Part II: Rhythms in the nociceptive system

Adopted from a presentation given by
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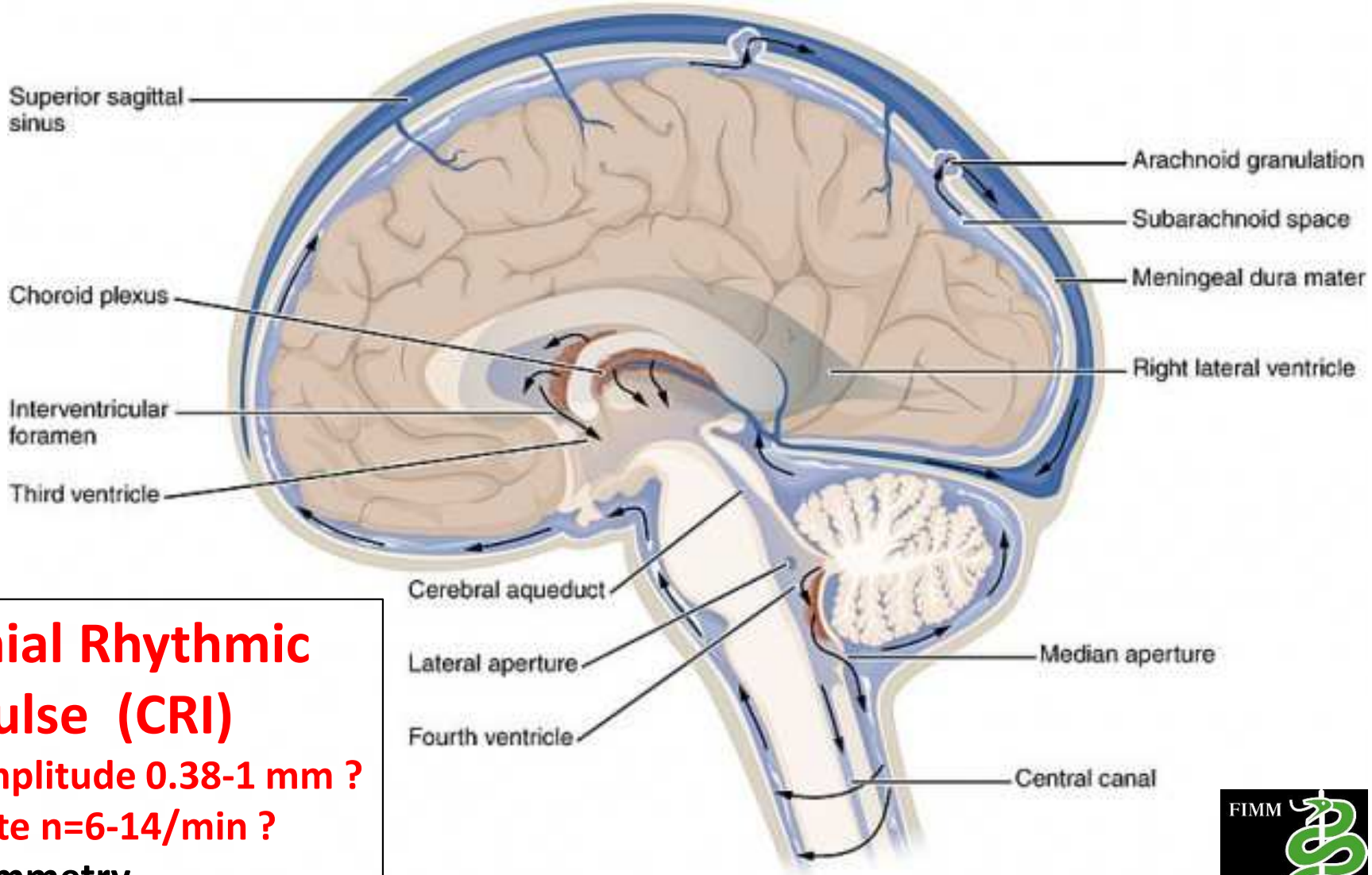
Lech (Austria), December 9, 2015

Headache as a result of rhythms in the nociceptive system?

Cranial osteopathic manipulative treatment (OMT) is based on an hypothetical model out of five components:

1. Motility of the central nervous system
2. Articular mobility of cranial bones
3. Fluctuation of cerebrospinal fluid
4. Mobility of intracranial & intra-spinal membranes
5. Involuntary motion of sacrum between iliac bones

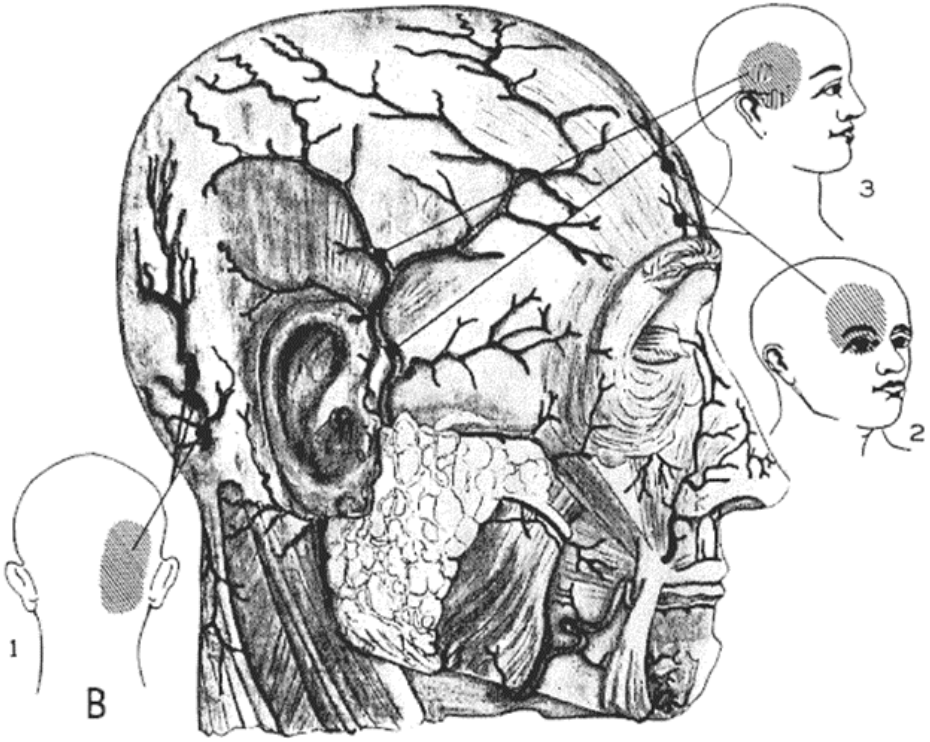
Secretion, flow and resorption of the Cerebrospinal Fluid ("fluctuation")



Cranial Rhythmic Impulse (CRI)

- Amplitude 0.38-1 mm ?
- Rate n=6-14/min ?
- Symmetry

> 100 years of theories, questions, and temporary answers on migraine…



Graham JR, Wolff HG. Mechanisms of migraine headache and action of ergotamine tartrate. Arch Neurol Psychiatry. 1938; 39:737-63

- 1938 establishment of vasodilation in migraine and the constrictive action of ergotamine
- 1941 identification of pain-sensitive structures in the head
- 1959 serotonin and the introduction of methysergide
- 1981 spreading oligemia in migraine with aura
- 1987 neurogenic inflammation theory of migraine
- 1988 the discovery of sumatriptan
- 1990 migraine and calcitonin gene-related peptide
- 1995 the brainstem "migraine generator" and PET studies
- 1996 meningeal sensitization, central sensitization, and allodynia

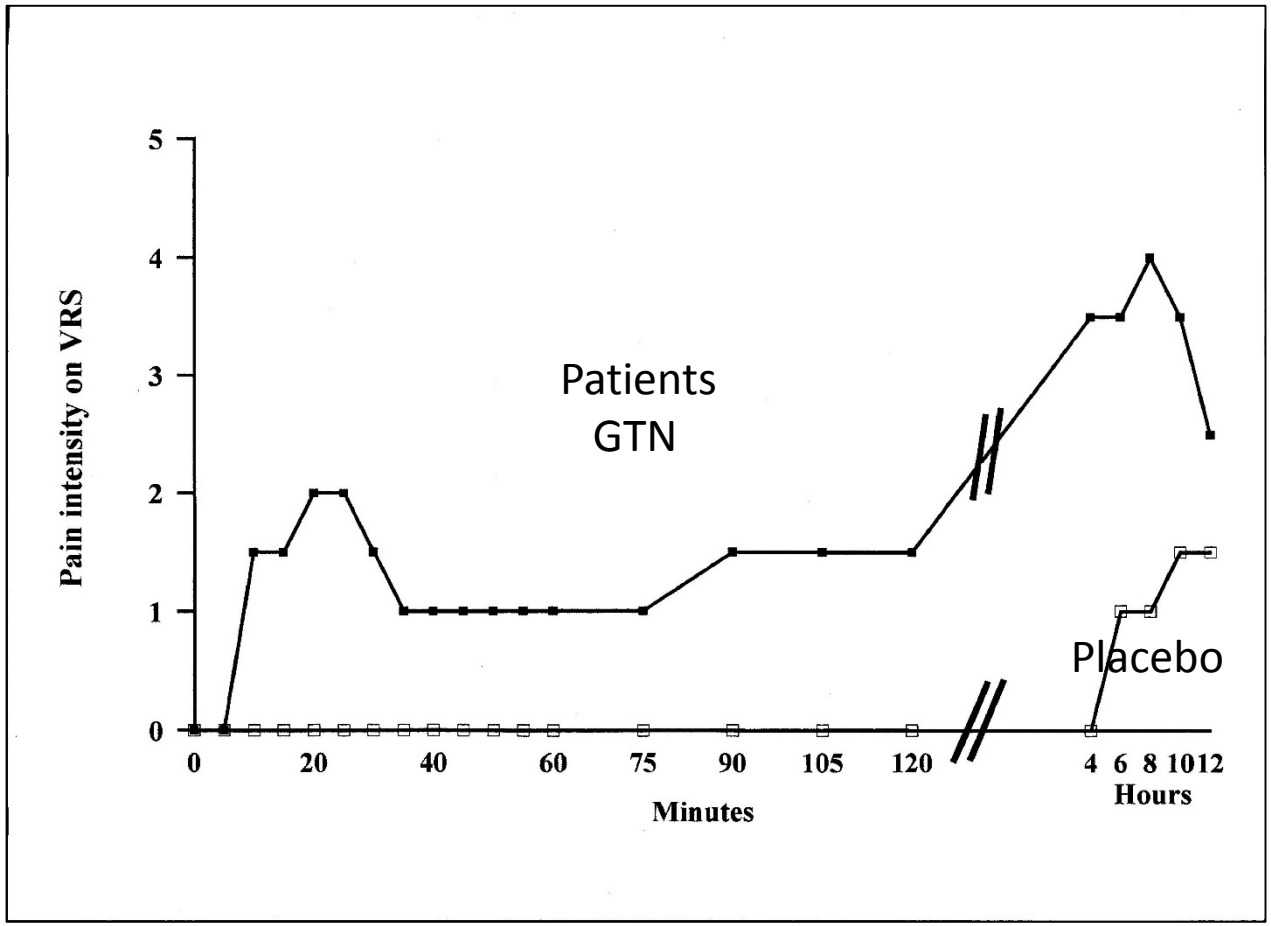
Dilatation of extra- and intracranial arteries in migraine?

