OTHER IMPORTANT ARTICLES FROM 2019

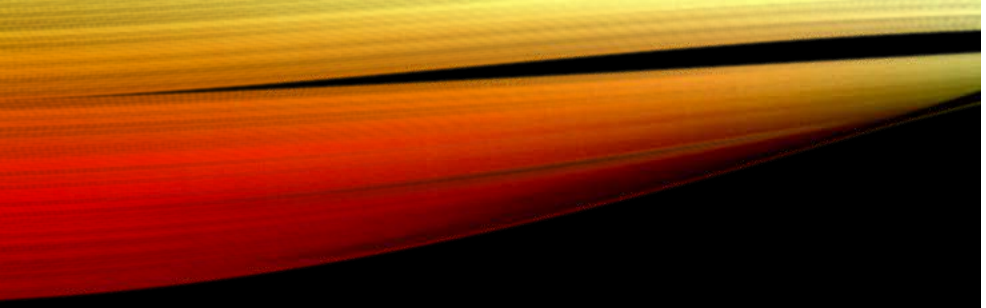
WITH RELEVANCE FOR HEADACHE MEDICINE

HACOP, OJAI 2020

Mo Levin, MD

Thomas N. Ward MD

DISEASE STATE UNDERSTANDING



Original Article

Cephalalgia
An International Journal of Headache

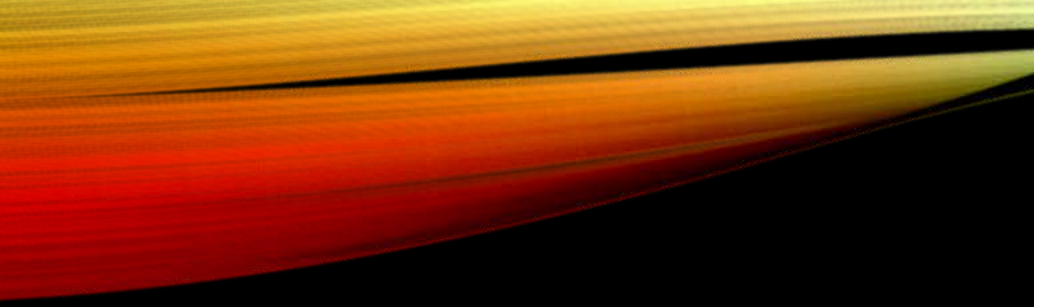
International Headache Society

Differences in fibertract profiles between patients with migraine and those with persistent post-traumatic headache

Cephalalgia
2019, Vol. 39(9) 1121–1133
© International Headache Society 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0333102418815650
journals.sagepub.com/home/cep
SAGE

Catherine D Chong[1], Jacob Peplinski[2], Visar Berisha[2], Katherine Ross[3] and Todd J Schwedt[1]

- Methods – Using diffusion tensor imaging (DTI) and a novel method for detecting subtle changes in fibertract integrity (18 fibertracts examined) by measuring node-by-node parameters along each tract to compare fibertract profiles in migraine (41) and persistent PTHA (n=49), and controls (n=41).
- 18 fibertracts: bilateral anterior thalamic radiations, cingulum (angular bundles and cingulate gyri), inferior longitudinal fasciculi, and uncinate fasciculi, the left corticospinal tract, and the right superior longitudinal fasciculi-parietal portion.
- For migraine patients, there was a significant positive correlation between headache frequency and forceps major mean diffusivity, whereas for persistent post-traumatic headache there was a positive correlation between headache frequency and cingulum angular bundle mean diffusivity and radial diffusivity.



Original Article

Cephalalgia
An International Journal of Headache

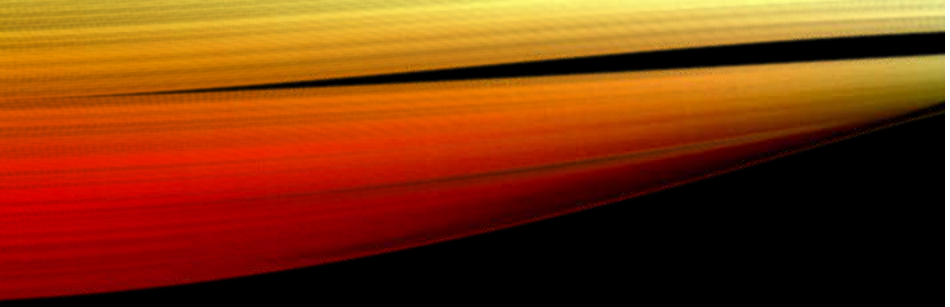
International Headache Society

Differences in fibertract profiles between patients with migraine and those with persistent post-traumatic headache

Cephalalgia
2019, Vol. 39(9) 1121–1133
© International Headache Society 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0333102418815650
journals.sagepub.com/home/cep
SAGE

Catherine D Chong[1], Jacob Peplinski[2], Visar Berisha[2], Katherine Ross[3] and Todd J Schwedt[1]

- Conclusions: unique differences in fibertract profiles between those with migraine vs. persistent post-traumatic headache.
- And for both migraine and persistent post-traumatic headache there was a positive relationship between fibertract alterations and headache frequency
- Suggests: **potential differences in the neuropathological mechanisms underlying migraine and persistent post-traumatic headache.**



Aberrant interactions of cortical networks in chronic migraine

A resting-state fMRI study

Neurology®

Gianluca Coppola, MD, PhD, Antonio Di Renzo, M.Eng, Barbara Petolicchio, MD, PhD, Emanuele Tinelli, MD, PhD, Cherubino Di Lorenzo, MD, PhD, Vincenzo Parisi, MD, Mariano Serrao, MD, PhD, Valentina Calistri, MD, PhD, Stefano Tardioli, MD, PhD, Gaia Cartocci, MD, Jean Schoenen, MD, PhD, Francesca Caramia, MD, PhD, Vittorio Di Piero, MD, PhD, and Francesco Pierelli, MD, PhD

Correspondence
Dr. Parisi
vmp_g@outlook.it

Neurology® 2019;92:e2550-e2558. doi:10.1212/WNL.0000000000007577

- A resting-state (RS)-fMRI to investigate the functional connectivity (FC) between networks in chronic migraine (CM) patients and their correlation with clinical features.
- Methods Twenty CM patients without preventive therapy or acute medication overuse underwent 3T
- MRI scans and were compared to a group of 20 healthy controls (HC). 3 networks were studied: the default mode network (DMN), the executive control network (ECN), and the dorsal attention system (DAS).
- Results - Compared to controls, CM patients had significantly reduced functional connectivity between the DMN and the ECN. Moreover, in patients, the DAS showed significantly stronger FC with the DMN and weaker FC with the ECN. The higher the severity of headache, the increased the strength of DAS connectivity, and the lower the strength of ECN connectivity.
- Conclusion
- These results provide evidence for **large-scale reorganization of functional cortical networks in chronic migraine.** They suggest that the severity of headache is associated with opposite connectivity patterns in **frontal executive and dorsal attentional networks.**

Abnormal thalamocortical network dynamics in migraine

Yiheng Tu, PhD,* Zening Fu, PhD,* Fang Zeng, MD, PhD,* Nasim Maleki, PhD, Lei Lan, MD, PhD, Zhengjie Li, MD, PhD, Joel Park, BA, Georgia Wilson, BA, Yujie Gao, MD, PhD, Mailan Liu, MD, PhD, Vince Calhoun, PhD, Fanrong Liang, MD, MS and Jian Kong, MD, MS, MPH

Neurology® 2019;92:e2706-e2716. doi:10.1212/WNL.0000000000007607

Correspondence
Dr. Kong
kongj@
nmr.mgh.harvard.edu
or Dr. Liang
acuresearch@126.com

Methods
Authors investigated dynamic functional network connectivity (dFNC) of the migraine brain in 89 interictal migraine patients and 70 healthy controls. They focused on the temporal properties of thalamocortical connectivity using sliding window cross-correlation, clustering state analysis, and graph-theory methods. Relationships between clinical symptoms and abnormal dFNC were evaluated using a multivariate linear regression model. Results
Five dFNC brain states were identified to characterize and compare dynamic functional connectivity patterns. Migraineurs spent more time in a strongly interconnected between-network state, but they spent less time in a sparsely connected state.
Authors found that abnormal posterior thalamus (pulvinar nucleus) dFNC with the visual cortex and the precuneus were significantly correlated with headache frequency of migraine. Further topologic measures revealed that migraineurs had significantly lower efficiency of information transfer in both global and local dFNC.

