New aspects about Headache

16th FIMM International Scientific Conference

Varna, September 17, 2016

“More Science – Less Pain”

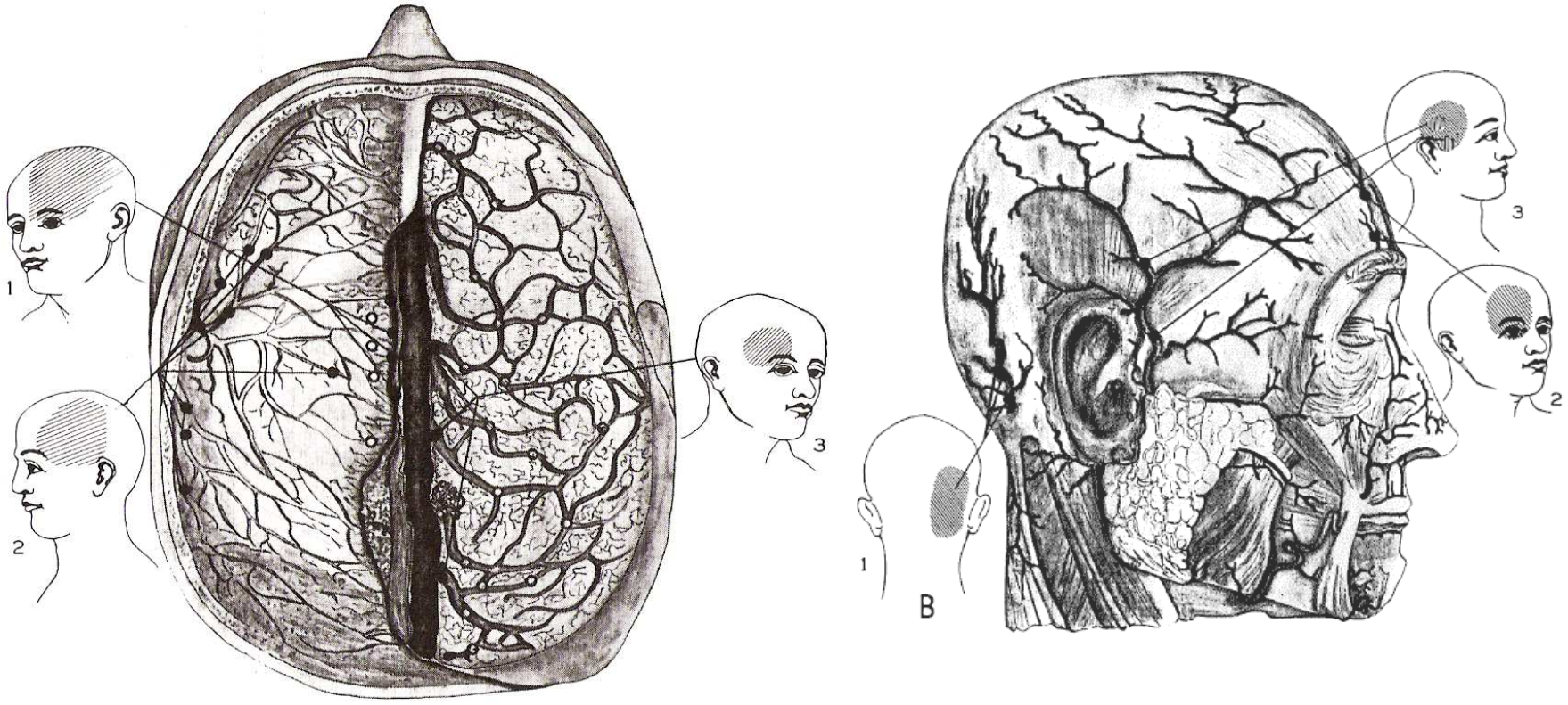
Part I
Innervation of extracranial tissue by meningeal afferents

Prof. Karl Messlinger
Markus Schueler (2014)

Institute for Physiology & Pathophysiology
University Erlangen-Nurnberg

Presented by Wolfgang von Heymann
Germany

Cranial structures whose stimulation will create headache



Ray & Wolff, Arch. Surg. 41: 613-856 (1940)