In a review, evidence is presented that confirms

1. vasodilatation is indeed a source of pain in migraine
2. this dilatation does not involve the intracranial vasculature
3. the extracranial terminal branches of the external carotid artery are a significant source of pain in migraine

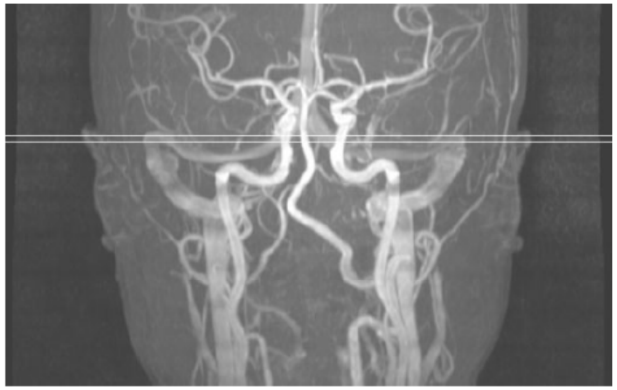
Shevel E.: The extracranial vascular theory of migraine – a great story confirmed by the facts. Headache. 2011 Mar;51(3):409-17

Nitroglycerin induces headache in tension type headache patients



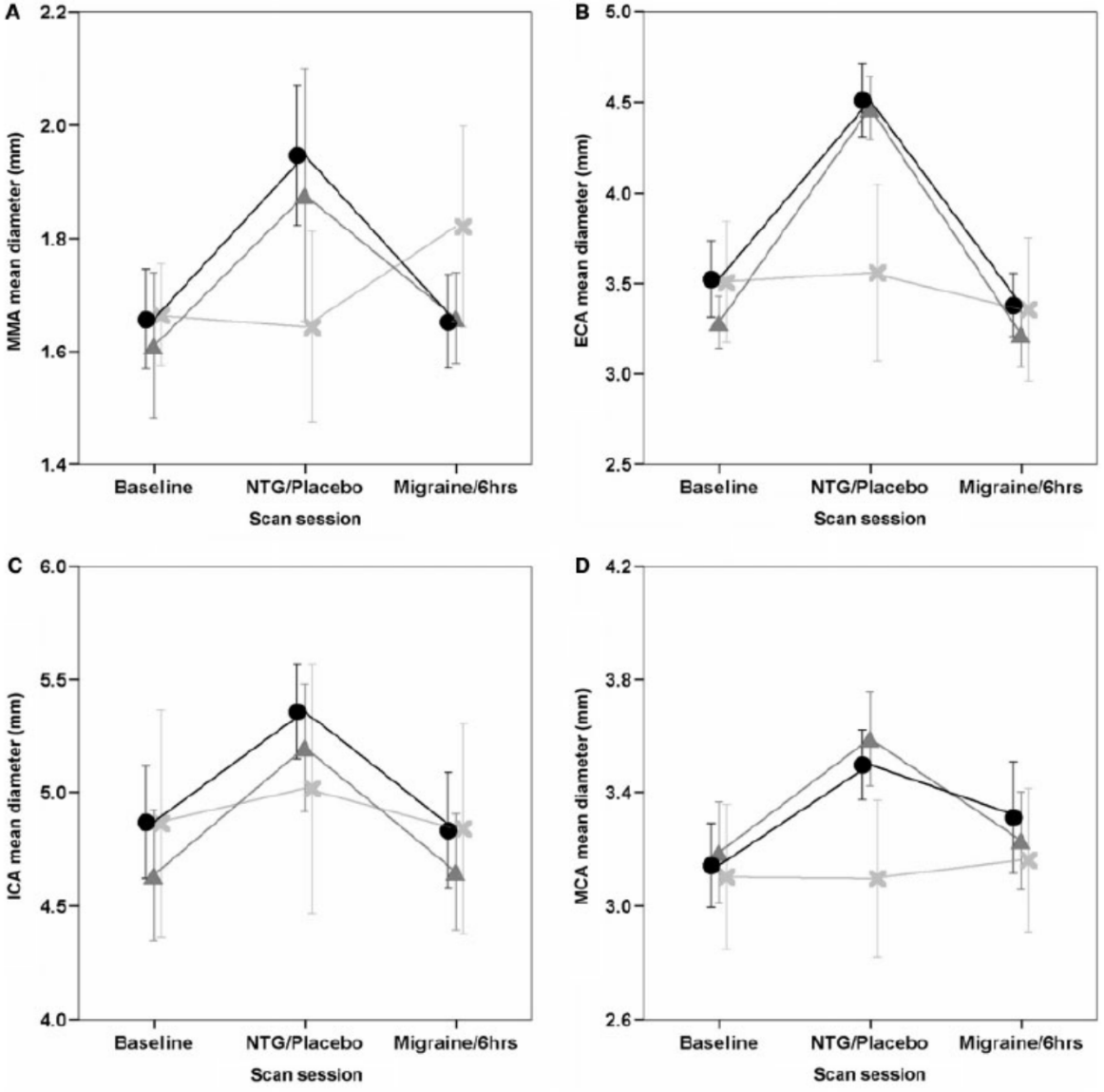
Ashina et al.: Possible mechanisms of glyceryl-trinitrate-induced immediate headache in patients with chronic tension-type headache. Cephalalgia. 2000; 20:919-24

Nitroglycerin causes vasodilatation independent of pain



- NTG with headache
- △ NTG without headache
- **x** Placebos

Schoonman et al.:
Migraine headache is not associated with cerebral or meningeal vasodilatation
Brain. 2008; 131:2192-200



A purely vascular origin of migraine ?

- It was hypothesized that intravenous infusion of the parasympathetic transmitter, vasoactive intestinal peptide (VIP), might induce migraine attacks in migraineurs
- Twelve patients with migraine without aura were allocated to receive 8 pmol kg(-1) min(-1) VIP or placebo in a randomized, double-blind crossover study
- None of the subjects reported a migraine attack after VIP infusion
- VIP mediates a marked dilation of cranial arteries, but does not trigger migraine attacks in migraineurs

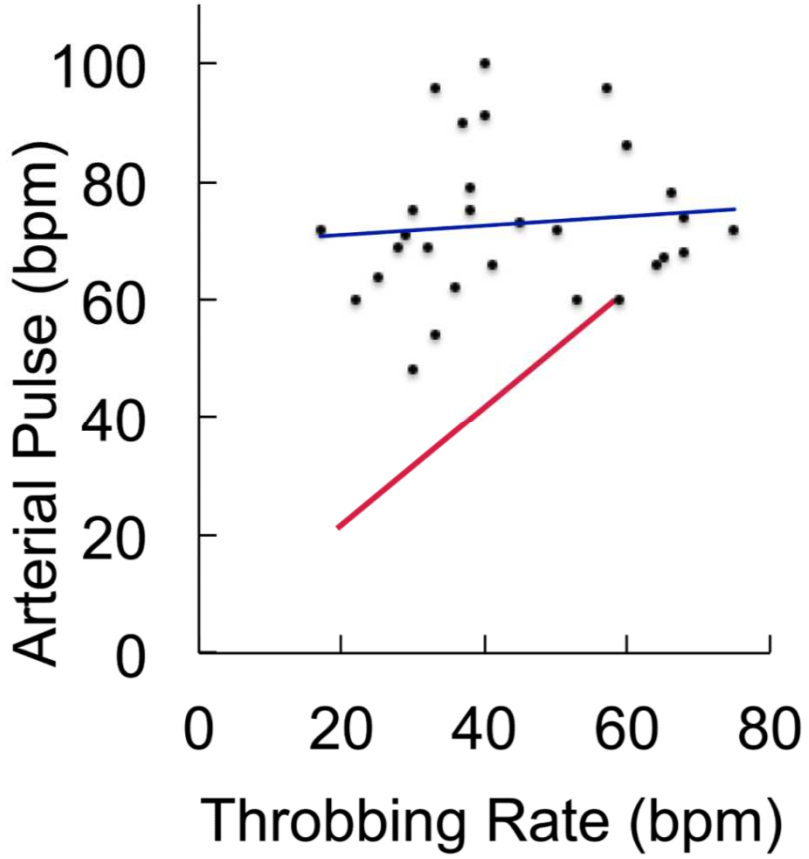
Rahmann et al.: Vasoactive intestinal peptide causes marked cephalic vasodilation, but does not induce migraine. Cephalalgia. 2008; 28:226-36