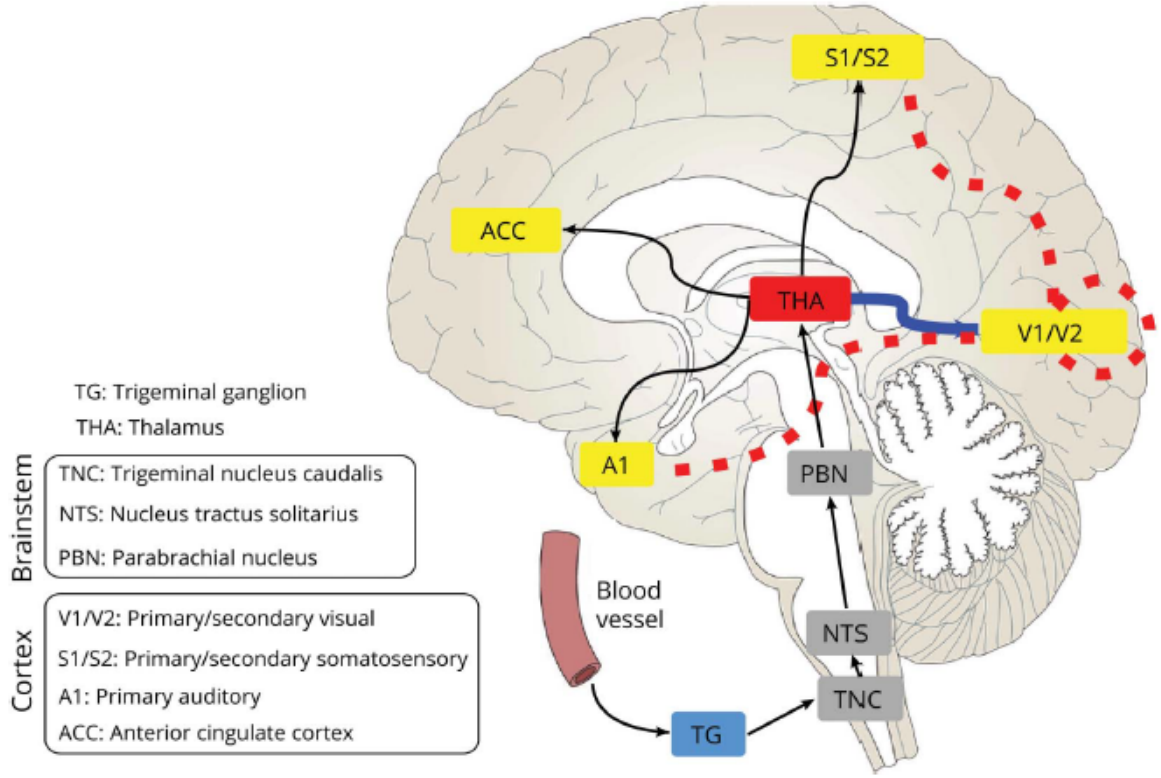
Abnormal thalamocortical network dynamics in migraine

Yiheng Tu, PhD,* Zening Fu, PhD,* Fang Zeng, MD, PhD,* Nasim Maleki, PhD, Lei Lan, MD, PhD, Zhengjie Li, MD, PhD, Joel Park, BA, Georgia Wilson, BA, Yujie Gao, MD, PhD, Mailan Liu, MD, PhD, Vince Calhoun, PhD, Fanrong Liang, MD, MS and Jian Kong, MD, MS, MPH

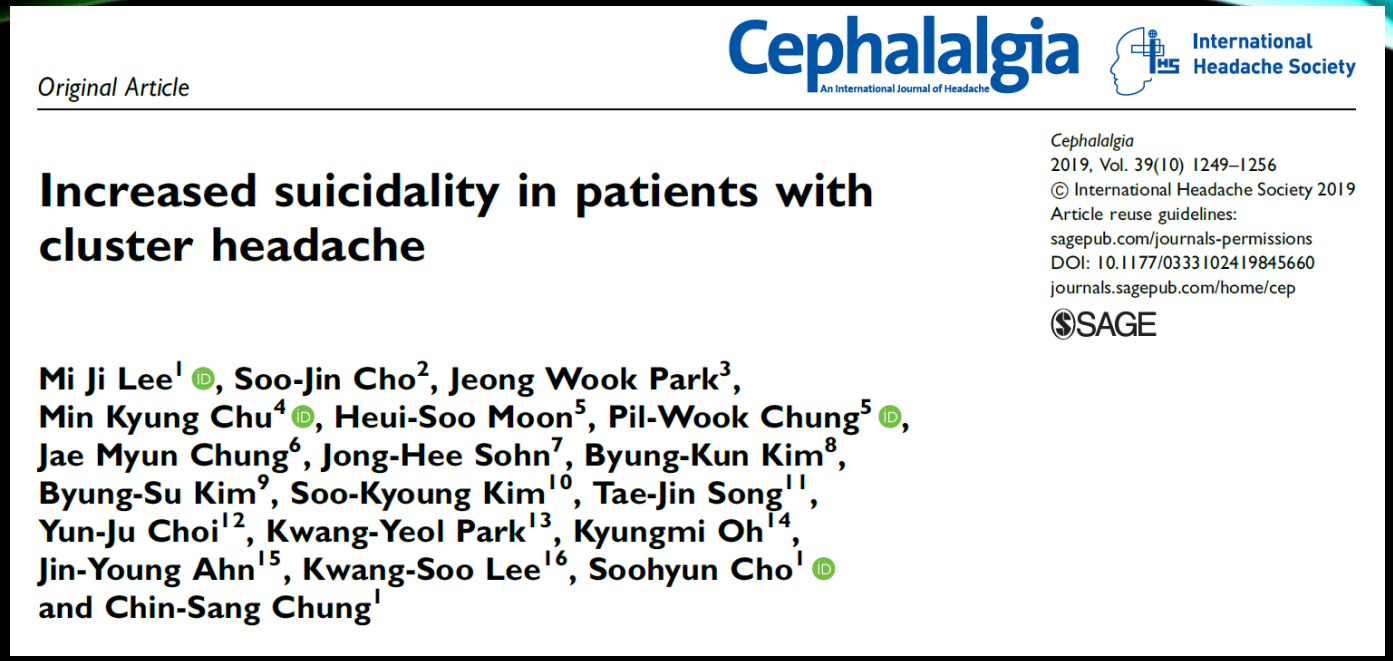
Correspondence
Dr. Kong
kongj@
nmr.mgh.harvard.edu

Neurology® 2019;92:e2706-e2716. doi:10.1212/WNL.0000000000007607

Conclusion
"Our results demonstrated a transient pathologic state with **atypical thalamocortical connectivity** in migraineurs and extended current findings regarding abnormal thalamocortical networks and dysrhythmia in migraine



The posterior nucleus of the thalamus (pTHA) receives projections from the brainstem and relays to the primary and secondary somatosensory cortices (S1 and S2), insula (not shown in the figure), primary and secondary visual cortices (V1/V2), primary auditory cortex (A1), and anterior cingulate cortex (ACC). A detailed review of migraine-relevant networks can be found in reference 27. We found abnormal connections between the pTHA and visual cortex (blue line) and hyperconnectivity (red dashed lines) between the sensory cortices (visual, somatosensory, and auditory) in the migraine pathologic state.



Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2019, Vol. 39(10) 1249–1256
© International Headache Society 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0333102419845660
journals.sagepub.com/home/cep

SAGE

Increased suicidality in patients with cluster headache

Mi Ji Lee[1], Soo-Jin Cho[2], Jeong Wook Park[3], Min Kyung Chu[4], Heui-Soo Moon[5], Pil-Wook Chung[5], Jae Myun Chung[6], Jong-Hee Sohn[7], Byung-Kun Kim[8], Byung-Su Kim[9], Soo-Kyoung Kim[10], Tae-Jin Song[11], Yun-Ju Choi[12], Kwang-Yeol Park[13], Kyungmi Oh[14], Jin-Young Ahn[15], Kwang-Soo Lee[16], Soohyun Cho[1] and Chin-Sang Chung[1]