Historical description of intracranial nerves to the dura

ICONES

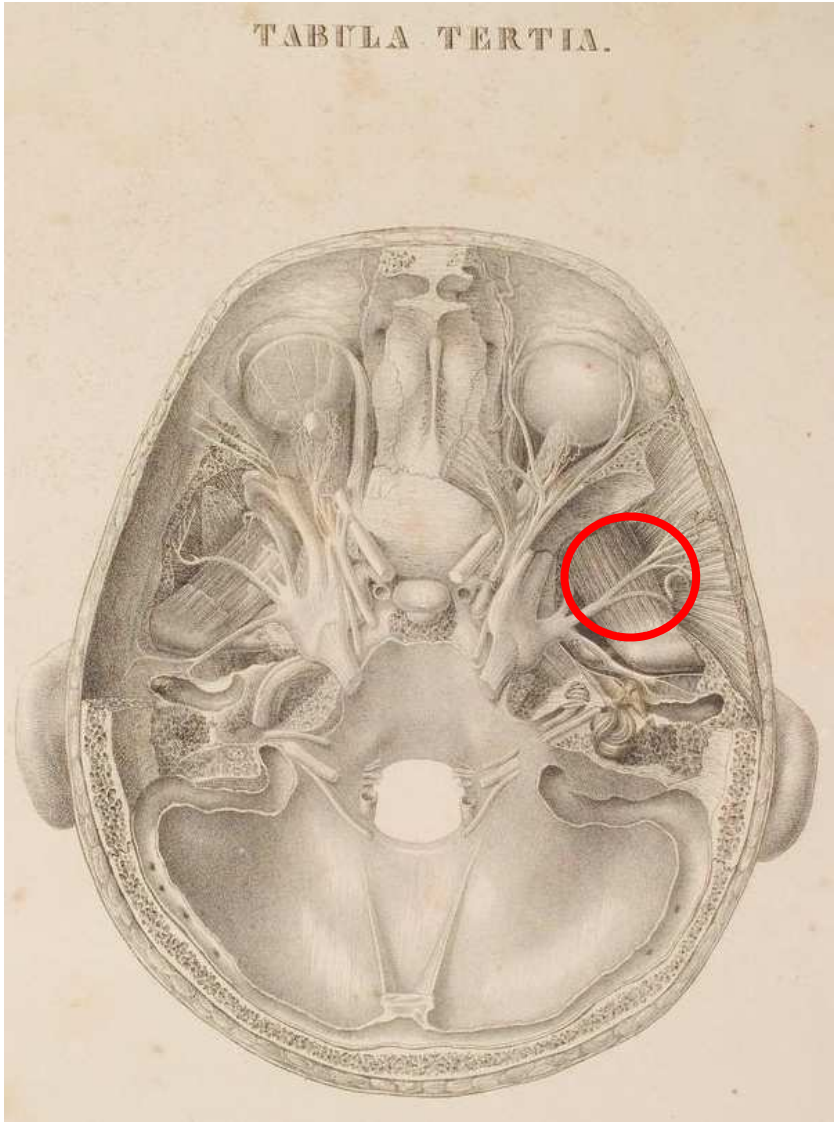
NERVORUM CAPITIS

First description of recurrent branches of the trigeminal nerve

IN LUCEM EDITAE

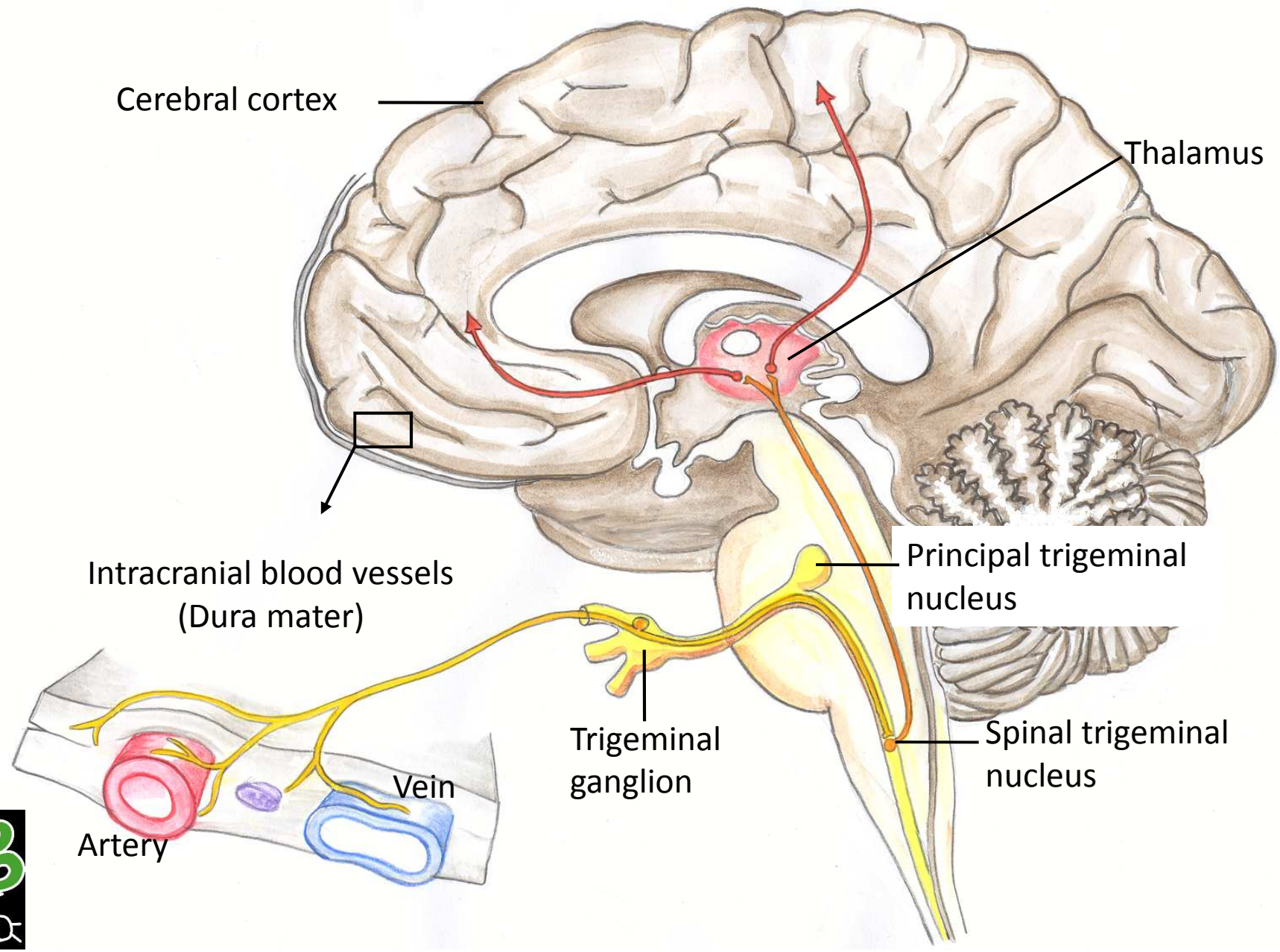
AUCTORE

FRIDERICO ARNOLDO.