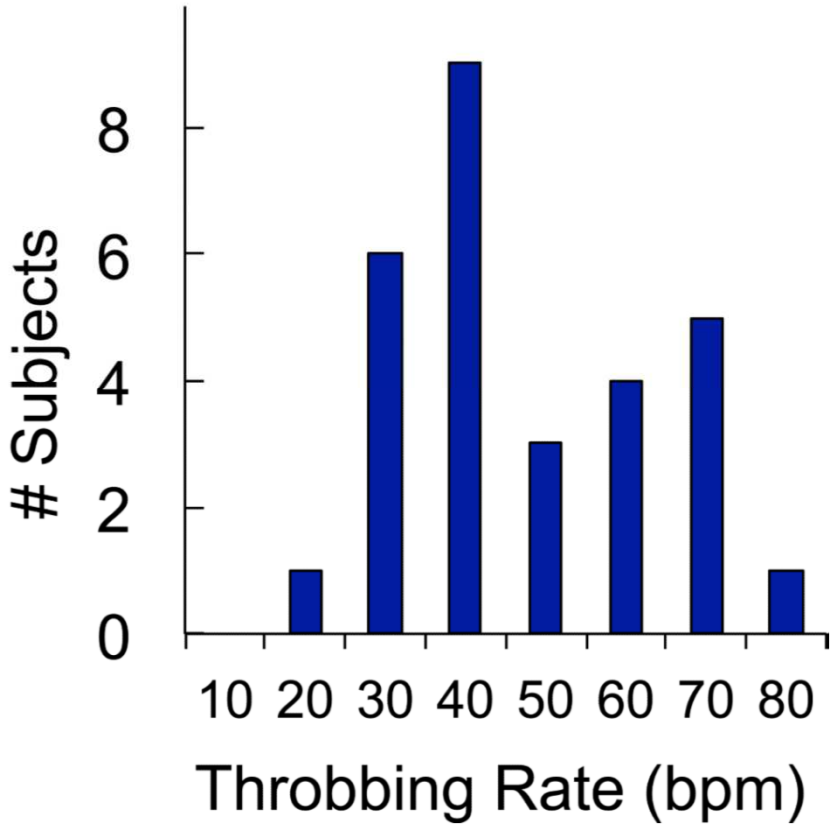
No evidence for vascular pathogenesis of migraine

- Only pituitary adenylate cyclase-activating peptide 38 (PACAP-38) caused delayed activation and sensitization of central trigeminovascular neurons, similar to its delayed effects in inducing migraine headache.
- After a 90-min delay, PACAP-38 induced a robust increase in ongoing spontaneous firing and hypersensitivity to intra- and extracranial somatosensory stimulation, which did not coincide with meningeal vasodilation.
- These data suggest that the endogenous mechanisms of migraine pathogenesis are located within the central nervous system, likely in the trigemino-cervical complex, and that the dural meninges and their primary afferent innervation are less likely to contribute to migraine initiation

Akerman, Goadsby: Neuronal PAC1 receptors mediate delayed activation and sensitization of trigeminocervical neurons: Relevance to migraine. Sci Transl Med. 2015;7:308

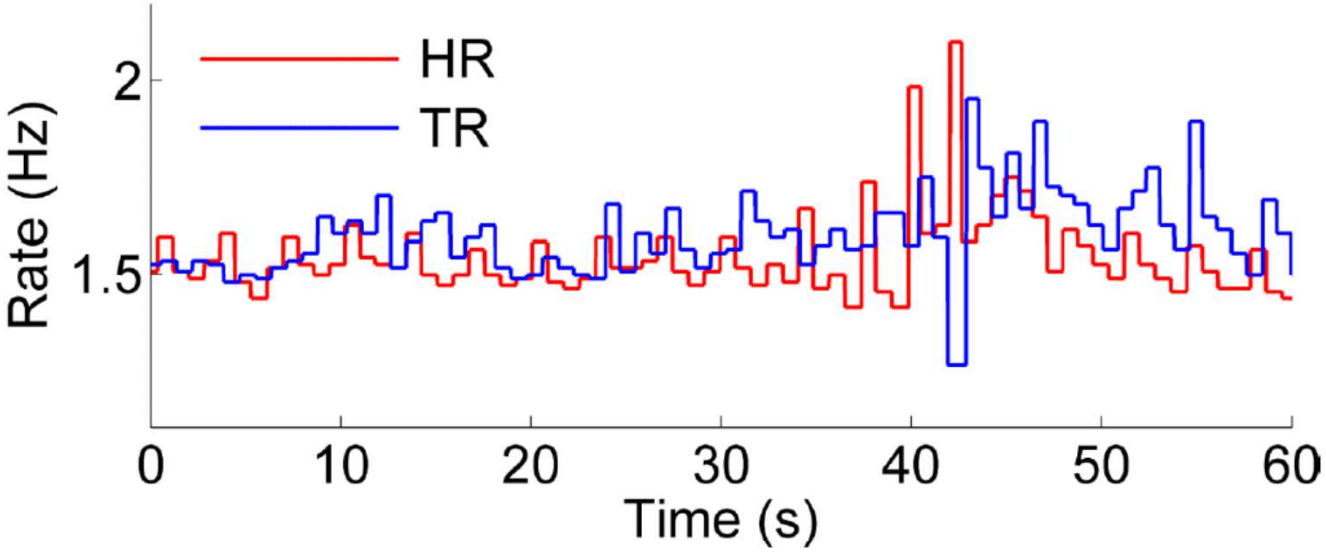
Throbbing pain does not correlate to heart beats

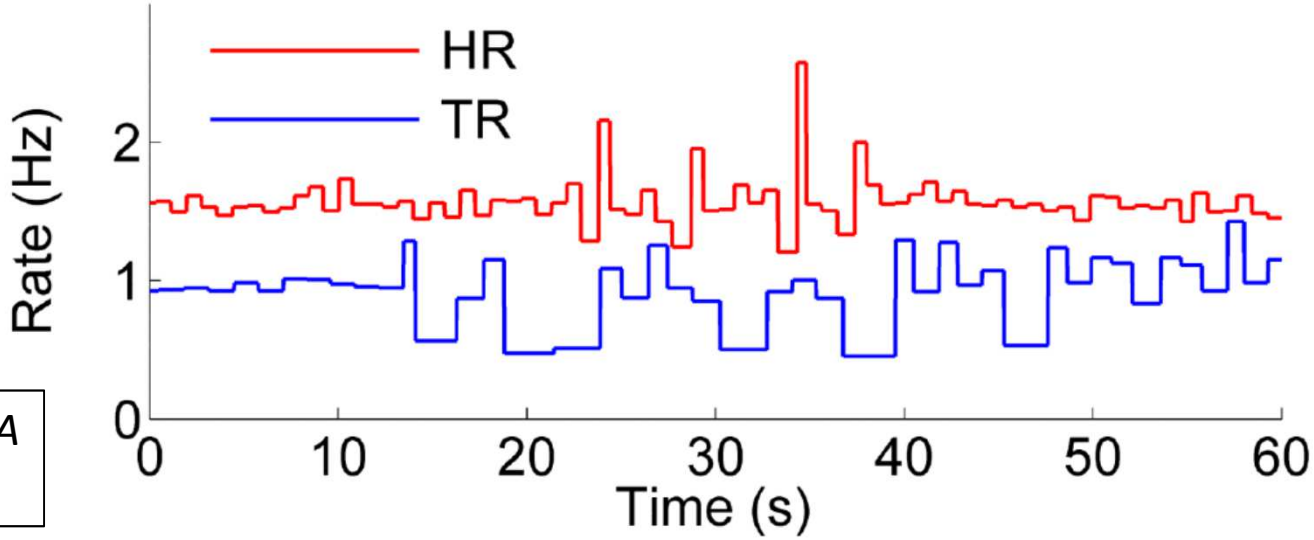




Mirza et al.: Is there a relationship between throbbing pain and Arterial pulsations? J Neurosci. 2012; 32: 7572–7576

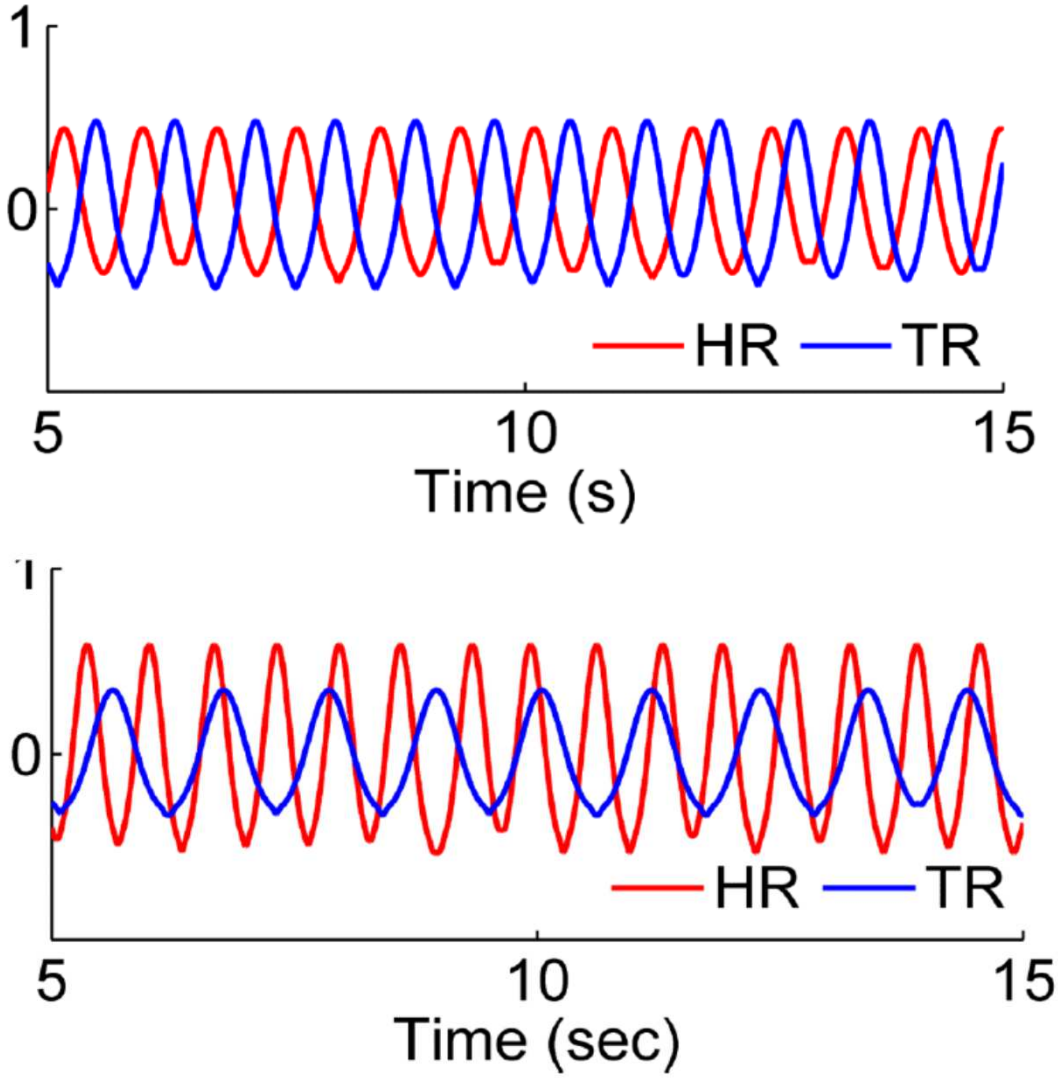
Throbbing dental pain is different to the heart rate