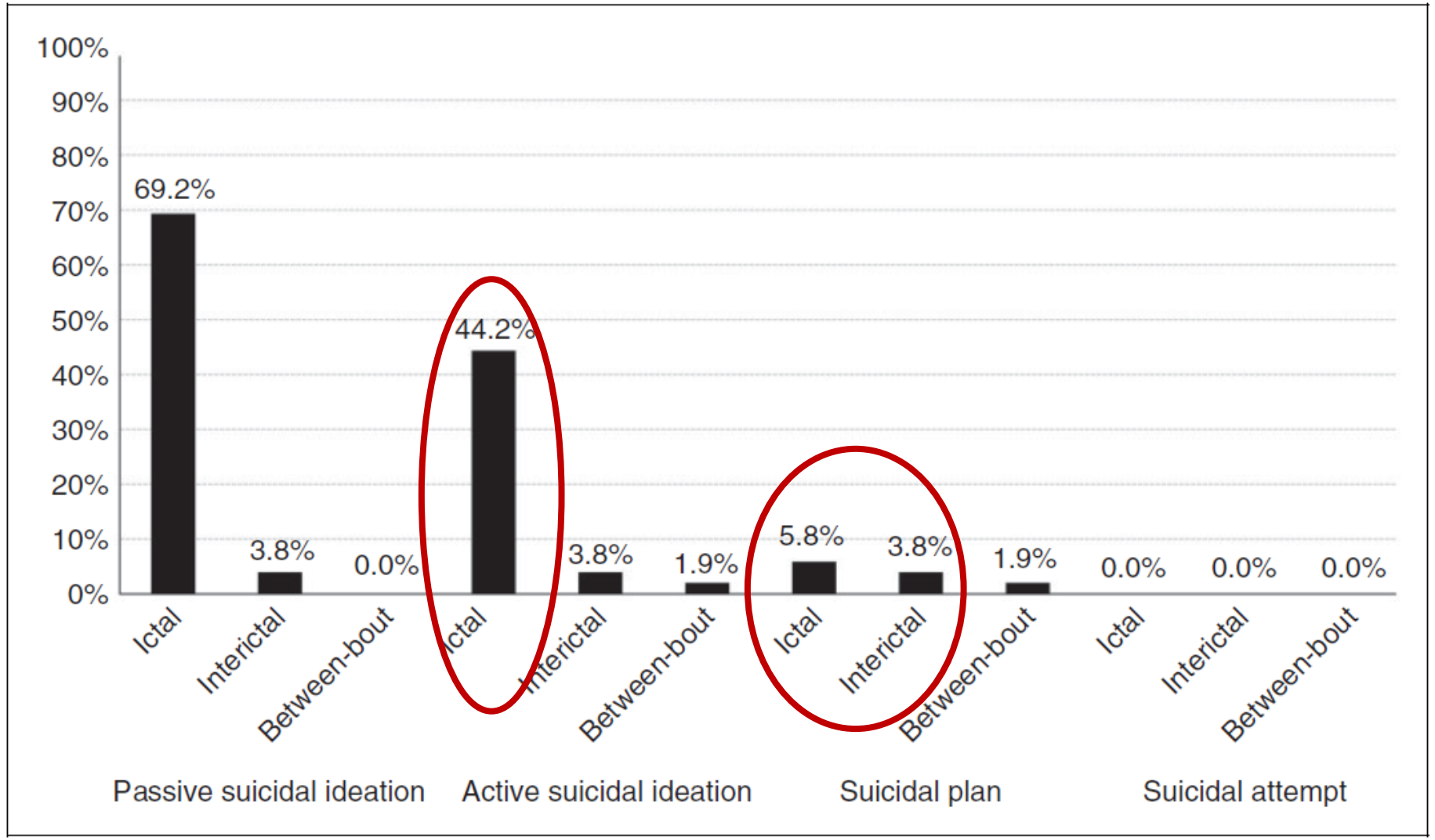
- Methods: 193 cluster headache patients were asked about their suicidality during and between attacks, specifically about passive suicidal ideation, active suicidal ideation, suicide plan, and suicide attempt. 175 cluster headache patients participated in the full study.
- Factors associated with high ictal suicidality were longer disease duration, the Headache Impact Test score, and the Patient Health Question 9 score.
- Conclusions: Cluster headache attack carries a high suicidality compared to the interictal or between-bouts state.

Original Article

Cephalalgia
International Headache Society

Cephalalgia
2019, Vol. 39(10) 1249–1256
© International Headache Society 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0333102419845660
journals.sagepub.com/home/cep
SAGE

Increased suicidality in patients with cluster headache



Original Article

Cephalalgia
An International Journal of Headache

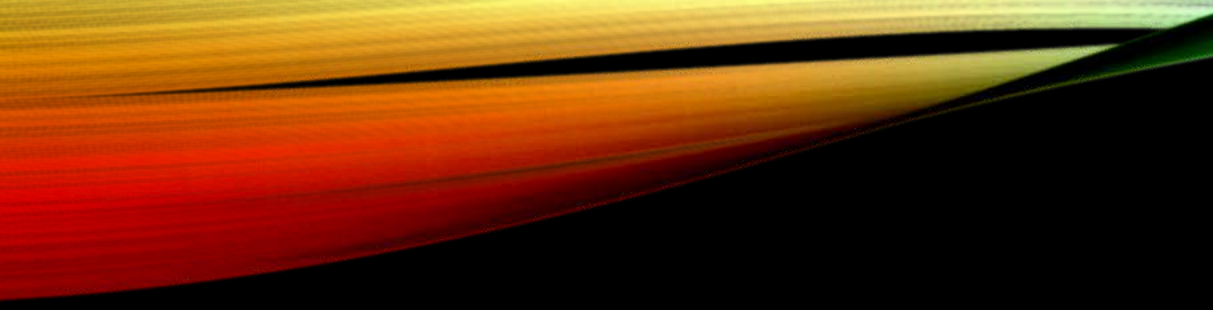
International Headache Society

Cephalalgia
2019, Vol. 39(2) 197–208
© International Headache Society 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0333102418783294
journals.sagepub.com/home/cep
SAGE

Prognostic factors for outcome of microvascular decompression in trigeminal neuralgia: A prospective systematic study using independent assessors

Tone Bruvik Heinskou[1], Per Rochat[2], Stine Maarbjerg[1], Frauke Wolfram[3], Jannick Brennum[2], Jes Olesen[1] and Lars Bendtsen[1]

- Methods: Clinical characteristics and outcome data were recorded prospectively from consecutive classical trigeminal neuralgia patients, using standardized interviews. Degree of neurovascular contact was evaluated by a 3.0 Tesla MRIblinded to symptomatic side. Patients were assessed before and 12 months after surgery by a neurologist.
- Results: 26 men and 33 women completed 12 months follow-up. Forty-one patients (69%) had an excellent outcome (no pain, no medication). Ten (18%) patients had a good outcome. Eight (12%) patients had no improvement or had worsening of pain. MRI showed neurovascular contact with morphological changes in 34 patients (58%).
- Odds ratio between neurovascular contact with morphological changes and excellent outcome was 4.4
- Odds ratio between male sex and excellent outcome was 11.38
- No significant association was found between excellent outcome and concomitant persistent pain, current age or disease duration.



Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2019, Vol. 39(11) 1358–1365
© International Headache Society 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0333102419873675
journals.sagepub.com/home/cep
SAGE

Exploring the effects of extracranial injections of botulinum toxin type A on prolonged intracranial meningeal nociceptors responses to cortical spreading depression in female rats

Agustin Melo-Carrillo[1,2], Andrew M Strassman[1,2], Aaron J Schain[1,2], Rodrigo Noseda[1,2], Sait Ashina[1,2], Aubrey Adams[3], Mitchell F Brin[3,4] and Rami Burstein[1,2]

- Using single-unit recording, to study C and Aδ meningeal nociceptors' responses to cortical spreading depression 7–14 days after injection of botulinum neurotoxin type A or saline along calvarial sutures.
- Results: **Extracranial administration of botulinum neurotoxin type A reduced significantly the prolonged firing of the meningeal nociceptors**
- Discussion / Conslusions: "The findings suggest that the mechanism of action by which botulinum neurotoxin type A prevents migraine differ from the one by which calcitonin gene-related peptide monoclonal antibodies prevent migraine and that even when the origin of migraine is central (i.e. in the cortex), a peripherally acting drug can intercept/prevent the headache."