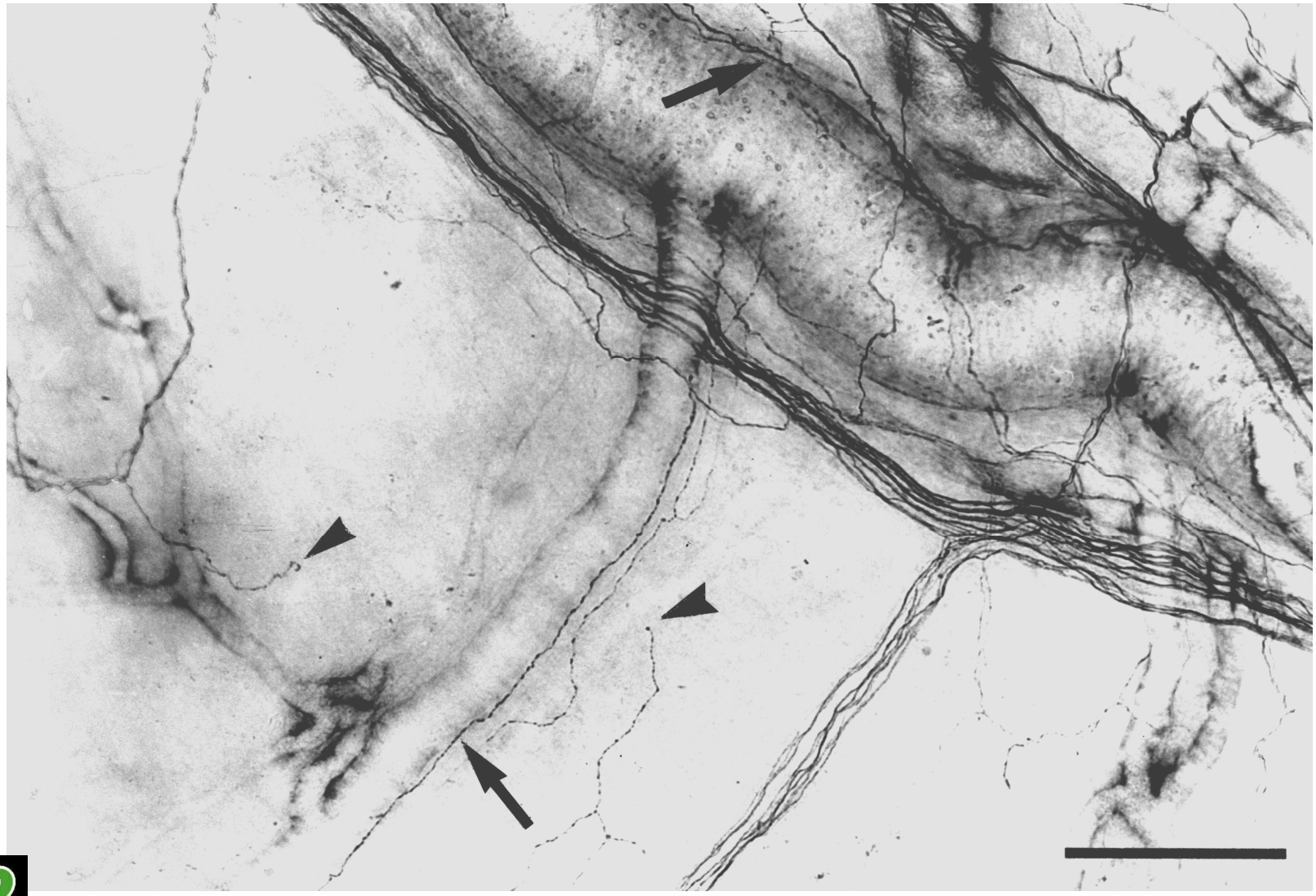
Arnold 1851

The human trigemino-vascular system



CGRP-ir nerve fibers around the A. meningea media

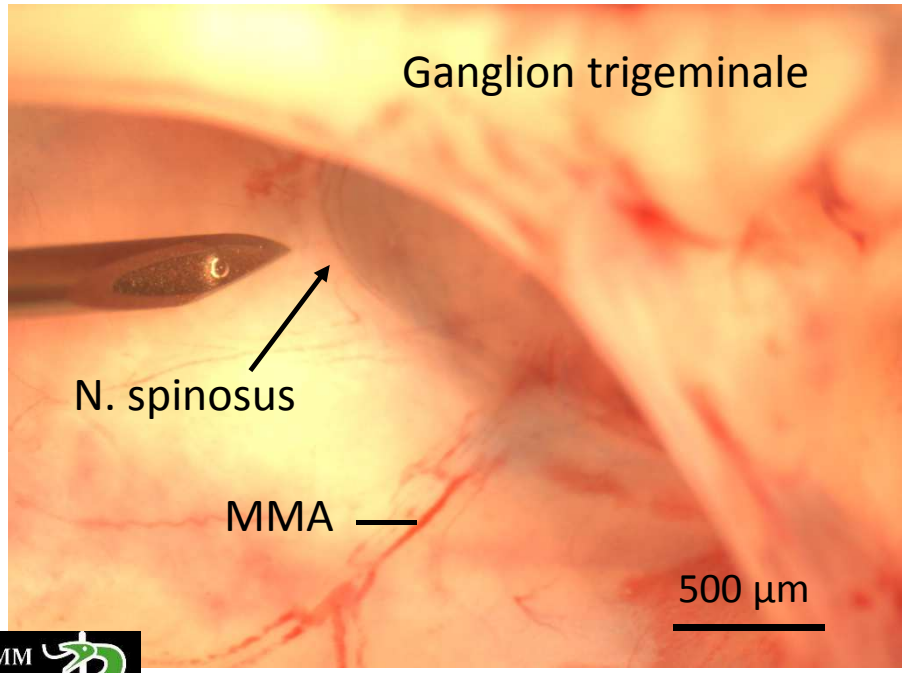
CGRP = Calcitonin gene-related peptide

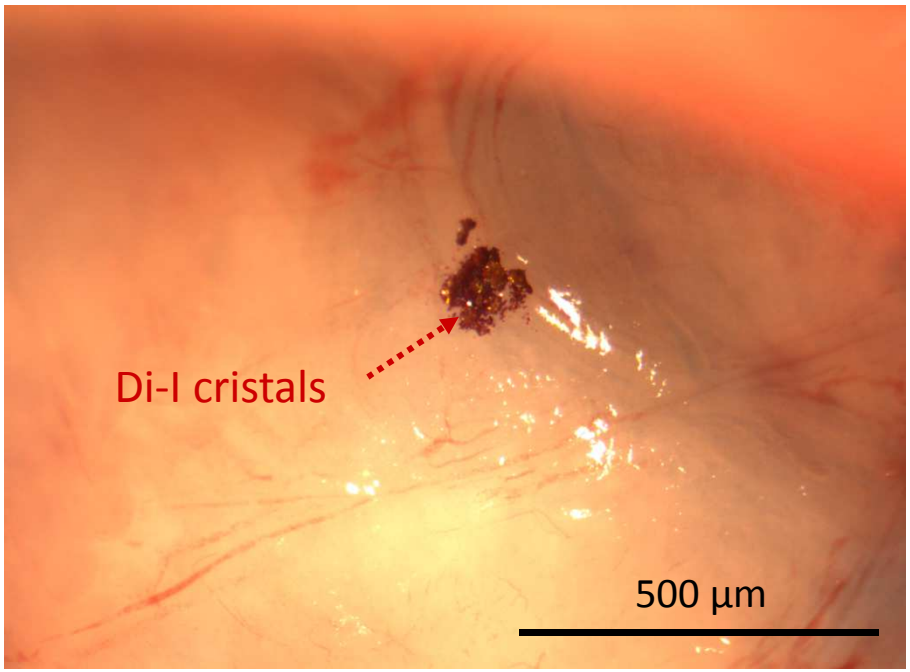


K. Messlinger et al., Anat. Embryol. 188 (1993)

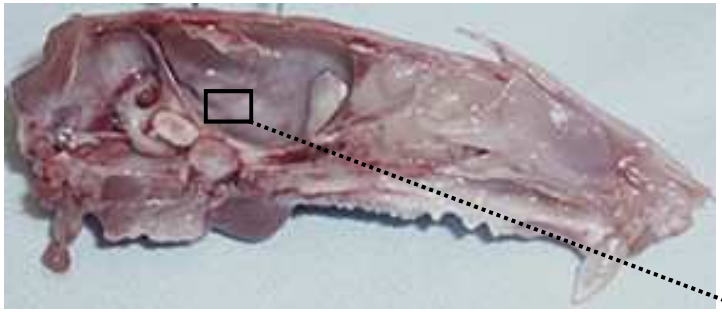
Retrograde and anterograde tracing: course of the N. spinosus

- Tracer: carbocyanin-dye ‘Di-I’, extremely lipophilic
- Application: as crystals to the distal nerve stump
- Incubation: 2 weeks up to 2 months in para-formaldehyde
- Speed of diffusion in cell membrane (2,5 mm/week)