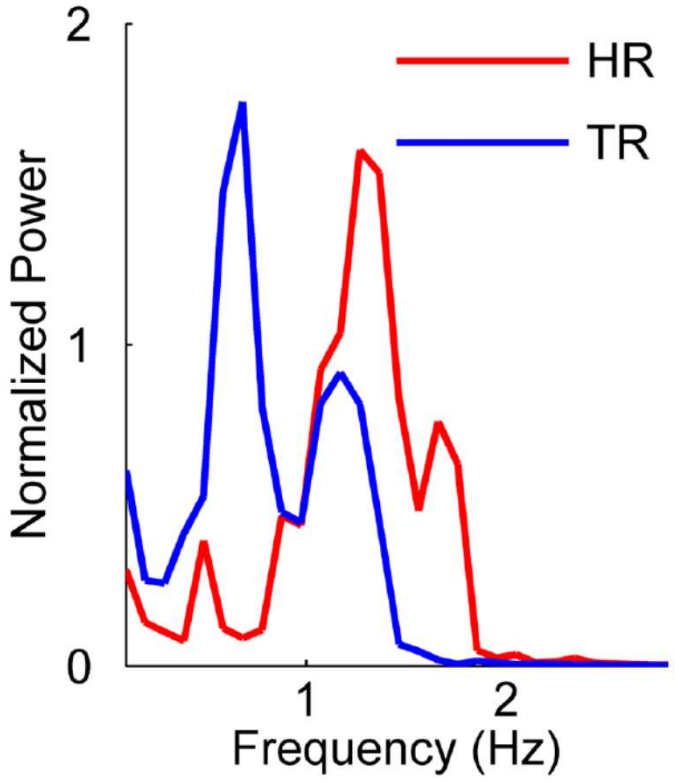




Mo J, Ahn A
Pain, 2013

Throbbing dental pain rate is asynchronous to heart rate

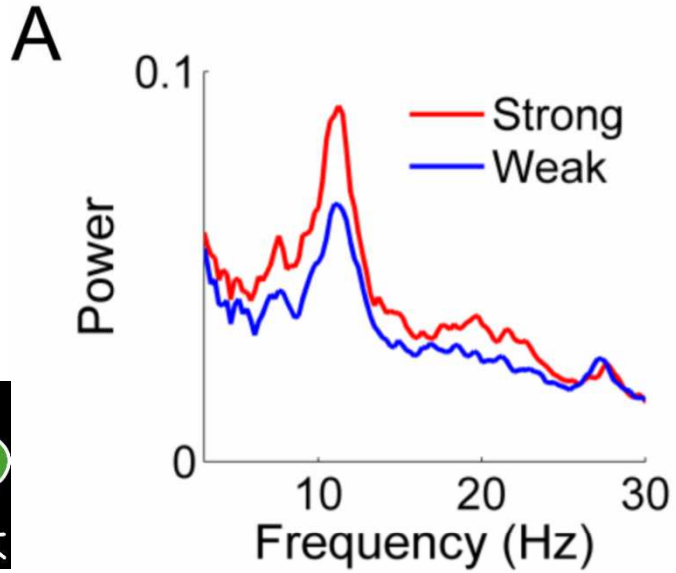




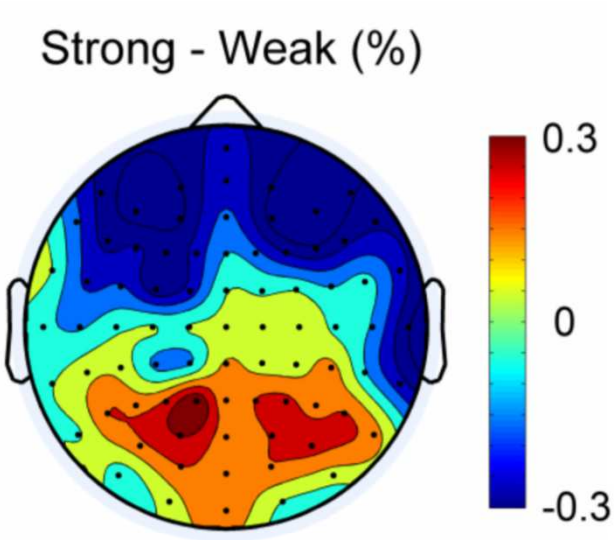
Mo J, Ahn A
Pain, 2013

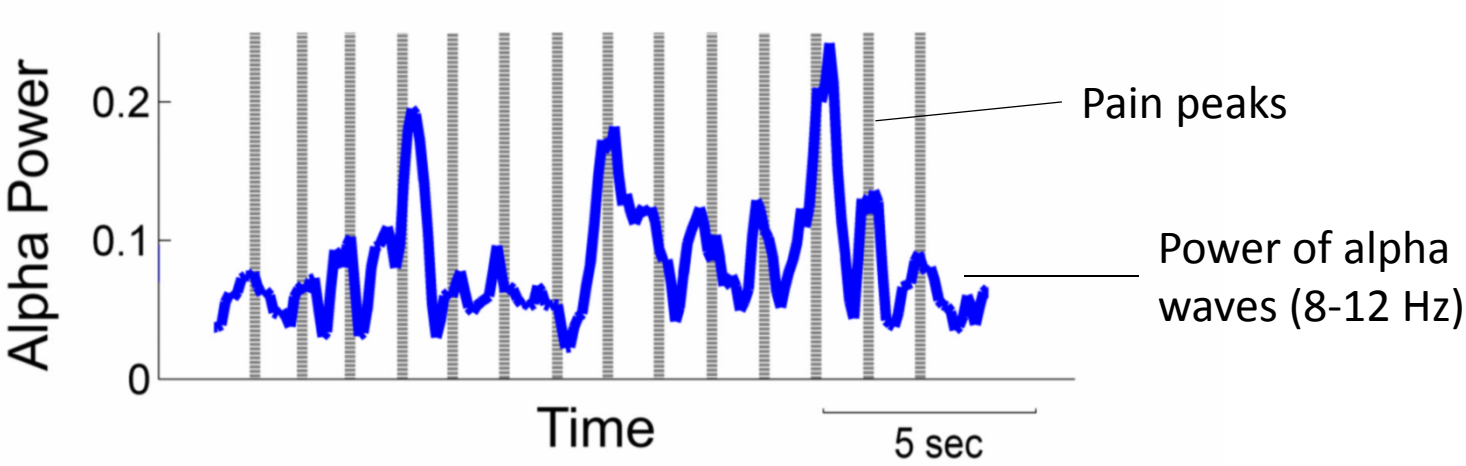
Throbbing pain rate is synchronous to alpha power of EEG

Power spectrum of alpha waves in one patient after migraine attack



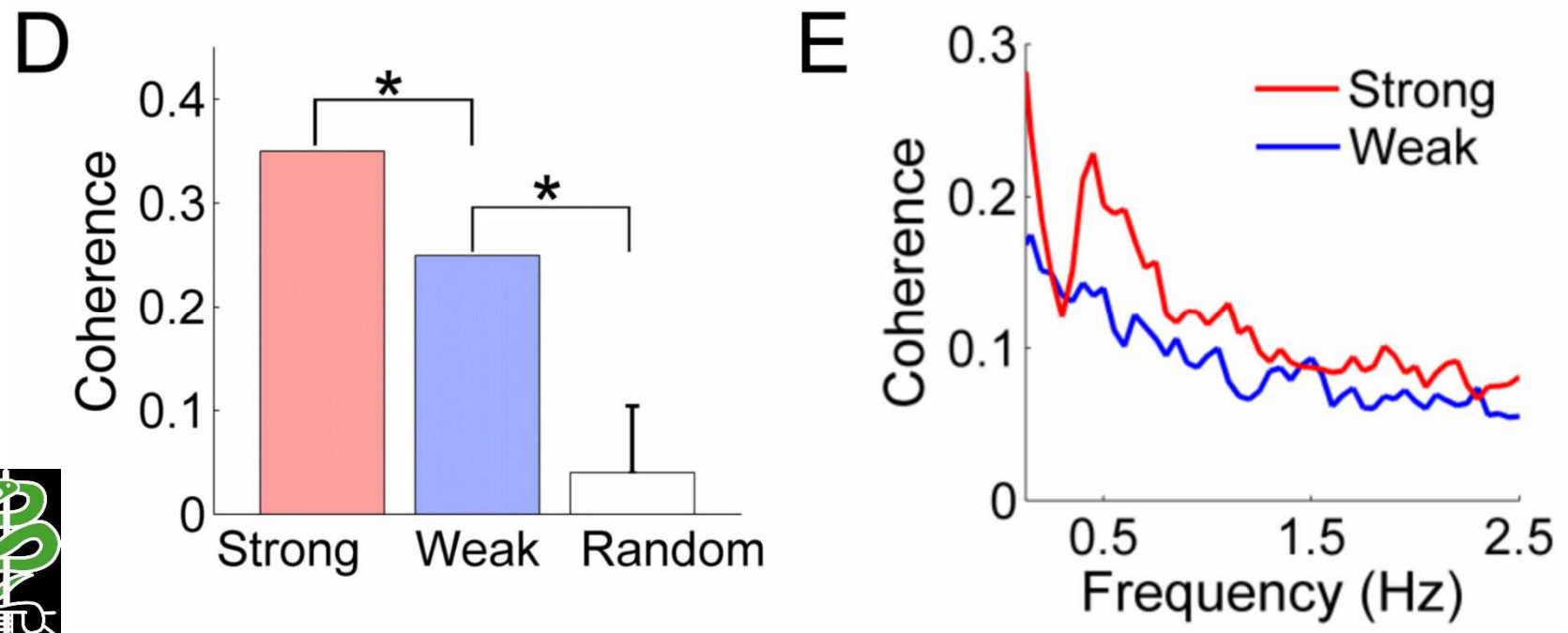
Variation of power in alpha waves (8-12 Hz) in different cortical regions





Mo J, Ahn A Pain, 2013

(D) Coherence around 0.7 to 1Hz between the alpha power time course and the throbbing reporting events. The coherence is significant compared to random permutation ($p < 0.05$) under either weak or strong throbbing session.
(E) Coherence of amplitude envelop of alpha oscillation was calculated between pairwise posterior