Facial presentations of migraine, TACs, and other paroxysmal facial pain syndromes

Christian Ziegeler, MD, and Arne May, MD, PhD

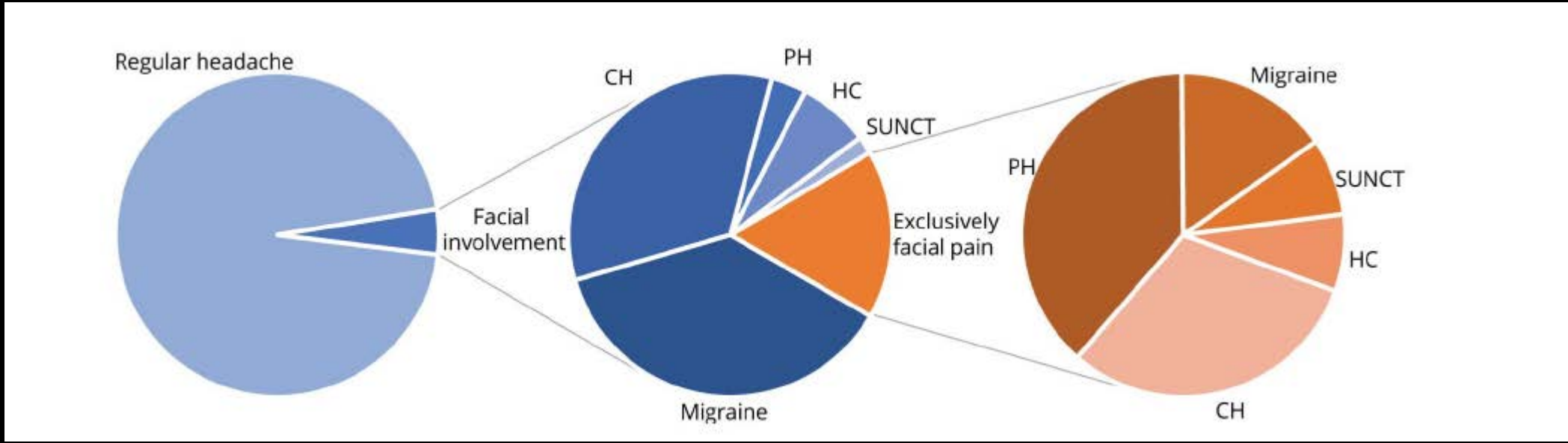
Neurology®

- Betw 2010 and 2018, authors assessed the prevalence of facial pain presentations in all patients with primary headaches.
- Of 2,912 patient datasets, 291 (10%) patients reported facial pain either as an independent or an additional symptom.
- Among patients with migraine, 2.3% (44 of 1,935) reported a facial involvement, most commonly in V2. Of these, 18 patients (40.9%) experienced the pain predominantly in the face.
- In patients with cluster headache, 14.8% (42 of 283) reported a facial involvement, of which 31.0% perceived the pain predominantly in the face.
- A facial involvement was seen in 45.0% of patients with paroxysmal hemicrania (9 of 20), 21.4% of patients with hemicrania continua (9 of 42), and 20.0% of patients with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (3 of 15).
- **In addition, 6 patients reported a constant side-locked facial pain with superimposed well-defined facial pain attacks of 10- to 30-minute duration that appeared several times per day.**

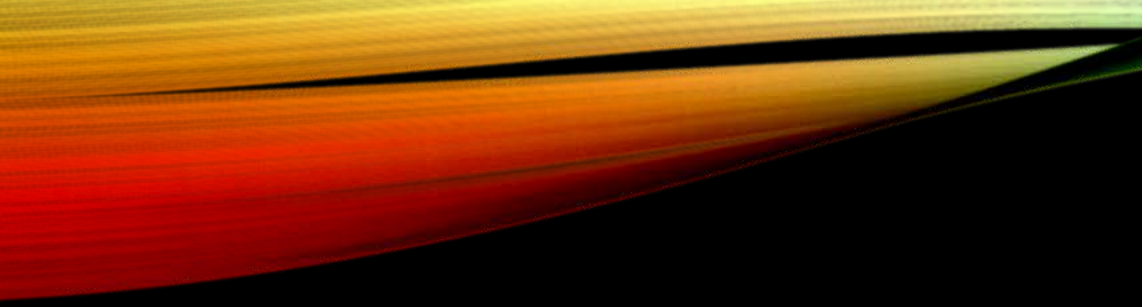
Facial presentations of migraine, TACs, and other paroxysmal facial pain syndromes

Christian Ziegeler, MD, and Arne May, MD, PhD

Neurology®



- Conclusion - Facial involvement in primary headaches is infrequent but not uncommon.
- A sole facial presentation of primary headache symptomatology seems to be rare.
- There seem to be patients with paroxysmal orofacial pain syndromes that have not been previously described. These patients may represent a new entity that could tentatively be called constant unilateral facial pain with added attacks.



Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2019, Vol. 39(10) 1236–1240
© International Headache Society 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0333102419844542
journals.sagepub.com/home/cep
SAGE

Cyclic vomiting syndrome and benign paroxysmal torticollis are associated with a high risk of developing primary headache: A longitudinal study

Romina Moavero[1,2], Laura Papetti[1], Maria Chiara Bernucci[1], Caterina Cenci[1], Michela Ada Noris Ferilli[1], Giorgia Sforza[2], Federico Vigevano[1] and Massimiliano Valeriani[1,3]

- Parents of pediatric patients with previous diagnosis of cyclic vomiting syndrome and/or benign paroxysmal torticollis were asked about the clinical features of the disorder as well as about the development of headache. (82 patients with cyclic vomiting syndrome and 33 with benign paroxysmal torticollis.)
- Results: Seventy-nine percent of patients with cyclic vomiting syndrome later presented with headache, with a mean age at onset of 6 years; 67% of patients with benign paroxysmal torticollis developed headache, with a mean age at onset of 5 years.
- Conclusion: Cyclic vomiting syndrome and benign paroxysmal torticollis are associated with a very high risk of developing headache, mostly migraine, later in life.