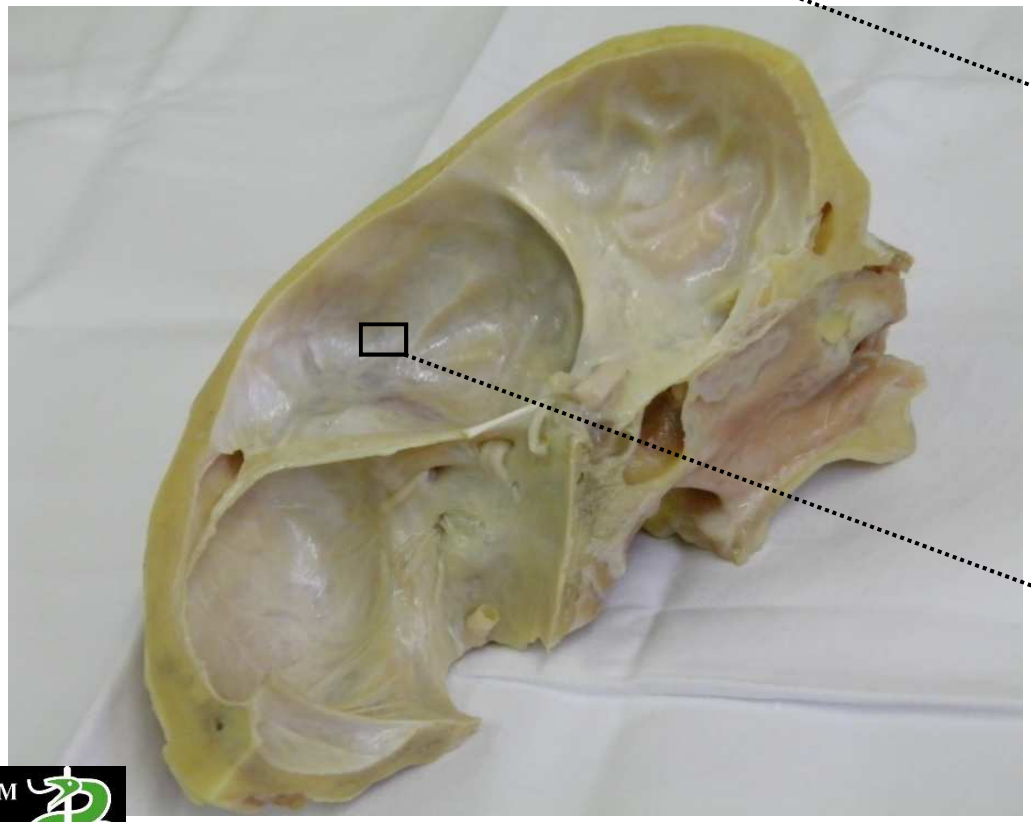


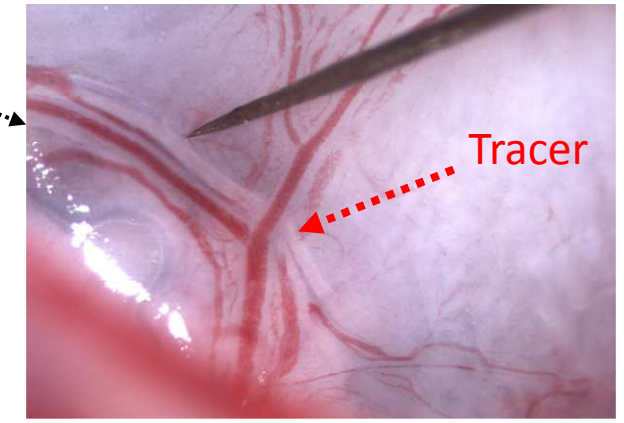
Preparation for tracing-experiments

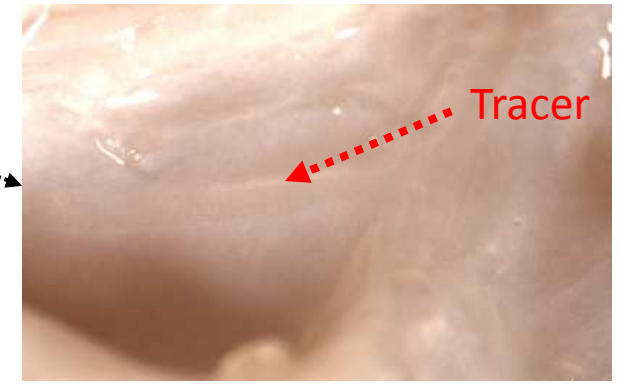


Sagittally separated skull of rat and man after removal of brain

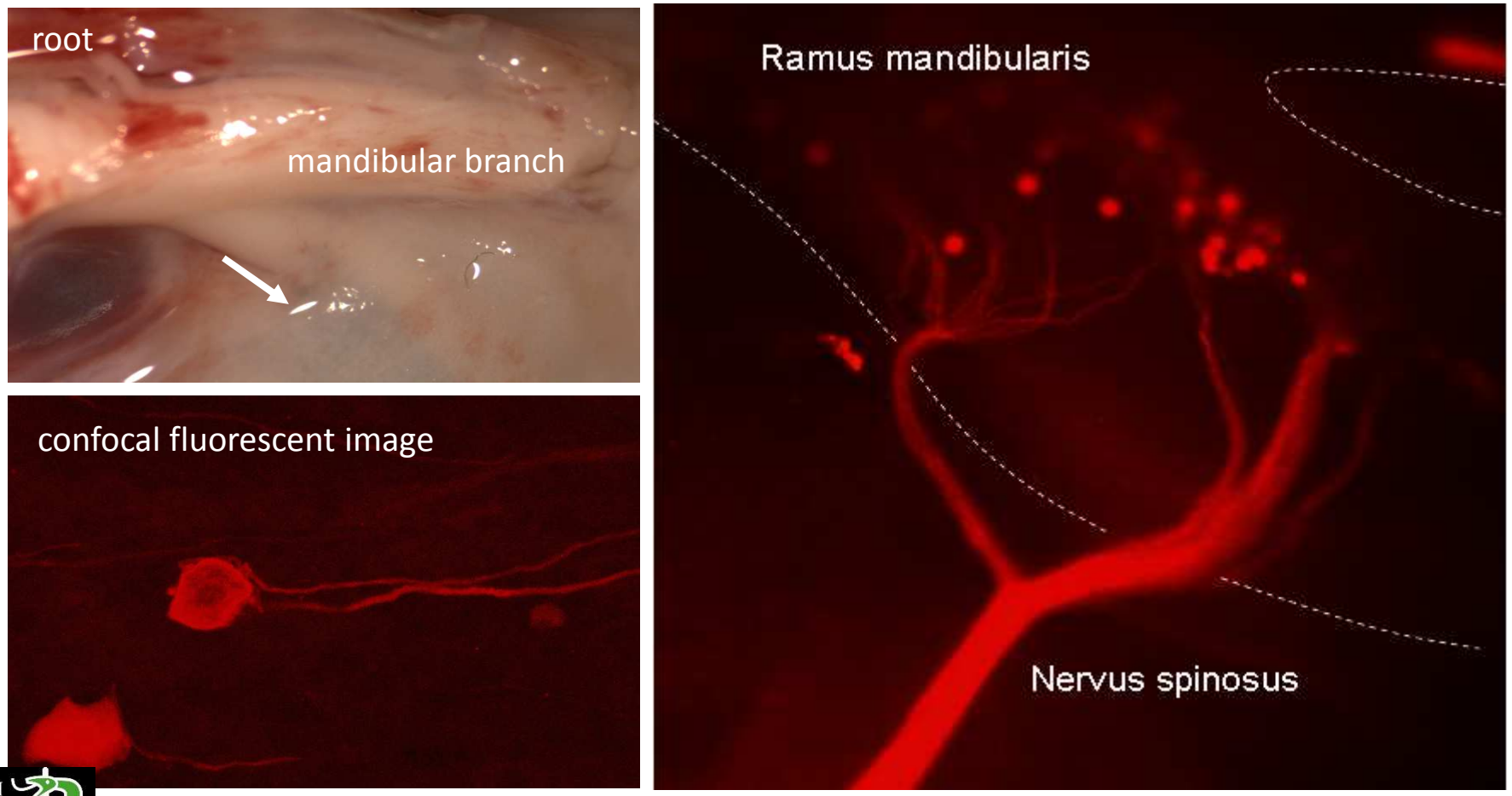
Application of fluorescent tracer to the severed N. spinosus resp. to distal branches