Mo J et al.: Does throbbing pain have a brain signature? Pain. 2013; 154: 1150–5

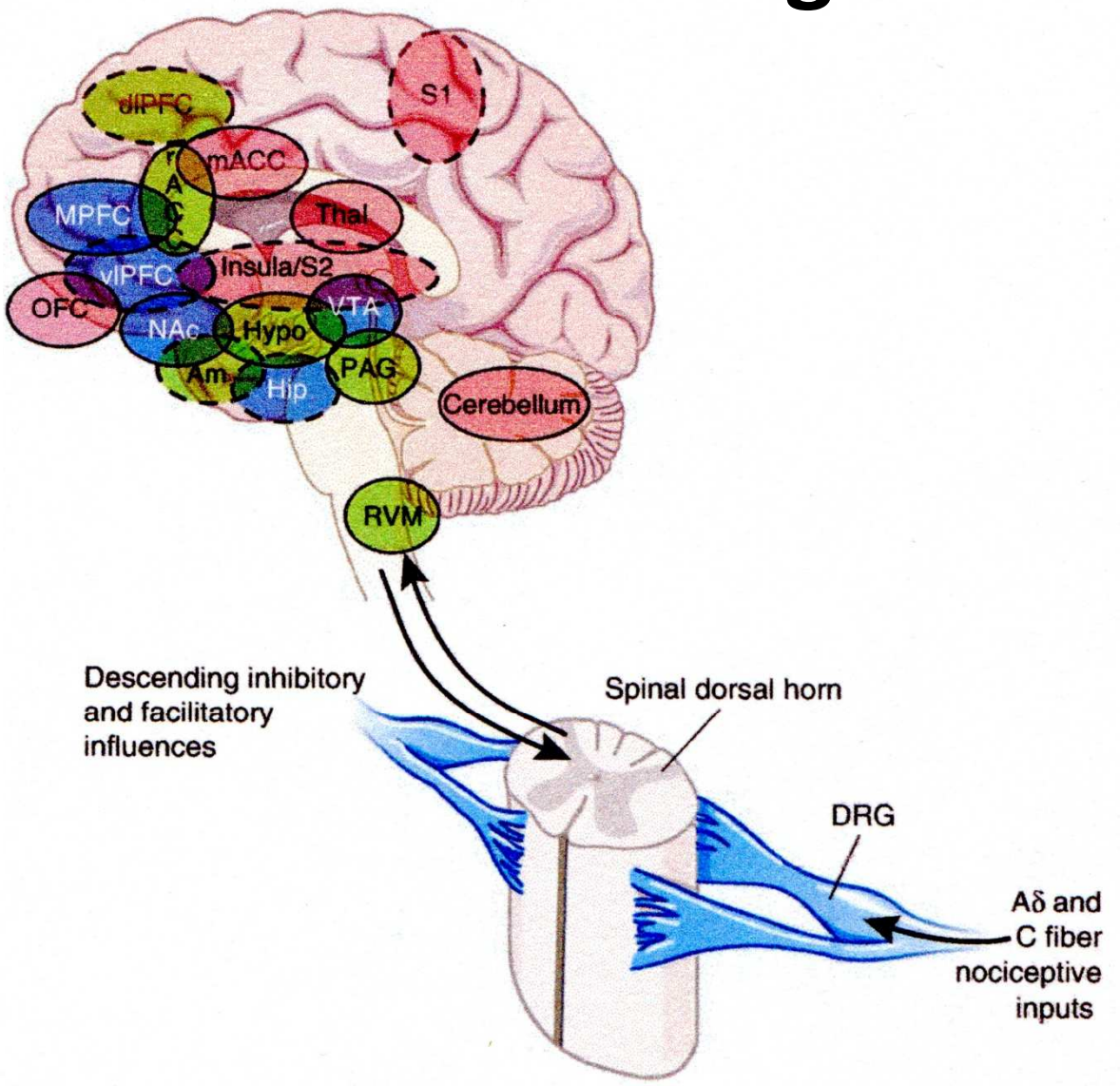
Throbbing pain rate is synchronous to alpha power of EEG

- EEG is generated by input through thalamo-cortical afferents
- EEG waves reflect synchronized afferent input to pyramidal cells
- Alpha power is generated cortically and desynchronizing control by brainstem activity

Central network involved in chronic pain conditions and learning

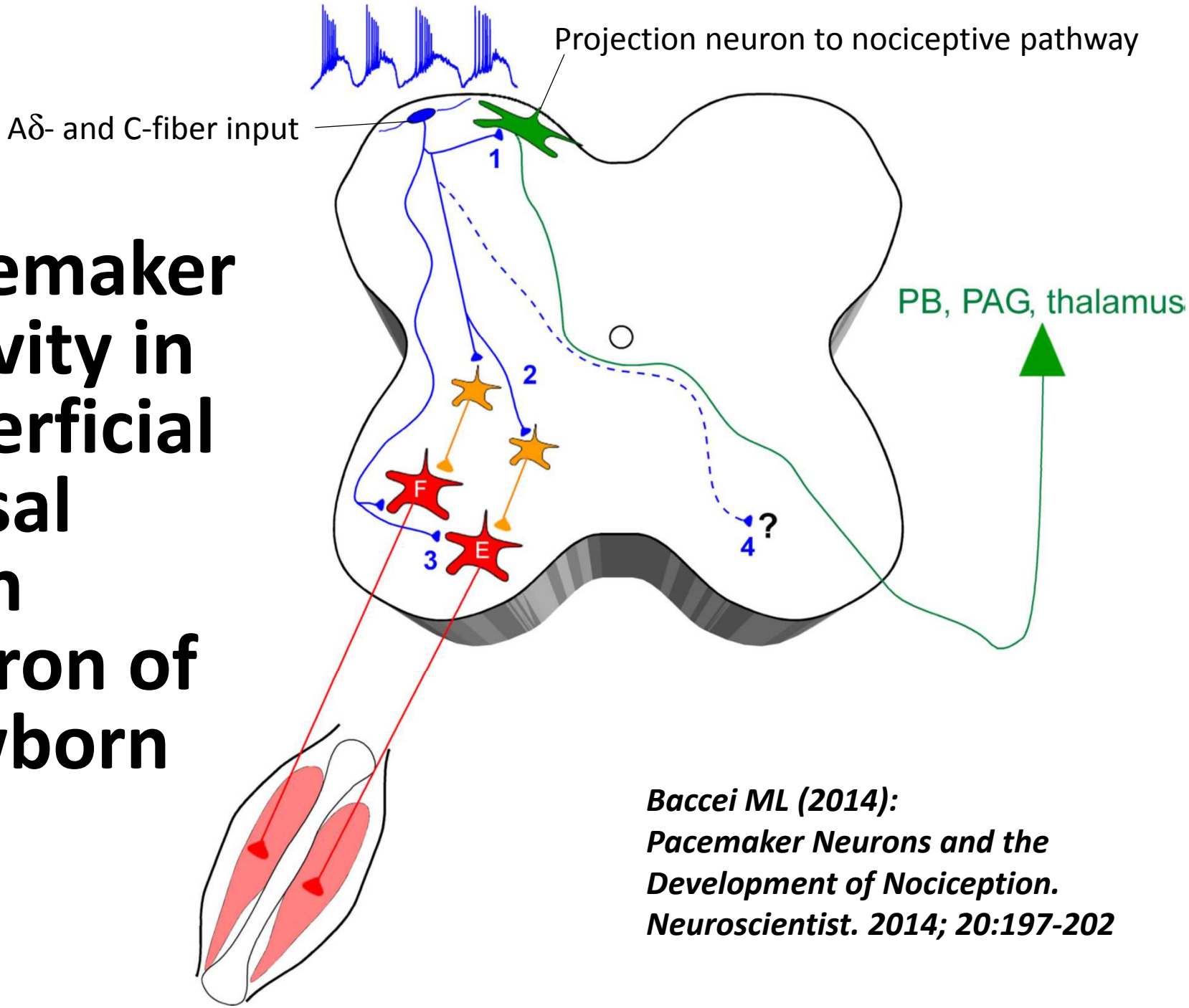
Networks with potential to affect risk for chronic pain

- Reward network
- Descending Pain Modulatory Systems (DPMS)
- Areas also relevant to pain percept, but that might not affect risk



Denk, McMahon & Tracey, 2014: Pain vulnerability: a neurobiological perspective. Nat Neurosci. 17:192-200

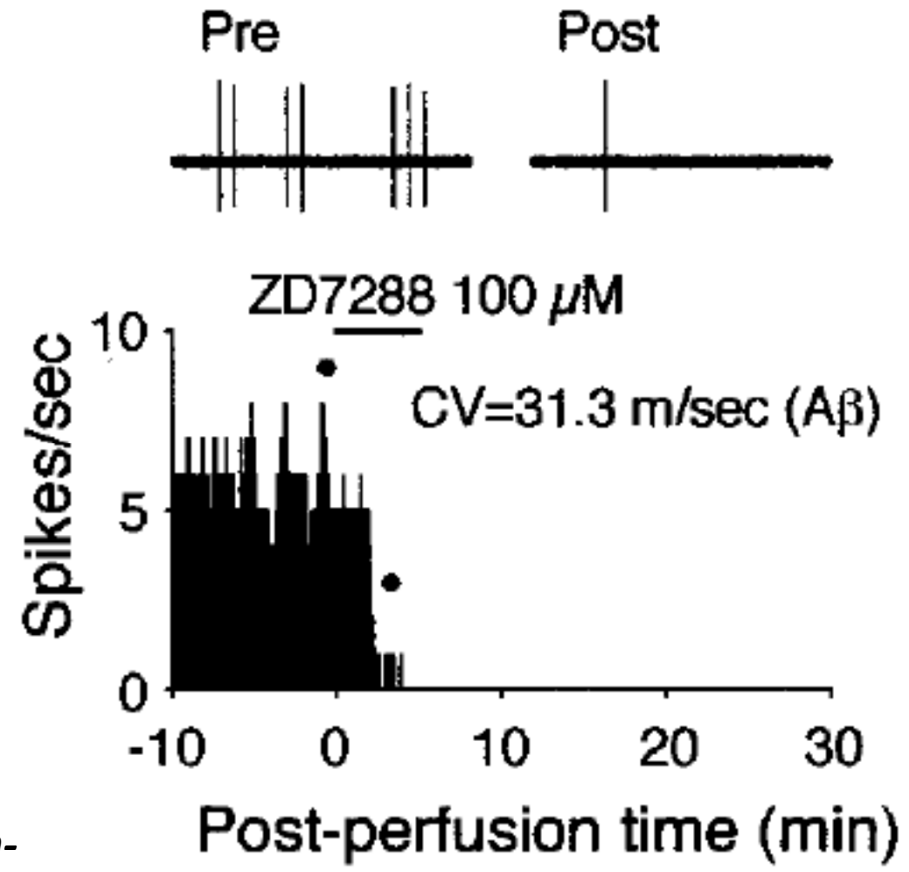
Pacemaker activity in superficial dorsal horn neuron of newborn rats