DISEASE MANAGEMENT

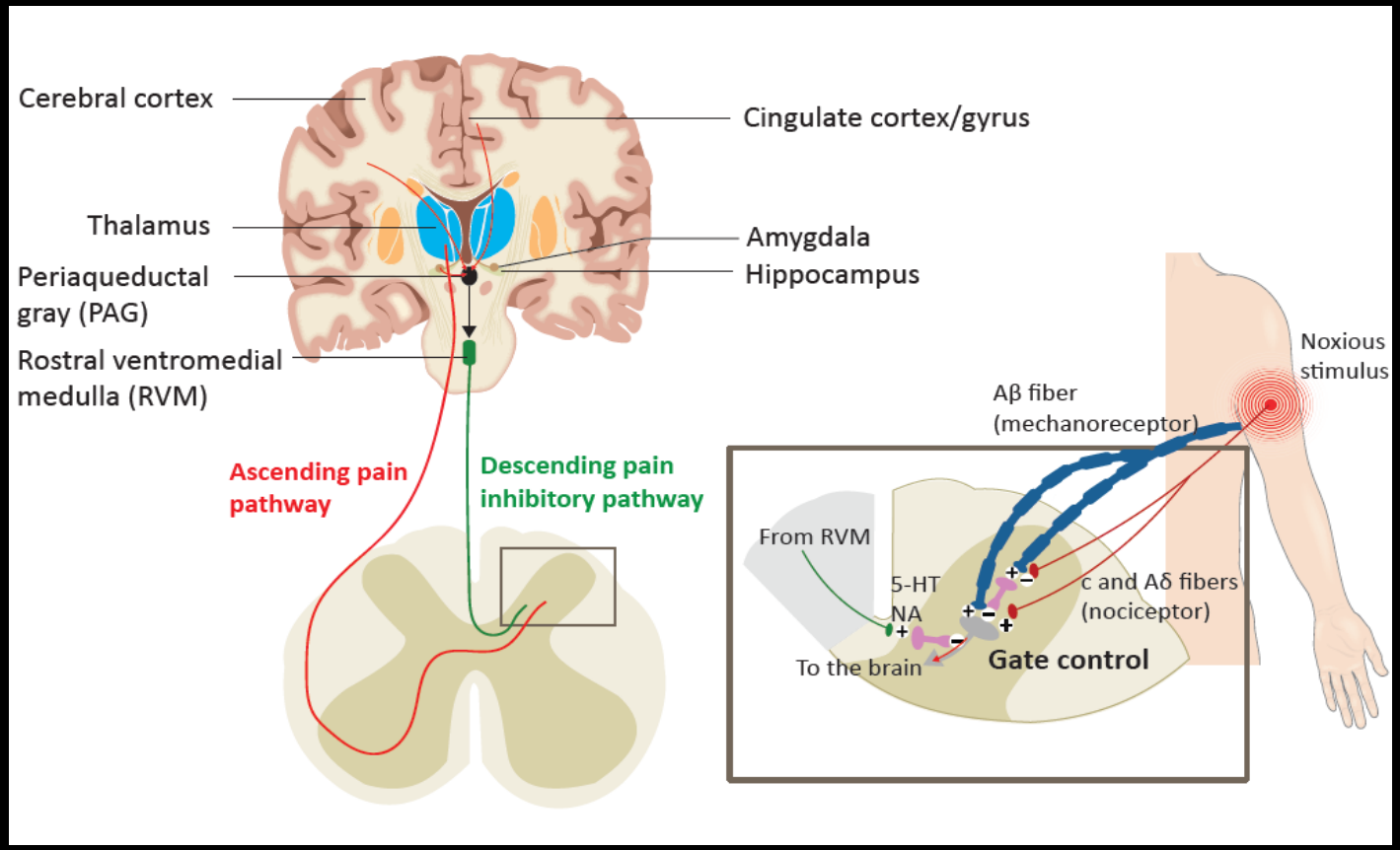
CONTINUOUS PAIN MODULATION

- Yarnitsy et al. Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial Headache 2019 59(8):1240-1252
- This was a randomized, double-blind, sham-controlled, multicenter study conducted at 7 sites in the United States and 5 sites in Israel. 252 adults meeting the ICHD3 criteria for migraine with 2-8 migraine headaches per month were randomized in a 1:1 ratio to active or sham stimulation. A smartphone-controlled wireless device was applied for 30-45 minutes on the upper arm within 1 hour of attack onset; electrical stimulation was at a perceptible but non-painful intensity level. Migraine pain levels were recorded at baseline, 2, and 48 hours post-treatment. Most bothersome symptoms (MBS) were also recorded. The primary efficacy endpoint was the proportion of participants achieving pain relief at 2 hours post-treatment (improvement from severe or moderate pain to mild or none, or from mild pain to none). Relief of MBS and pain-free at 2 hours were key secondary endpoints.
- **RESULTS:** Active stimulation was more effective than sham stimulation in achieving pain relief (**66.7% [66/99] vs 38.8%** [40/103]; therapeutic gain of 27.9% [$CI_{95\%}$, 15.6-40.2]; P < .0001), pain-free (37.4% vs 18.4%, P = .003), and MBS relief (46.3% vs 22.2%, P = .0008) at 2 hours post-treatment. The pain relief and pain-free superiority of the active treatment was sustained 48 hours post-treatment. The incidence of device-related adverse events was low and similar between treatment groups (4.8% [6/126] vs 2.4% [3/126], P = .499).

CONTINUOUS PAIN MODULATION

- Yarnitsy et al. Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial Headache 2019 59(8):1240-1252

CPM describes a descending pain modulating system originating in the lower brainstem.
In animals: DNIC - diffuse noxious inhibitory control
Supposedly, REN activates this system



Acute vestibular migraine treatment with noninvasive vagus nerve stimulation

Shin C. Beh, MD, and Deborah I. Friedman, MD, MPH

Neurology® 2019;93:e1715-e1719. doi:10.1212/WNL.0000000000008388

Neurology®

- Methods - chart review of patients with VM treated with nVNS in a single tertiary referral center between November 2017 and January 2019. 18 patients (16 F) mean age 45.7 [±14.8] years); 14 were treated for a VM attack and 4 for bothersome interictal dizziness consistent with persistent perceptual postural dizziness (PPPD).
- Patients graded the severity of vestibular symptoms and headache using an 11-point visual analog scale (VAS; 0 = no symptoms, 10 = worst ever symptoms) before and 15 minutes after nVNS.
- Results - In those with acute VM, vertigo improved in 13/14 (complete resolution in 2, at least 50% improvement in 5). The mean vertigo intensity before nVNS was 5.2 (±1.6; median 6), and 3.1 (±2.2; median 3) following stimulation; mean reduction in vertigo intensity was 46.9% (±31.5; median 45%). Five experienced headache with the VM attack; all reported improvement.

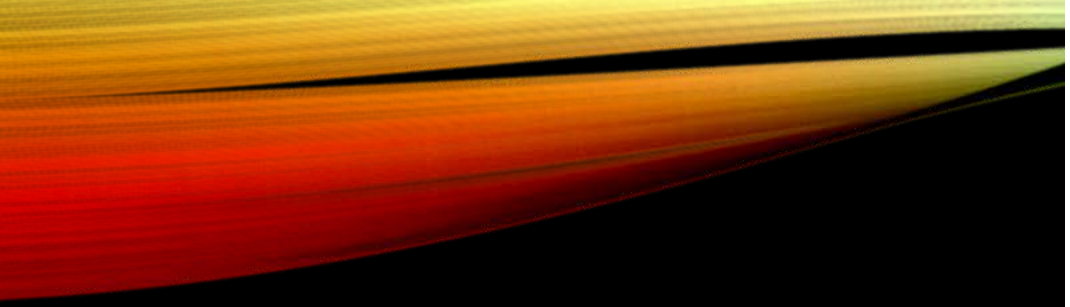
Acute vestibular migraine treatment with noninvasive vagus nerve stimulation

Shin C. Beh, MD, and Deborah I. Friedman, MD, MPH

Neurology® 2019;93:e1715-e1719. doi:10.1212/WNL.0000000000008388

Neurology®

- Mean headache severity was 6 (±1.4; median 6) prior to treatment and 2.4 (±1.5; median 3) following nVNS; mean reduction in headache intensity was 63.3% (±21.7; median 50). All 4 treated with nVNS for interictal PPPD reported no benefit.
- Conclusion
- “Our study provides preliminary evidence that nVNS may provide rapid relief of vertigo and headache in acute VM.



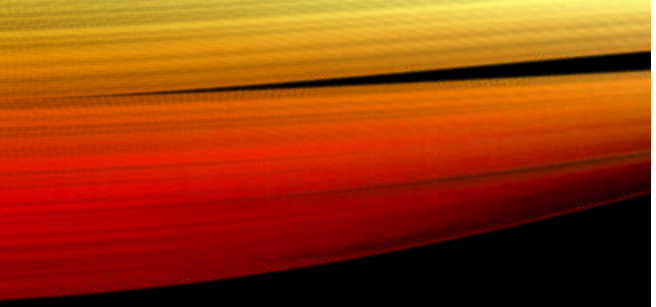
BRAIN
A JOURNAL OF NEUROLOGY

CLINICAL TRIAL

Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine

Peter J. Goadsby,[1] Linda A. Wietecha,[2] Ellen B. Dennehy,[2,3] Bernice Kuca,[4] Michael G. Case,[2] Sheena K. Aurora[2] and Charly Gaul[5]

- Double-blind, phase 3 multicenter study in patients with migraine with and without aura (1:1:1:1 ratio) to oral lasmiditan 200 mg, 100 mg, 50 mg, or placebo.
- Patients were instructed to dose at home within 4 h of onset of migraine attack of at least moderate intensity and not improving. Outcomes: proportion of patients' headache pain-free and most bothersome symptom-free at 2 h post-dose for each dose of lasmiditan versus placebo
- Most patients (79.2%) had a cardiovascular risk factor at baseline, in addition to migraine. Lasmiditan was associated with significantly more pain freedom at 2 h - **lasmiditan 200 mg: 38.8%; 100 mg: 31.4%; 50 mg: 28.6%, versus placebo 21.3%**
- Most adverse events were CNS-related and included dizziness, somnolence and paraesthesia.



Lasmiditan is an effective acute treatment for migraine

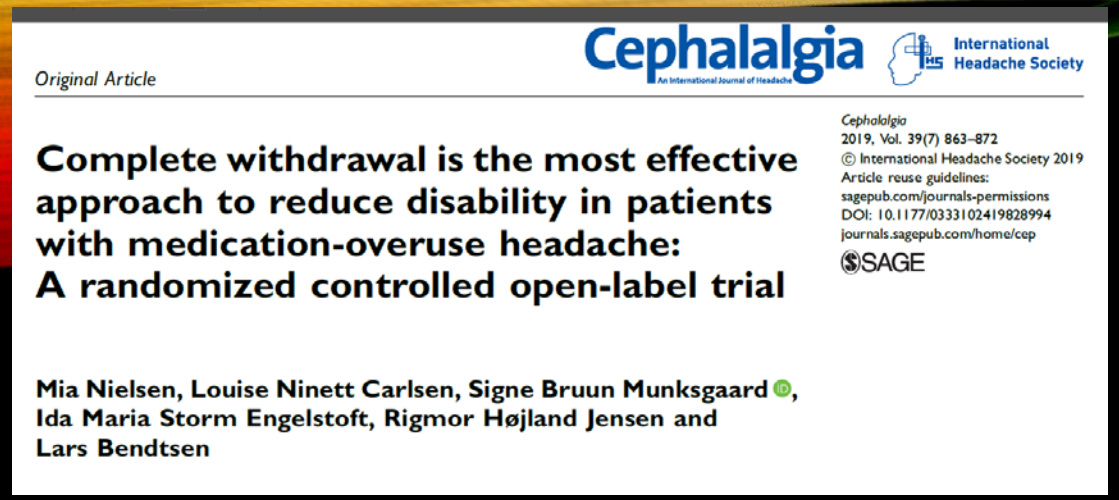
A phase 3 randomized study

Bernice Kuca, BA, MS, Stephen D. Silberstein, MD, Linda Wietecha, BSN, MS, Paul H. Berg, MS, Gregory Dozier, MPH, and Richard B. Lipton, MD, on behalf of the COL MIG-301 Study Group

