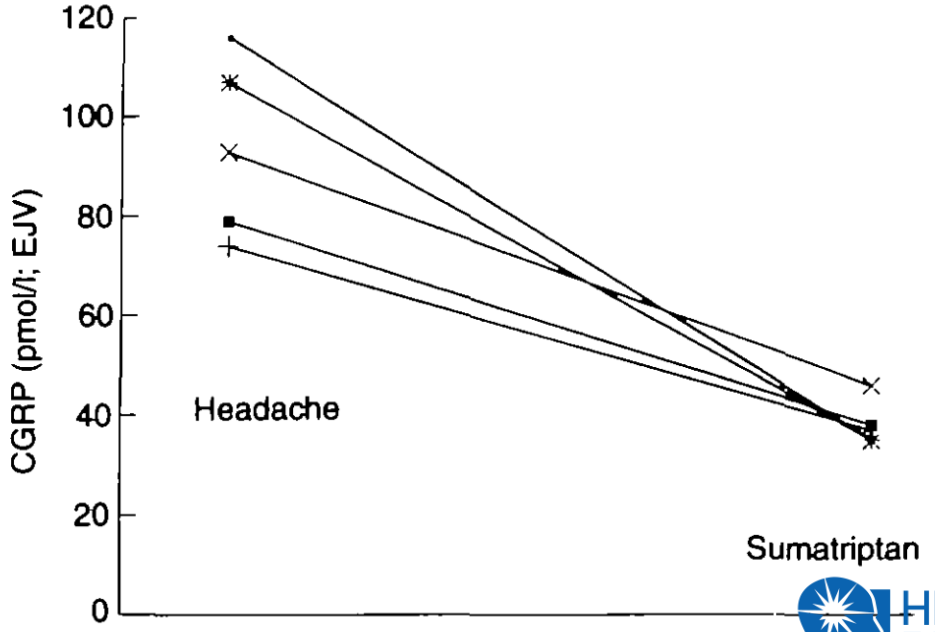
- DBS of the posterior hypothalamic region has been proposed as a prophylactic treatment for refractory chronic CH.
- Its efficacy has been reported in several open studies and case series but not confirmed in randomised controlled studies.
- DBS is efficient in about 60–70% of the patients (decrease of attack frequency >50%).
- Risks: rare but serious; intracranial hemorrhage -- reserve DBS for medically refractory chronic CH patients.

Fontaine, D., Chabardes, S. (2020). Neuromodulation in Headache and Facial Pain Management. Headache. Springer, Cham.

Neuropeptide Changes During Cluster Headache Attacks







Adapted from Goadsby and Edvinsson L. *Brain*. 1994;117 (Pt 3):427-34

HEADACHE RESEARCH

Genetics of Cluster Headache

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
AMERICAN NEUROLOGICAL ASSOCIATION

Research Article | Open Access

Genome-Wide Association Study Identifies Risk Loci for Cluster Headache

Emer O'Connor MB, BCH, BAO, Carmen Fourier MSc, Caroline Ran PhD, Prasanth Sivakumar PhD, Franziska Liesecke PhD, Laura Southgate PhD, Aster V. E. Harder MD ... See all authors

- Identified and replicated several genome-wide significant associations supporting a genetic predisposition in cluster headache
- Downstream analyses implicated immunological processes in the pathogenesis of cluster headache.

Chen *et al. The Journal of Headache and Pain* (2022) 23:147
https://doi.org/10.1186/s10194-022-01517-6

The Journal of Headache and Pain

RESEARCH Open Access

Genome-wide analyses identify novel risk loci for cluster headache in Han Chinese residing in Taiwan

Check for updates

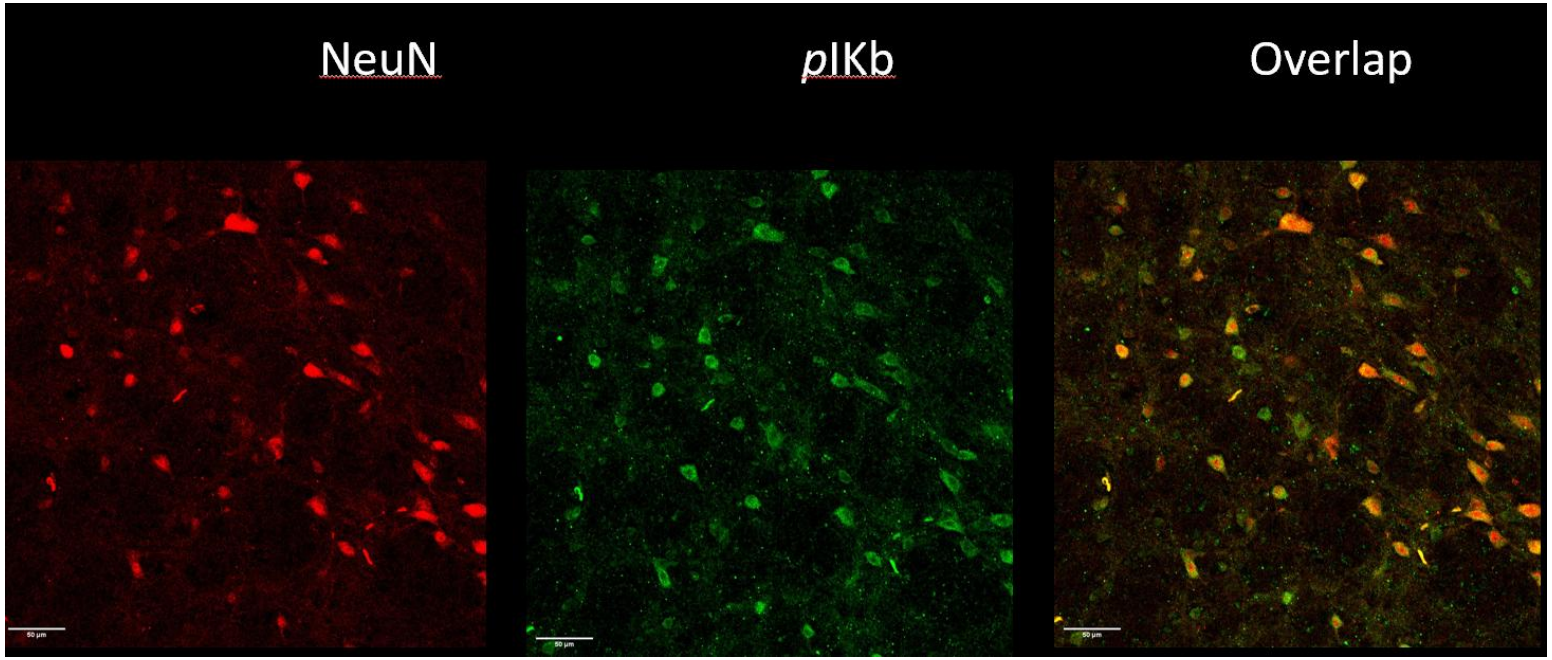
- Poly- genic risk score diferentiated patients from controls.
- Downstream analyses implicated circadian regulation and immunological processes in the pathogenesis of cluster headache.