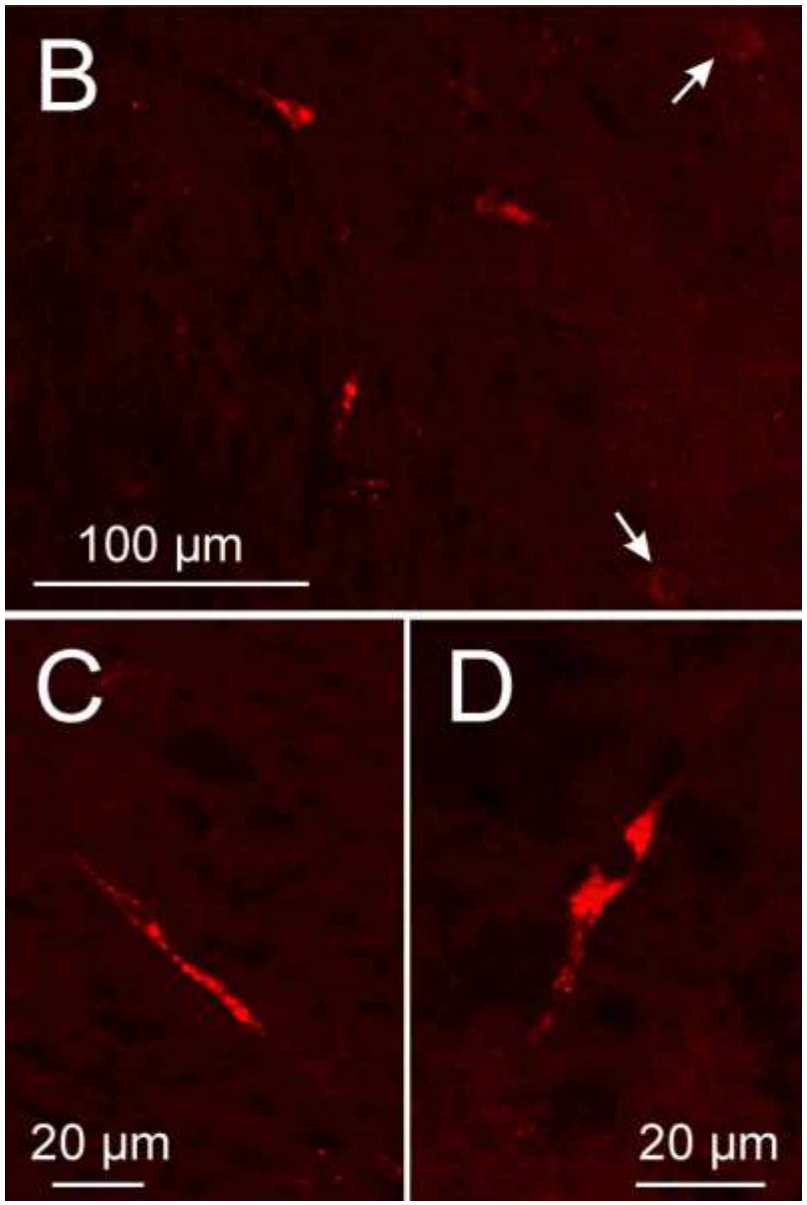


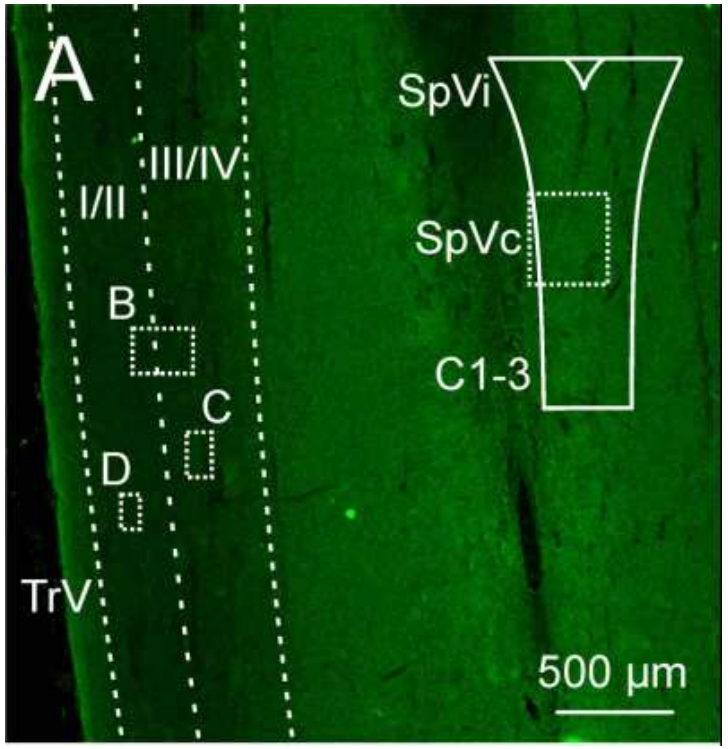


Retrograde tracing: origin of the N. spinosus in trigeminal ggl.