Neurology® 2018;91:e2222-e2232. doi:10.1212/WNL.0000000000006641

Neurology®

- Methods- Adult patients with migraine were randomized (1:1:1) to a double-blind dose of oral lasmiditan 200 mg, lasmiditan 100 mg, or placebo and were asked to treat their next migraine attack within 4 hours of onset. Over 48 hours after dosing, patients used an electronic diary to record headache pain and the presence of nausea, phonophobia, and photophobia, one of which they designated their most bothersome symptom (MBS).
- Results - Of the 1,856 patients who treated an attack, 77.9% had ≥1 cardiovascular risk factors in addition to migraine.
- Compared with placebo, more patients dosed with lasmiditan 200 mg were free of headache pain at 2 hours after dosing (32.2% vs 15.3%; odds ratio [OR] 2.6), similar to those dosed with lasmiditan 100 mg (28.2%; OR 2.2,
- And compared with those dosed with placebo, more patients dosed with lasmiditan 200 mg (40.7% vs 29.5) and 100 mg (40.9%; OR 1.7) were free of their MBS at 2 hours after dosing. Adverse events were mostly mild or moderate in intensity.
- Conclusions - Lasmiditan dosed at 200 and 100 mg was efficacious and well tolerated in the treatment of acute migraine among patients with a high level of cardiovascular risk factors.



Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

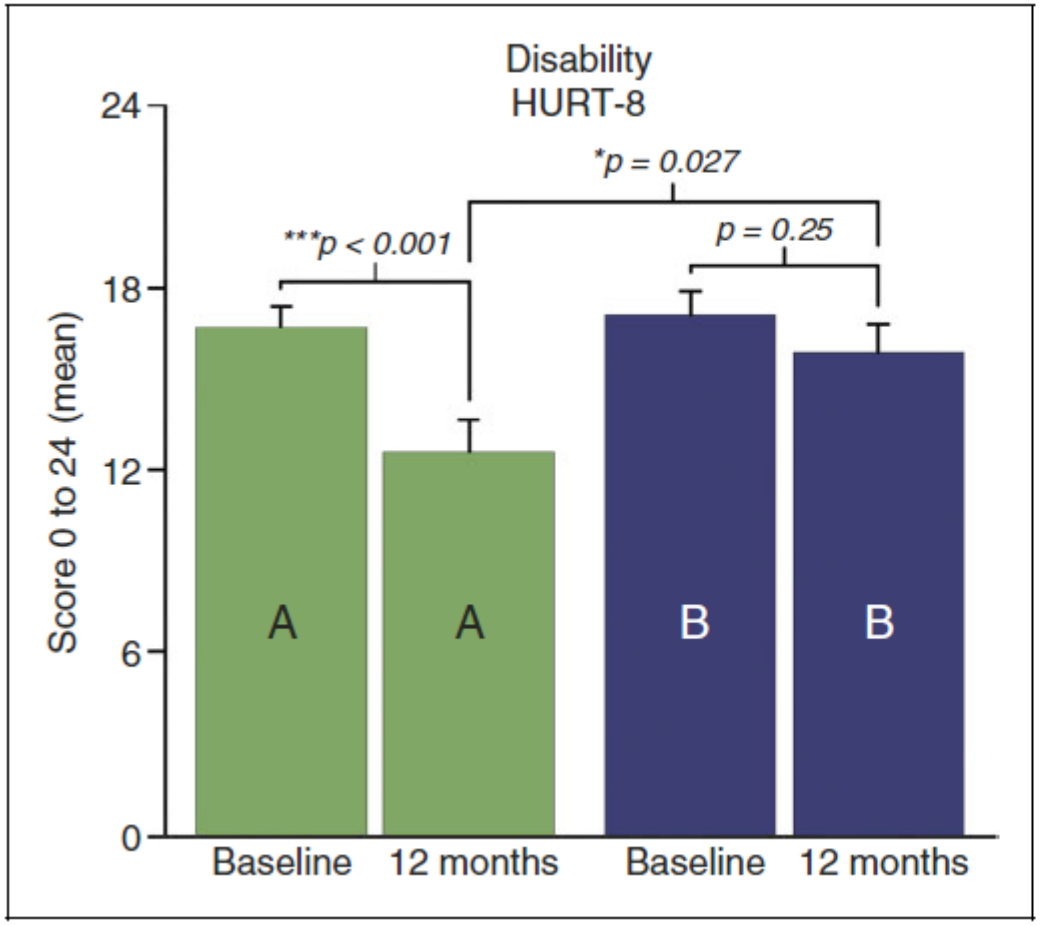
Complete withdrawal is the most effective approach to reduce disability in patients with medication-overuse headache: A randomized controlled open-label trial

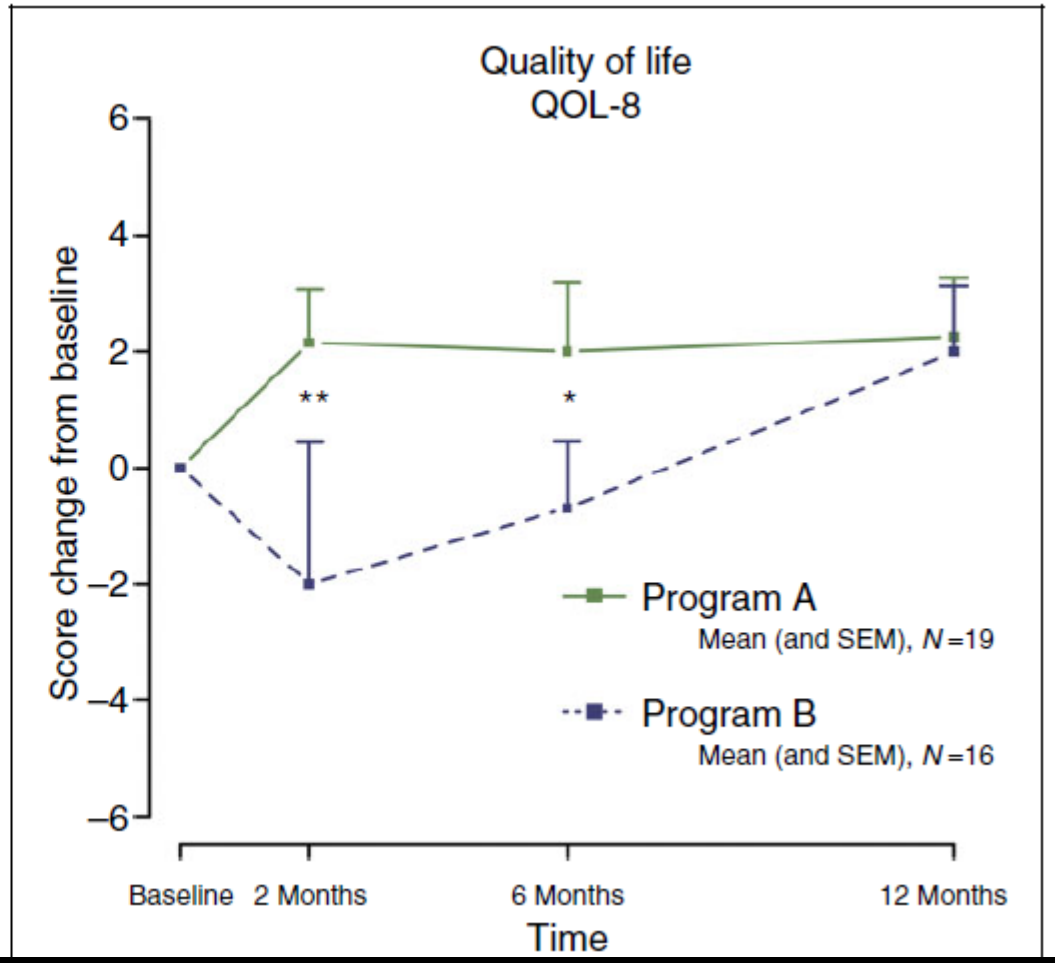
Mia Nielsen, Louise Ninett Carlsen, Signe Bruun Munksgaard, Ida Maria Storm Engelstoft, Rigmor Højland Jensen and Lars Bendtsen

Cephalalgia
2019, Vol. 39(7) 863–872
© International Headache Society 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0333102419828994
journals.sagepub.com/home/cep
SAGE