Baccei ML (2014): Pacemaker Neurons and the Development of Nociception. Neuroscientist. 2014; 20:197-202

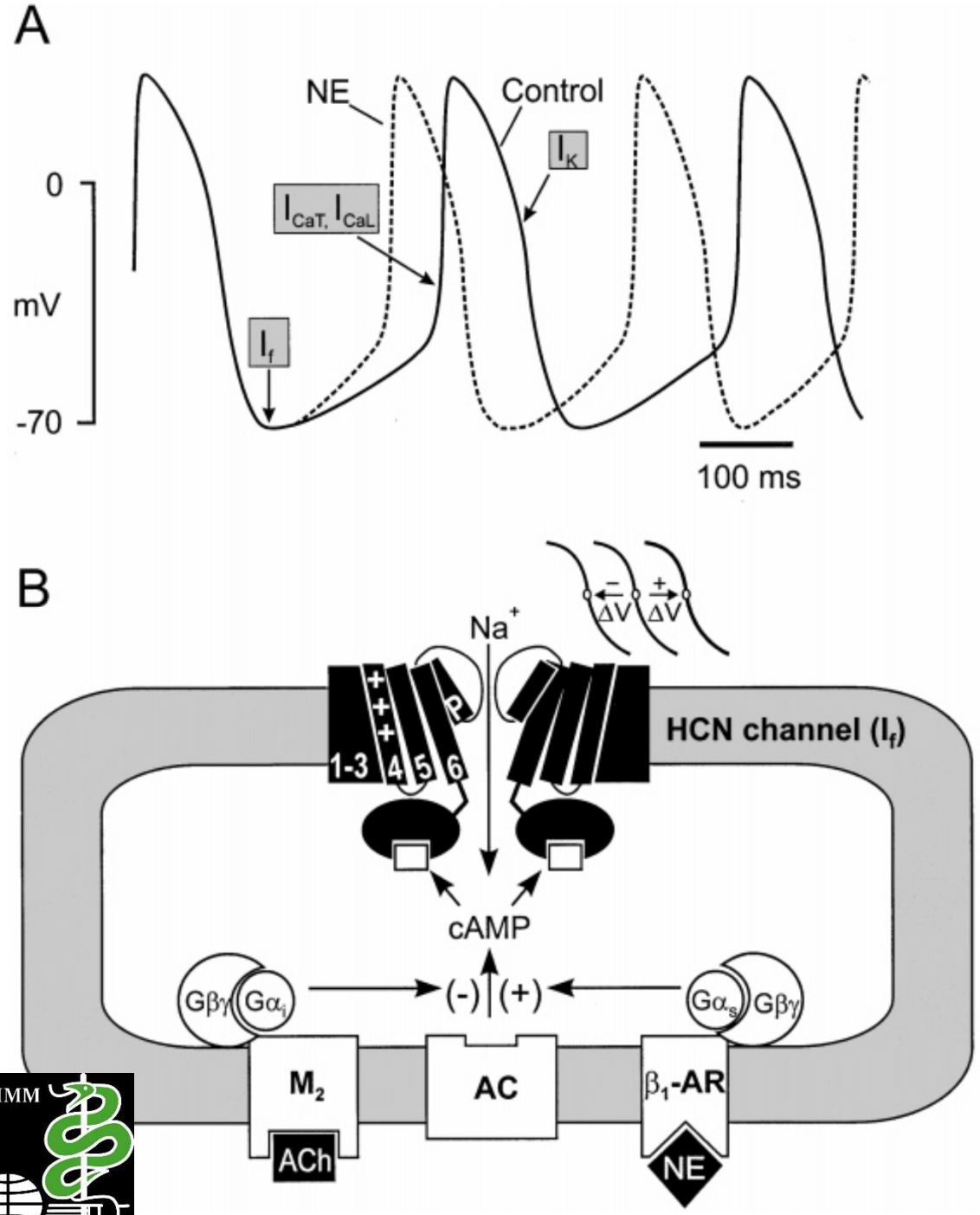
Rhythmic discharge of DRG neurons in a chronically injured nerve

Hyperpolarization-activated, cyclic nucleotide-modulated (HCN) “pacemaker” channels can be inhibited by specific pharmacological agents like “ZD7288”, leading to a new concept of pain therapy



Chaplan SR et al.: Neuronal Hyperpolarization-Activated Pacemaker Channels Drive Neuropathic Pain. J Neurosci, 2003; 23:1169 –78

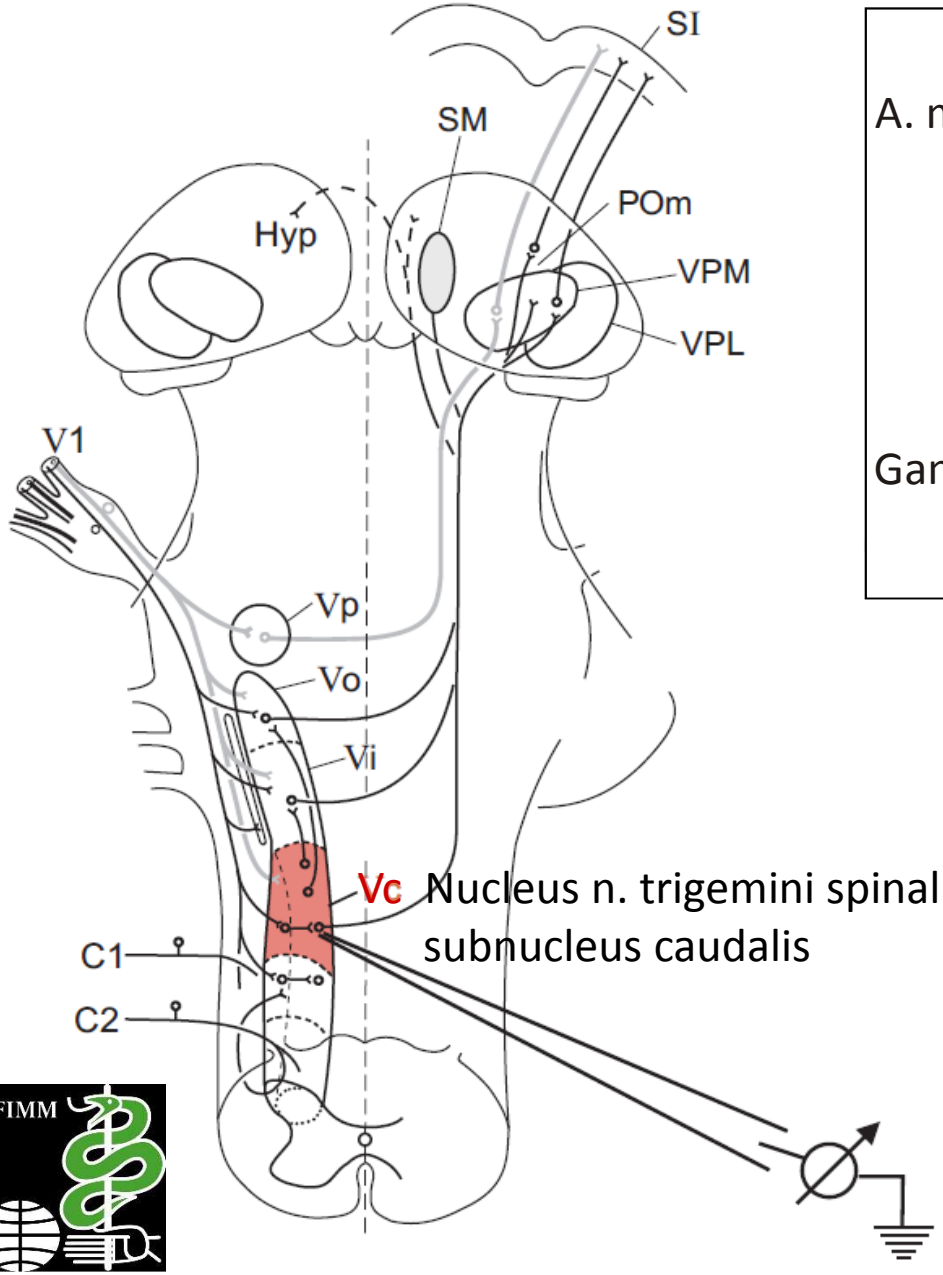
HCN channels mediate spontaneous depolarization in pacemaker



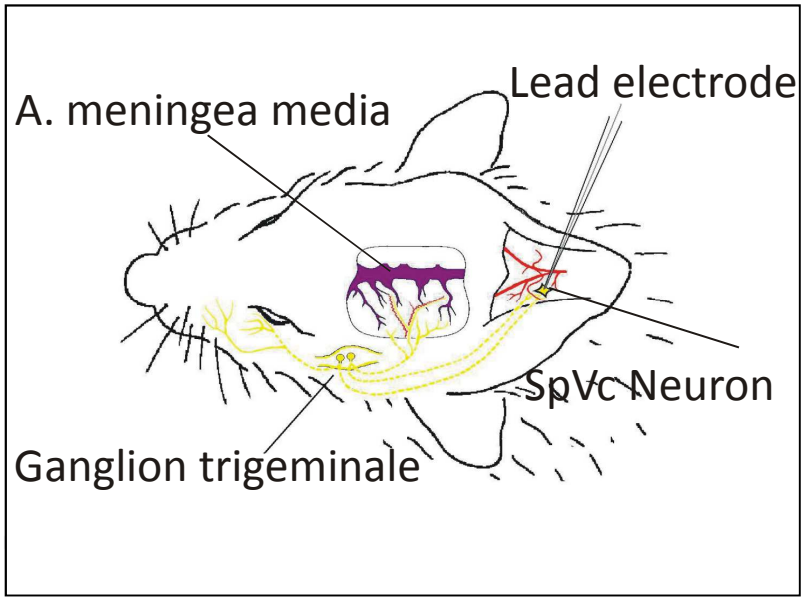
HCN channels activated by hyperpolarization and regulated by cyclic monophosphates (cAMP) produce I_f (funny current)