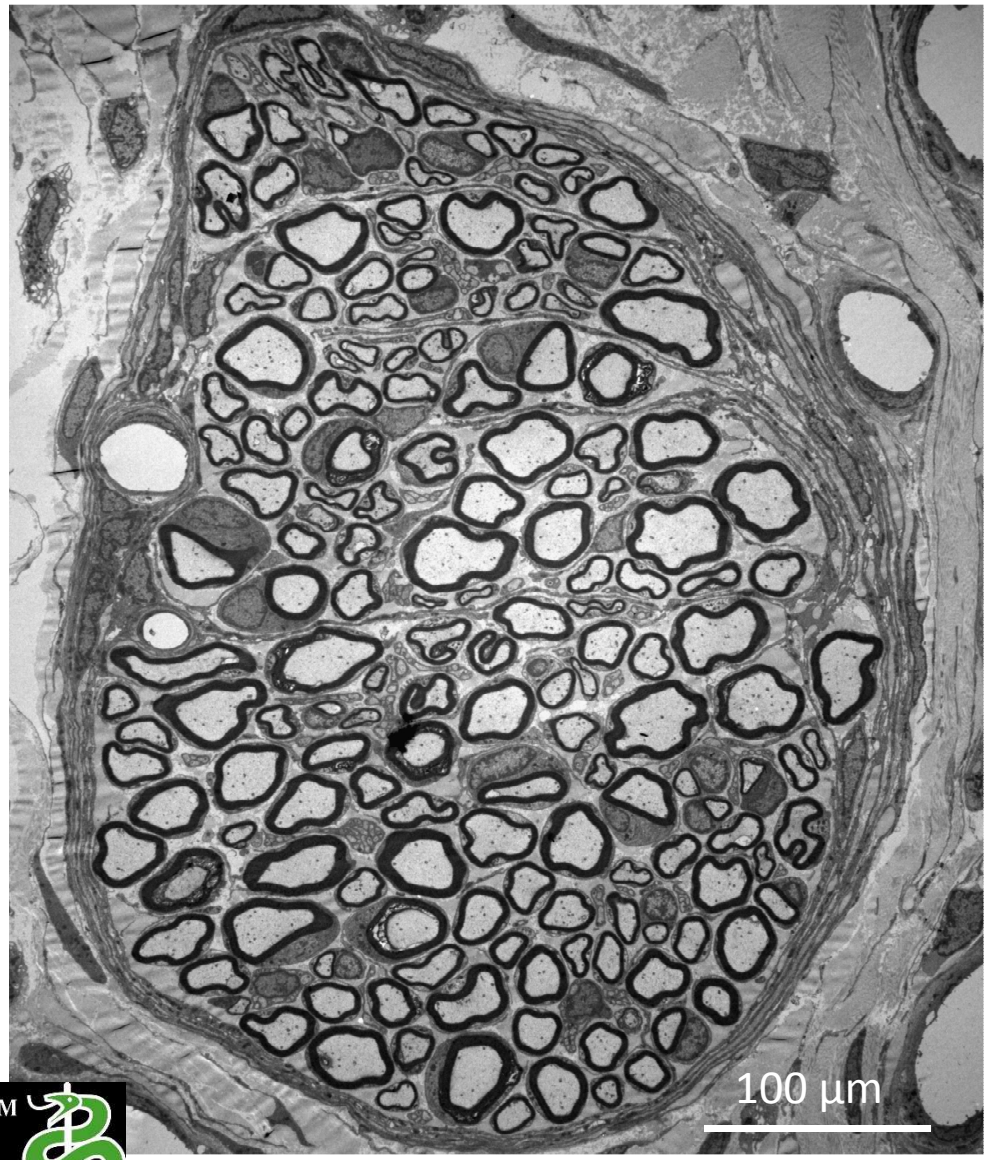


Retrograde tracing to caudal spinal subnucleus of trigeminal nerve (SpVc) in brainstem