TREATING MOH
COMPLETE DC OR REDUCTION

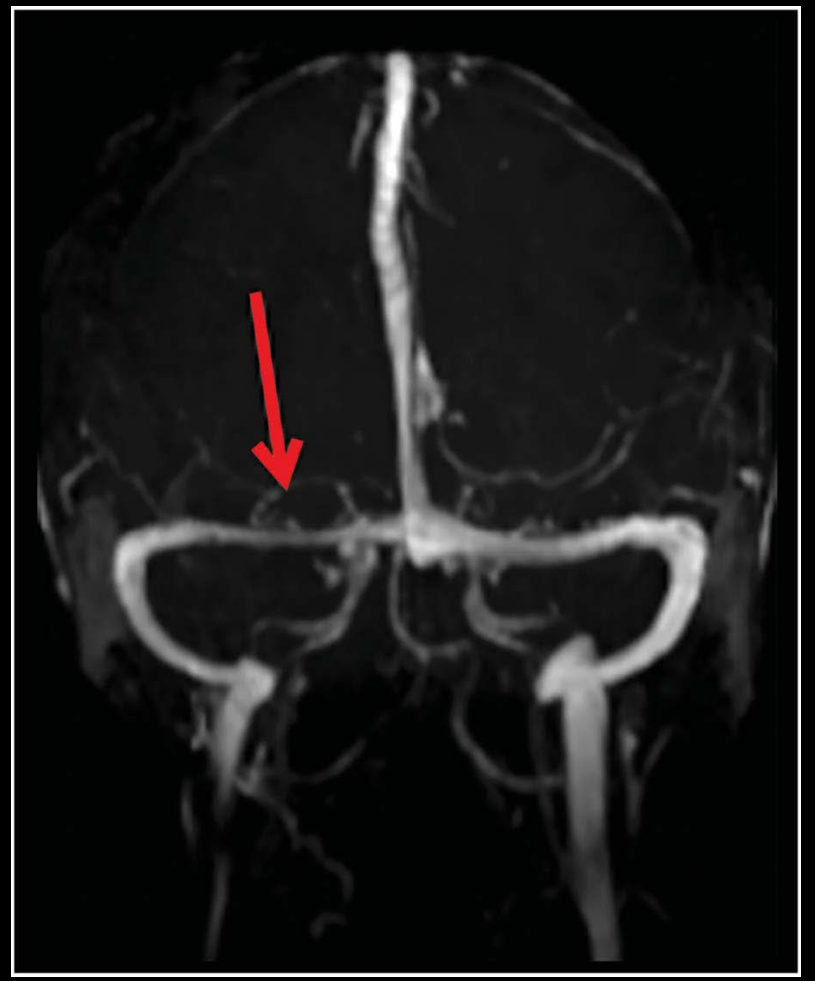
Methods: Authors randomized MOH patients to program A (two months without acute analgesics or migraine medications) or program B (two months with acute medications restricted to two days/week) in a prospective, outpatient study. At 6 and 12 months, we measured disability and headache burden And quality of life at 2-, 6-, and 12-monthfollow-up. Primary endpoint was disability change at 12 months.
Results: 72 medication-overuse headache patients with primary migraine and/or tension-type headache. 54 completed 12-month follow-up.
Disability reduction was 25% in program-A and 7% in program-B
Headache-burden reduction was 33% in program-A and 3% in program-B.
Quality of life was increased by 8% in both programs without significant difference between the programs
At 2-month follow-up, quality of life increased significantly more in program-A than program-B
Conclusion: Both withdrawal programs reduced disability and increased quality of life. Withdrawal without acute medication was the most effective in reducing disability in medication-overuse headache patients.


Disability
HURT-8
Score 0 to 24 (mean)
24
18
12
6
0
*p = 0.027
***p < 0.001
p = 0.25
A
A
B
B
Baseline
12 months
Baseline
12 months


Quality of life
QOL-8
Score change from baseline
6
4
2
0
−2
−4
−6
**
*
Program A
Mean (and SEM), N=19
Program B
Mean (and SEM), N=16
Baseline
2 Months
6 Months
12 Months
Time

IIH

- Yiangou, et al (Univ Birmingham) Therapeutic lumbar puncture for headache in idiopathic intracranial hypertension: Minimal gain, is it worth the pain? Cephalalgia 2019, Vol. 39(2) 245–253 – **No;** in 52 patients who had LPs, 71% percent had some (usually mild improvement but at some time within the next week 64% worsened, 30% significantly. Also noted – OP did not influence the HA response.
- Schievink, W, et al. Rebound high-pressure headache after treatment of spontaneous intracranial hypotension: MRVstudy. Neurology: Clinical Practice April 2019 vol. 9:93-100. **Rebound high-pressure headache** a (reverse orthostatic headache responsive to acetazolamide) **occurs in about one-fourth** of patients following treatment of SIH and is more common in those with restriction of cerebral venous outflow.




Vox Clamantis

The Emperor's New Gepants: Are the Effects of the New Oral CGRP Antagonists Clinically Meaningful?

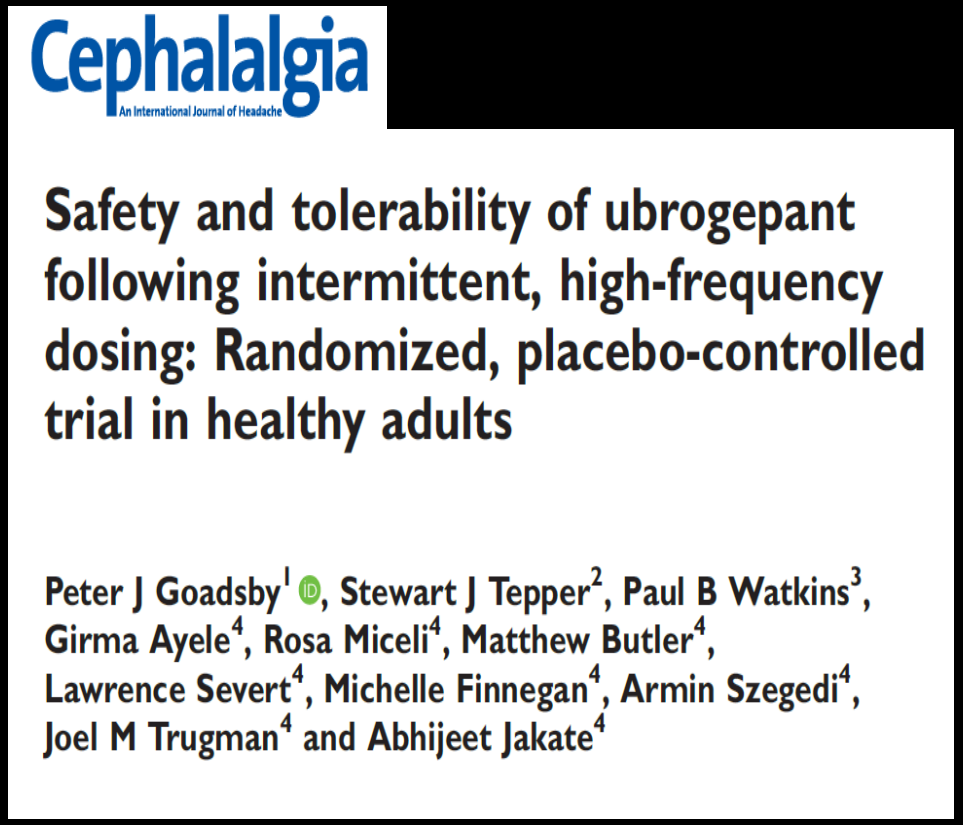
Peer Tfelt-Hansen, MD, DMSc; Elizabeth Loder, MD, MPH

GEPANTS

- Tfeldt Hansen – The Emperor's New Gepants Headache 2019
- "…ubrogepant and rimegepant…appear to have far lower efficacy than the triptans, and are not more effective than simple analgesics that can be purchased without a prescription. Their purported safety or tolerability advantages over triptans are speculative and likely to be relevant for only a small proportion of migraineurs.
- We therefore find it justified to suggest that it is very difficult to see the Emperor's new gepants.

- Trugman, et al. Efficacy, Safety, and Tolerability of Ubrogepant for the Acute Treatment of Migraine: Results From a Single-Attack Phase 3 Study, ACHIEVE II
- Croop, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled

- Healthy adults (age 18–50 years) received placebo or ubrogepant. Ubrogepant was dosed at 100 mg (250 mg tablets) on 2 consecutive days followed by 2 consecutive days of placebo, alternating for **8 weeks**. Primary outcome measures were safety and tolerability.
- Results: Treatment-emergent adverse events were reported in 45% of placebo and 44% of ubrogepant participants.
- The most common was headache (10% placebo; 11% ubrogepant). 7 cases of elevated ALT and/or AST levels (five placebo, two ubrogepant) were reported. 2 cases (one placebo, one ubrogepant) were judged possibly related, and one (ubrogepant) probably related. Also several cases of upper limits of normal enzyme levels were noted which were transient.
- Conclusion: **Ubrogepant was well tolerated following intermittent, high-frequency dosing in healthy participants, with no clinically relevant signal of hepatotoxicity**.