Biel M, Schneider A, Wahl C (2002) Cardiac HCN Channels: Structure, Function, and Modulation Trends Cardiovasc. Med., 5: 206-13

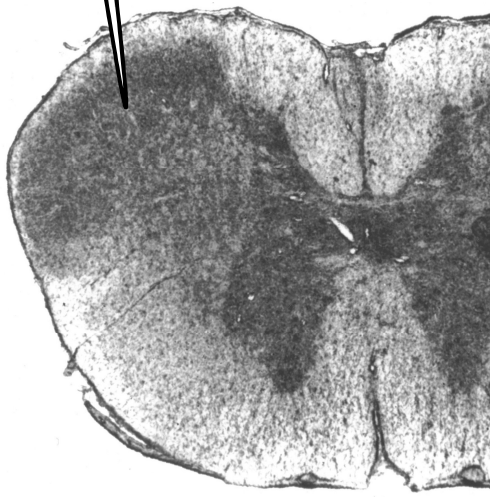
Central trigeminal system & SpVc



Nucleus n. trigemini spinalis, subnucleus caudalis

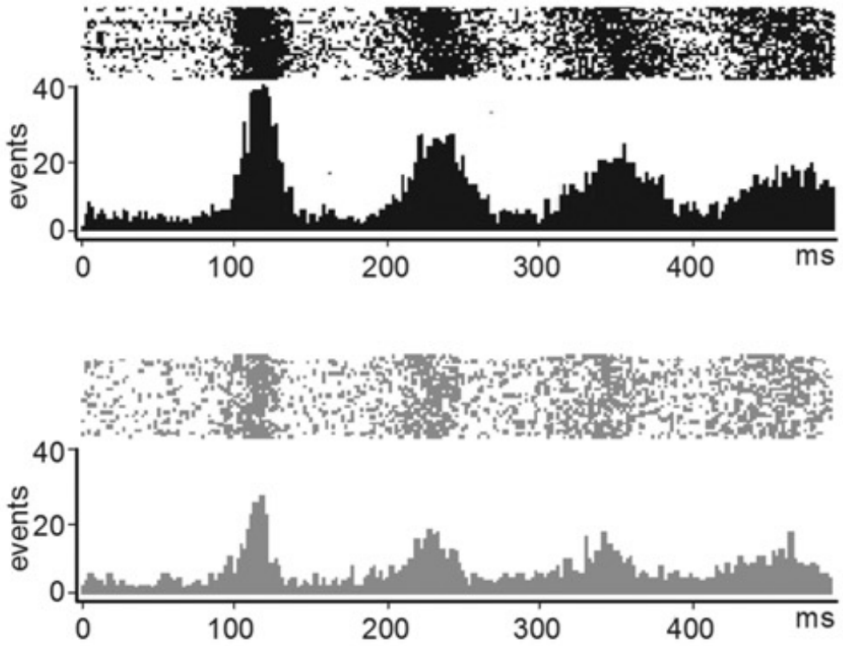


Spinal trigeminal nucleus (SpVc)



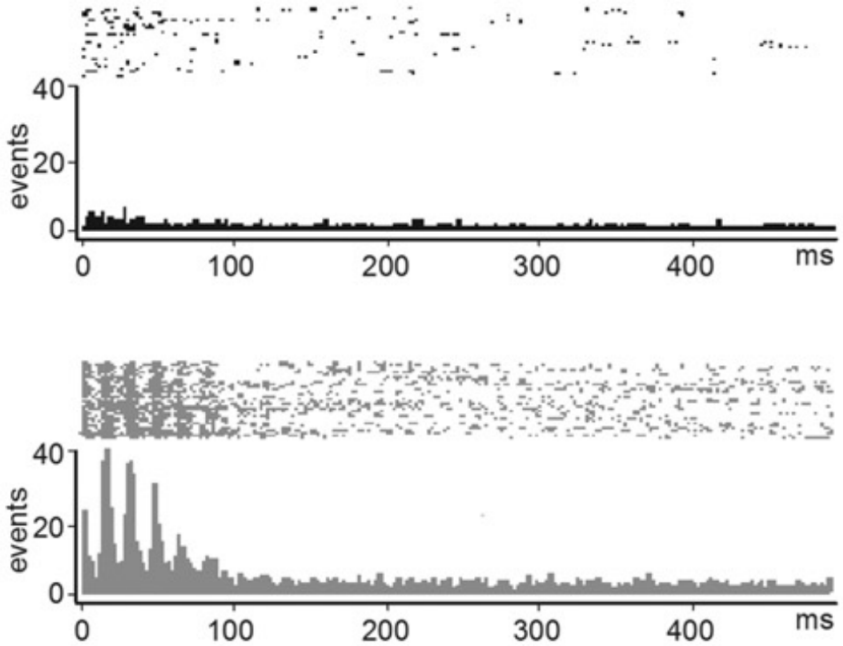
Neurons in the trigeminal subnuclei show rhythmic activity (rat)

26% of Sp5i neurons



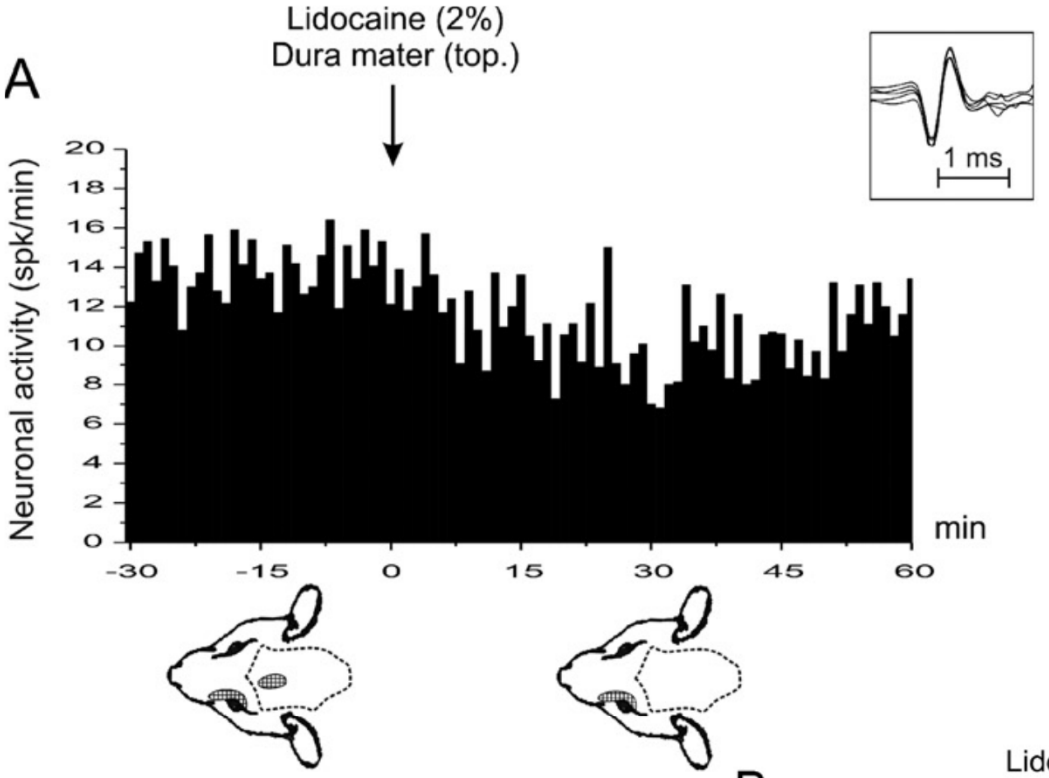
Spontaneously oscillating low frequency (8 Hz) spinal subnucleus interpolaris (Sp5i) neuron

18% of Pr5 neurons

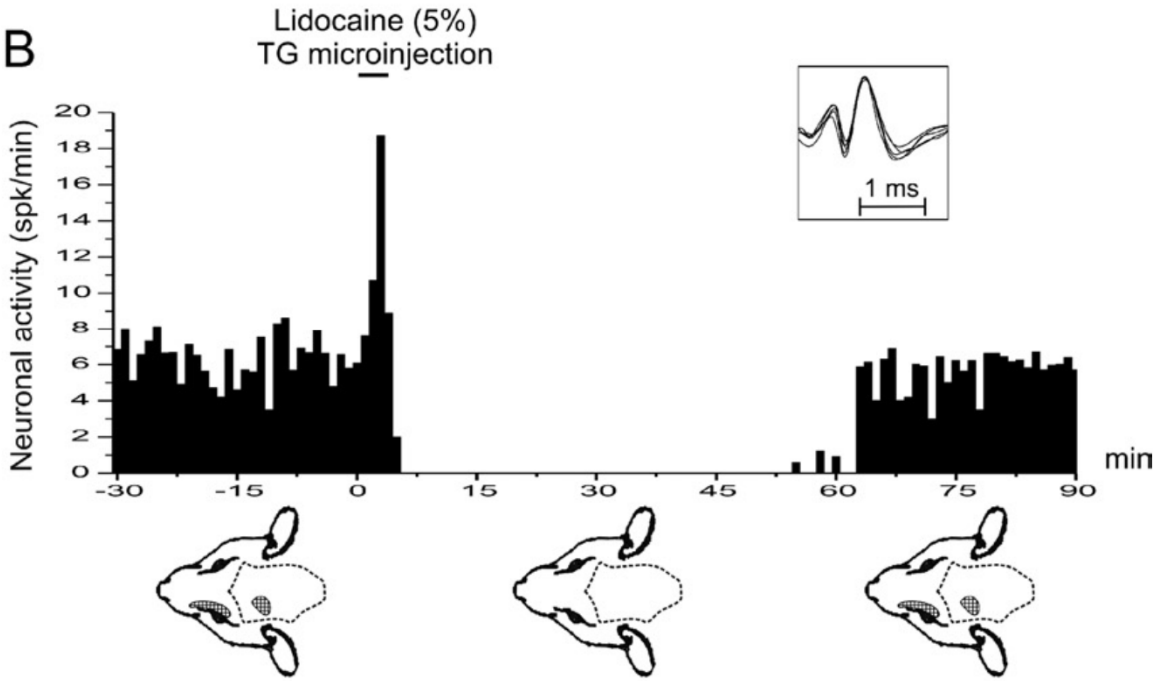


Only under stimulation of vibrissae (bottom) oscillating high frequency (45 Hz) principle nucleus (Pr5) neuron