HEADACHE RESEARCH

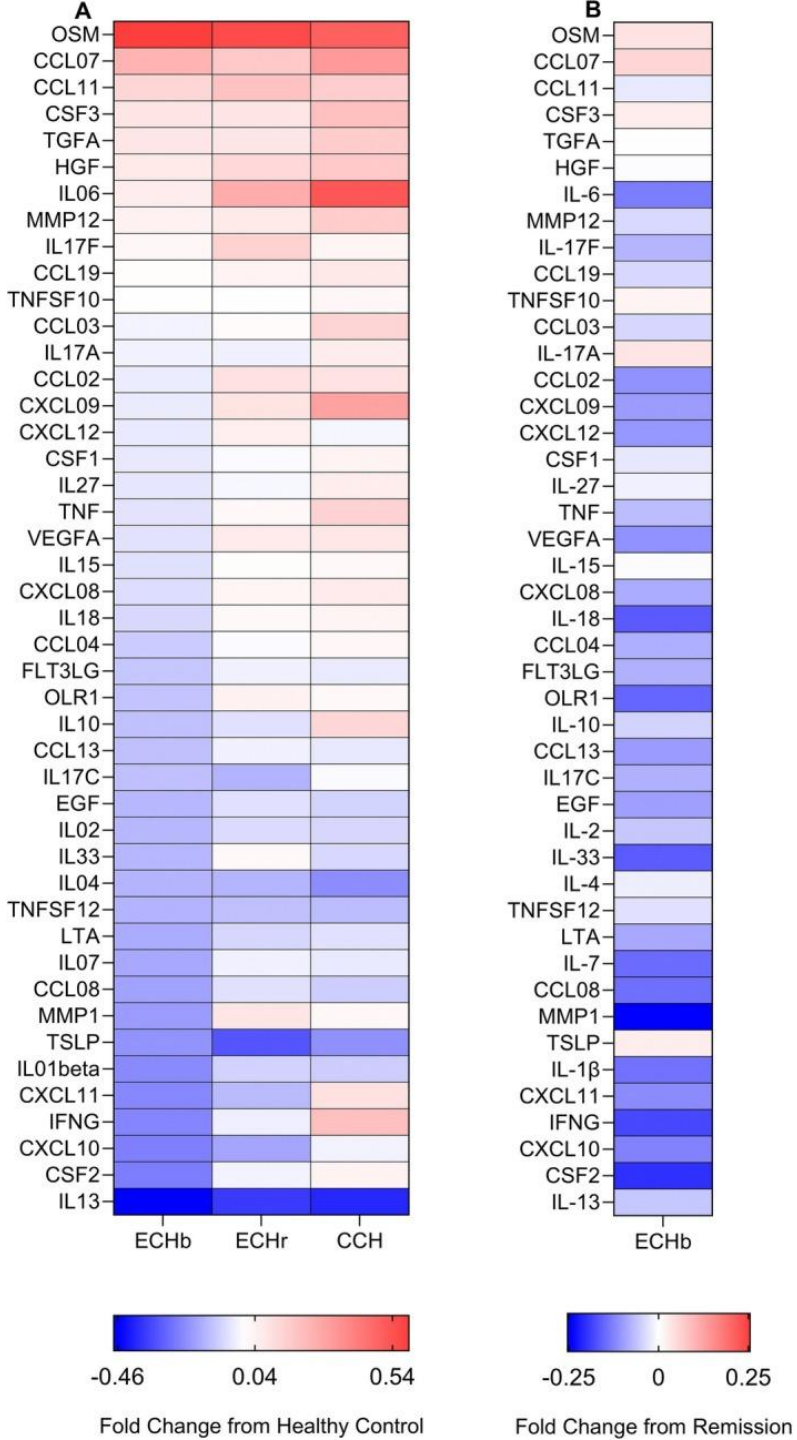
HEADACHE RESEARCH

Inflammatory Biomarkers in Cluster Headache & Hypothalamic Microinflammation

NF-kB pathway activation in the posterior hypothalamic area



Andreou lab



Lund et al., Ann Neurol. 2025 Jul;98(1):4-18

Headache Centre

Guy's and St Thomas' NHS
NHS Foundation Trust

Thank you!

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the migraine trust

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