Year long data are available - abstracts

AND CGRP MABS FOR CM

Galcanezumab in chronic migraine

The randomized, double-blind, placebo-controlled REGAIN study

Holland C. Detke, PhD, Peter J. Goadsby, MD, PhD, Shufang Wang, PhD, Deborah I. Friedman, MD, MPH, Katherine J. Selzler, PhD, and Sheena K. Aurora, MD

Corresponde
Dr. Detke
detkehc@lilly.

Neurology® 2018;91:e2211-e2221. doi:10.1212/WNL.0000000000006640

Original Article

Cephalalgia
An International Journal of Headache

Eptinezumab for prevention of chronic migraine: A randomized phase 2b clinical trial

David W Dodick[1], Richard B Lipton[2], Stephen Silberstein[3], Peter J Goadsby[4,5], David Biondi[6], Joe Hirman[7], Roger Cady[6] and Jeff Smith[8]

Cephalalg
2019, Vo
© Interr
Article r
sagepub.
DOI: 10.
journals.
SA

Erenumab in chronic migraine

Patient-reported outcomes in a randomized double-blind study

Richard B. Lipton, MD, Stewart J. Tepper, MD, Uwe Reuter, MD, Stephen Silberstein, MD, Walter F. Stewart, PhD, Jon Nilsen, PhD, Dean K. Leonardi, PhD, Pooja Desai, PhD, Sunfa Cheng, MD, Daniel D. Mikol, MD, PhD, and Robert Lenz, MD, PhD

Corresp
Dr. Lipto
Richard.L

DIAGNOSES I DON'T LIKE

- Chronic fatigue syndrome
- Fibromyalgia
- In my opinion, can be many things
- Clinicians disagree
- Result may be inadequate diagnosis/wrong diagnosis
- Lost treatment opportunities
- "fibromyalgia" often coexists with migraine (Nicolodi)
- Specific diagnosis should always be the goal (prognosis and treatment)

JAMA NEUROLOGY

- Not many articles on headache
- Review article: Scientific Advances in and Clinical Approaches to Small-Fiber Neuropathy: A Review. JAMA Neurology 2019; 76 (10):1240-1251.

SMALL-FIBER NEUROPATHY

Preferential damage to thinly-myelinated A-delta fibers, and unmyelinated C fibers, autonomic or trophic fibers.

- Common, but most patients undiagnosed (not detected by EMNG).
- Cardinal symptoms: chronic bilateral neuropathic pain, fatigue and nausea
- Can coexist with other neuropathies

- Perhaps only 10% of patients are diagnosed
- Seen in diabetes, post-infectious (human papilloma virus), toxic (vitamin B6), genetic (Fabry's disease, amyloidosis), paraneoplastic, and inflammatory causes

SMALL-FIBER NEUROPATHY

- Can present as erythromelalgia (red burning feet/hands, or in the head/face)
- Release of substance P, CGRP
- Can present as POTS, postprandial nausea, vomiting, lower dysmotility syndromes
- Chronic fatigue due to preload failure (impaired venous contractility in the LEs decreases cardiac return/cardiac output)
- 49% of patients diagnosed with fibromyalgia have small-fiber neuropathy!!!!

DIAGNOSIS

- History (including FH), exam, blood tests. Sometimes genetic testing
- Biomarker ! : measuring epidermal neurite density within a 3 mm protein gene product 9.5 (PGP9.5)-immunolabeled lower leg skin biopsy.
- Early diagnosis is important: potentially treatable causes in 1/3 to ½ of cases.
- Some cases may respond to IVIg or steroids.
- Take home: if your patient has migraine they may have fibromyalgia. If they carry a diagnosis of “fibromyalgia” rule out or rule in small fiber neuropathy

SUPPLEMENTARY REFERENCE

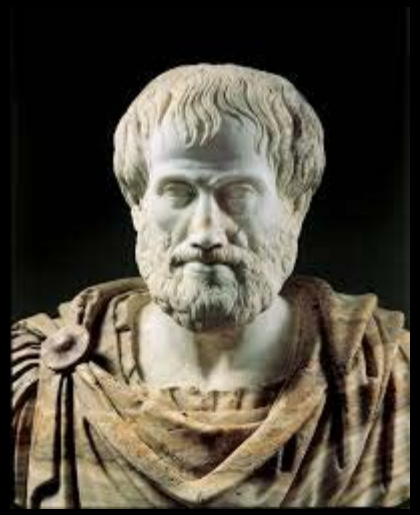
- Grayston R, Czanner G, Elhadd K et al. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: implications for a new paradigm in fibromyalgia etiopathogenesis. Semin Arthritis Rheum 2019; 48(5): 933-940.

WITH APOLOGIES

SHOWN AT IHC DUBLIN 2019 AND SCOTTSDALE 2019

- But this is really cool
- And lets me showcase Drs. Cowan and Loder
- Important to read the literature……
- And, yes, the Delta House is open again…at least until their next transgressions

LASTLY, SOME PHILOSOPHY

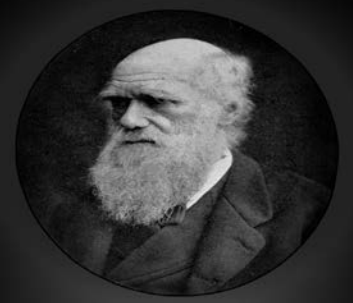


MAKES ME THINK OF ONE THING

https://www.youtube.com/watch?v=y1Mk7idVfcA

PHILOSOPHY, EPIGENETICS AND EVOLUTION

- Concepts about the very basis of having migraine and its expression, questions that perhaps no experimental model can ever fully solve, but certainly animal models of any sort are not likely to get us to the answers.
- So, let's talk briefly about evolution and migraine, then a little philosophy and then a little more about evolution (Charles Darwin, by the way, likely had migraine……)



VOX CLAMANTIS HEADACHE 2019;59:632-634

Did Going North Give Us Migraine? An Evolutionary Approach on Understanding Latitudinal Differences in Migraine Epidemiology

Alessandro Viganò, MD, PhD; Andrea Manica, PhD; Vittorio Di Piero, MD, PhD; Michela Leonardi, PhD

· Commentary: discusses a recent publication by evolutionary biologists of potential importance to the field of migraine*

· A gene polymorphism associated with migraine conferred an evolutionary advantage when colonizing norther/colder territories

· The prevalence of migraine may vary in countries due to climatic adaptation

*Key FM, Abdul-Aziz MA, Mundry R, et al. Human local adaptation of the TRPM8 cold receptor along a latitudinal cline. PLOS Genet. 2018;14:e1007298.

VOX

- TRPM8 gene/TRPM8 receptor
- Receptor for cold sensation and physiological thermoregulation, regulated by the SNP rs10166942, one of the polymorphisms most reliably associated with migraine.
- 2 variants: “C” which is ancestral and protective against migraine, and “T” which appeared after a mutation and is associated with an increased risk of migraine.
- T variant significantly correlates with both latitude and temperature
- These individuals have more migraine but better adapted to the cold
- This links the geographical distribution of migraine with natural selection/evolutionary mechanisms

GUEST EDITORIAL

HEADACHE 2019; 59(4): 481-483

- Toward a Philosophy of Migraine (Robert P. Cowan)
- Questions: what are the evolutionary advantages/disadvantages for individuals and for the species?
- What are the long-term consequences?
- If there are advantages, will treating it cause problems?
- Pain is a central issue, but perhaps a short-term one
- So does having migraine give alerts to early threats from the environment?
- He references an article from Dr. Loder…..

LODER E. WHAT IS THE EVOLUTIONARY ADVANTAGE OF MIGRAINE? CEPHALALGIA 2002; 22:624–632.

- Genetic factors in migraine implies effects of natural selection (“survival of the fittest”)
- If migraine prevalence truly is increasing does this imply a survival advantage?
- 5 possibilities: migraine as a defense mechanism, as a result of conflict with other organisms, as a result of novel environmental factors, as a trade-off between genetic harms and benefits, or migraine as a design constraint.
- The CNS of migraineurs is exquisitely sensitive to environmental stimuli
- It does not habituate (although some of those studies have been criticized)
- Lower tolerance to chronobiological changes (lack of sleep/skipped meals)

LODER

- Stress as a trigger
- Are migraineurs better able to avoid threats (avoid novel/unfamiliar (i.e. dangerous) environments)?
- So perhaps there are reasons migraine has continued/is increasing…
- But they are not obvious….

THANKS