PANETSOS F, SANCHEZ-JIMENEZ A (2010) SINGLE UNIT OSCILLATIONS IN RAT TRIGEMINAL NUCLEI AND THEIR CONTROL BY THE SENSORIMOTOR CORTEX. Neuroscience 169: 893–905



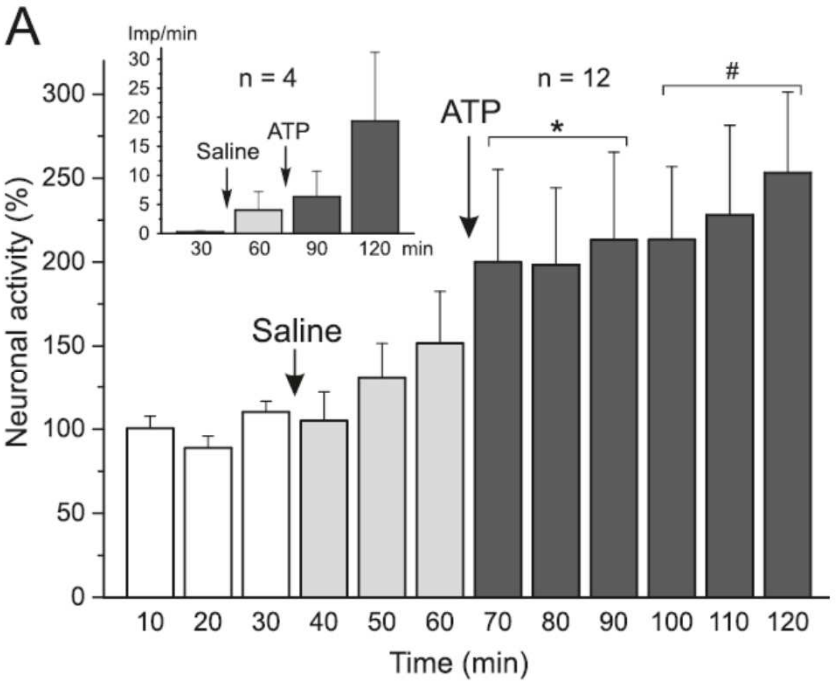
(A) Effect of topical application of 2% lidocaine onto the injured area (exposed dura mater and cut edges of cranial bone) on the ongoing activity of a Sp5c neuron and its receptive fields.
(B) Effect of microinjection of 5% lidocaine into the maxillary/ ophthalmic region of the trigeminal ganglion on the activity of a Sp5c neuron and its receptive fields.



ROCH M, MESSLINGER K et al. (2007) ONGOING ACTIVITY IN TRIGEMINAL WIDE-DYNAMIC RANGE NEURONS IS DRIVEN FROM THE PERIPHERY. Neuroscience 150: 681–91

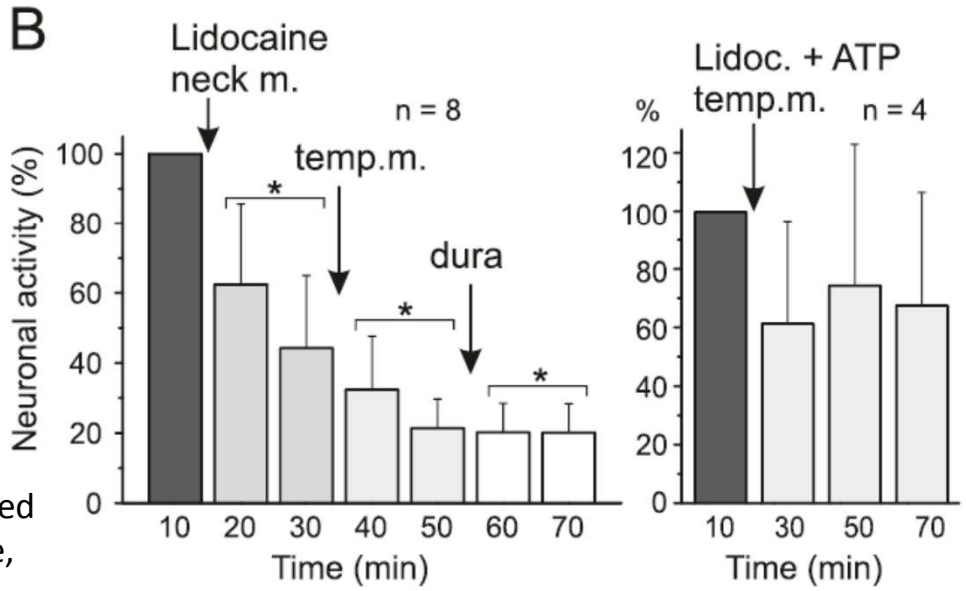
ATP-sensitive muscle afferents activate spinal trigeminal neurons with meningeal afferent input in rat

Nöbel M, Feistel S, Ellrich J, Messlinger K
J Headache Pain (2016) 17:75-83

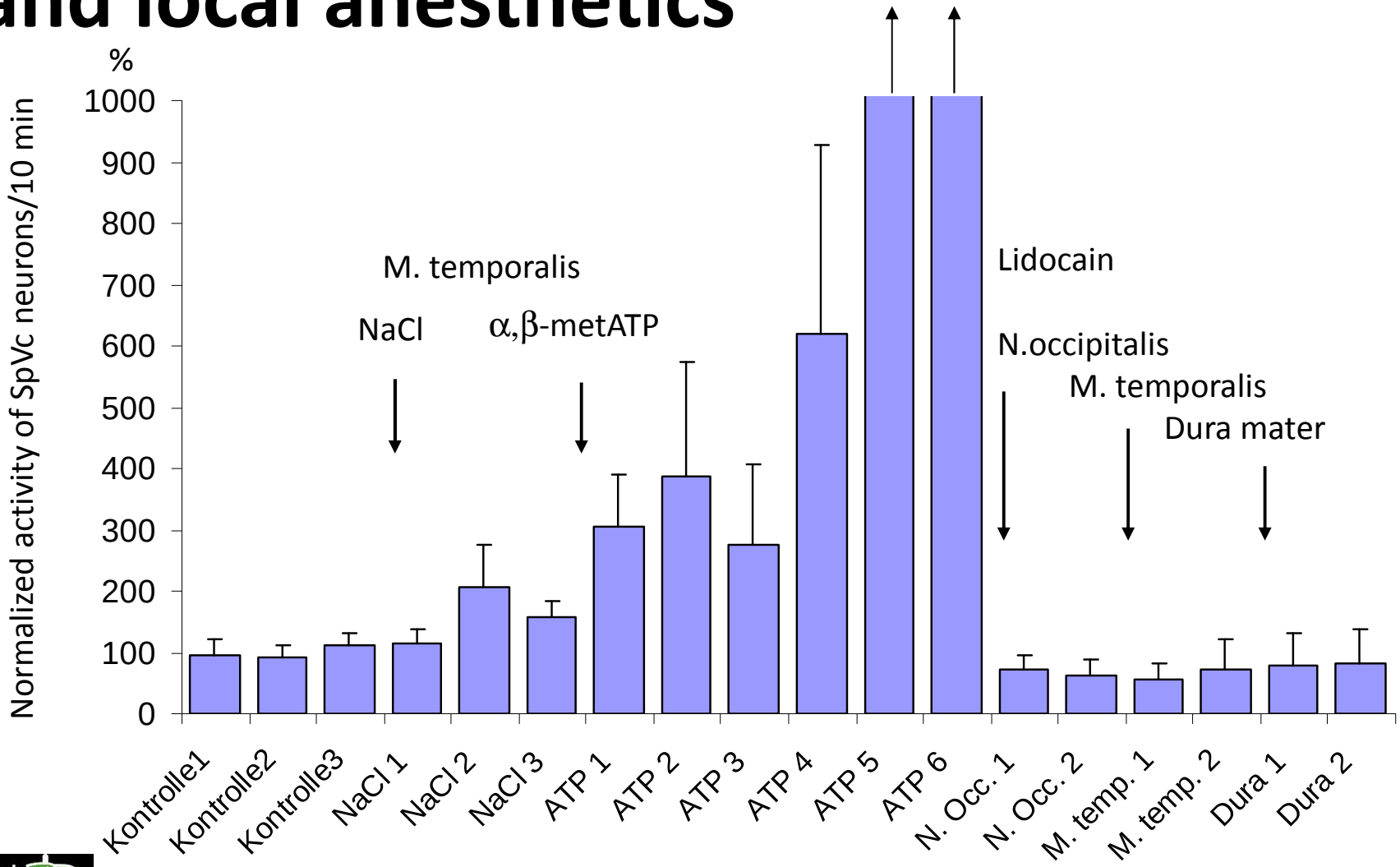


Activity of spinal trigeminal neurons pre-treated by injection of α,β-meATP into the ipsilateral temporal muscle. Left: The activity (normalized to the 10 min interval following the experiment is significantly (*) reduced after injection of lidocaine into the occipital muscles and further after injection into the temporal muscle (left) but not more after application of lidocaine onto the dura mater. Right: Four additional units recorded during lidocaine injection only into the temporal muscle, three of them showing decreased activity.

The normalized activity displayed in 10 min intervals increased more and more after injection of vehicle (saline) and α,β-meATP (ATP) into the ipsilateral temporal muscle (* significant difference to baseline, # to baseline and intervals after vehicle). The inset shows four additional units (activity displayed in 30 min intervals) which did not fit to the normalized sample because of their low spontaneous activity and relatively high activation following α,β-meATP injection.



Modulation of neuronal activity by ATP and local anesthetics



Noebel M et al.: ATP-sensitive muscle afferents activate spinal trigeminal neurons with meningeal afferent input in rat. The Journal of Headache and Pain (2016) 17:75-83

Summary – part 2

- The existence of a “craniosacral” rhythm is doubtful
- Primary headaches like migraine do not have a vascular origin
- Pulsating headache is not a result of vascular pulsation
- Throbbing pain is not synchronous to arterial pulsation
- The rhythm of throbbing pain is synchronous to the alpha-power in the EEG
- The cycling alpha power depends probably on thalamic networks
- Central and peripheral neurons can produce rhythmic activity
- One basis of oscillating neuronal activity is the expression of HCN channels
- Rhythms in the trigeminal pain system depend probably on central networks

Thank you for your attention!