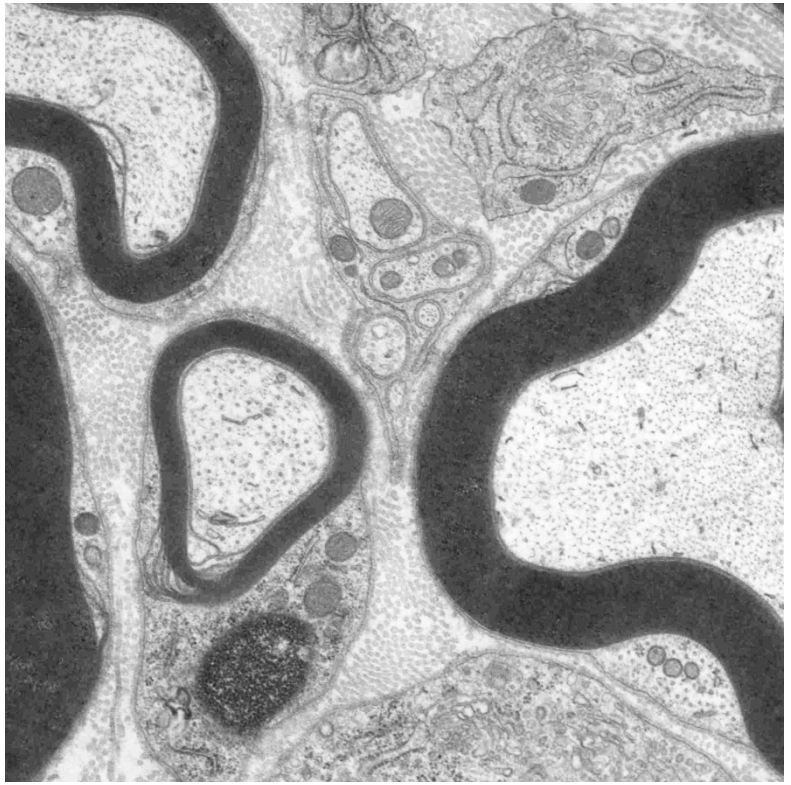




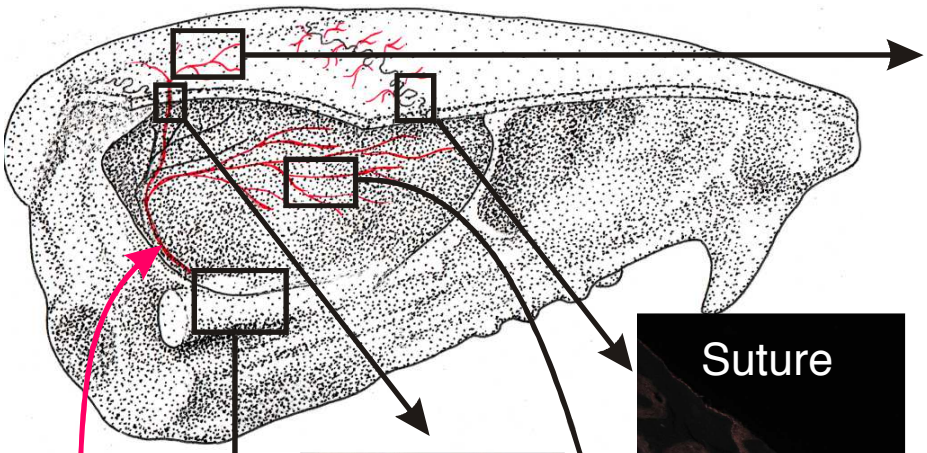
Structure of the proximal N. spinosus (rat)



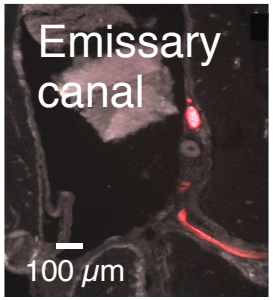
70% non-myelinated fibers
30% myelinated fibers

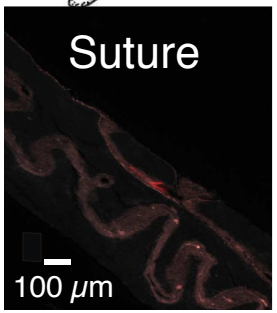


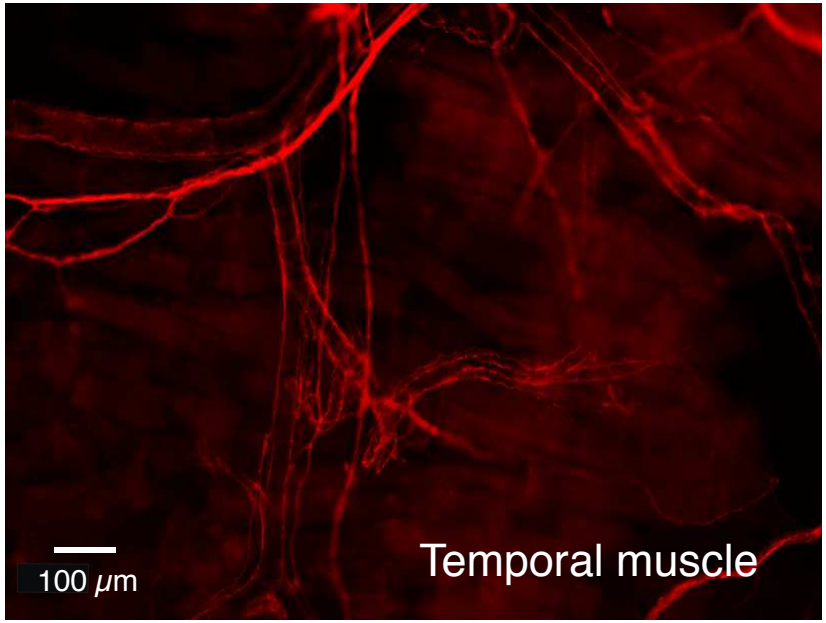
Anterograde tracing: intra- and extracranial collaterals

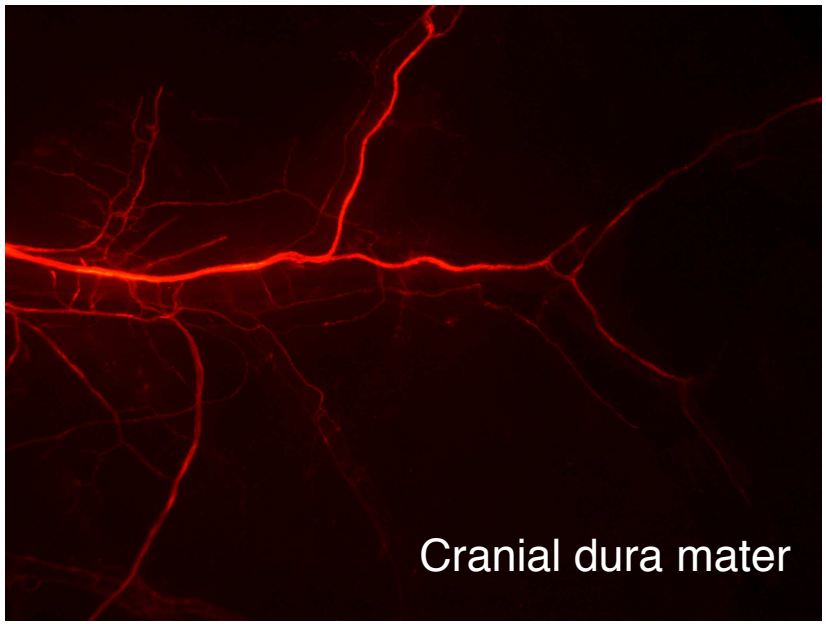


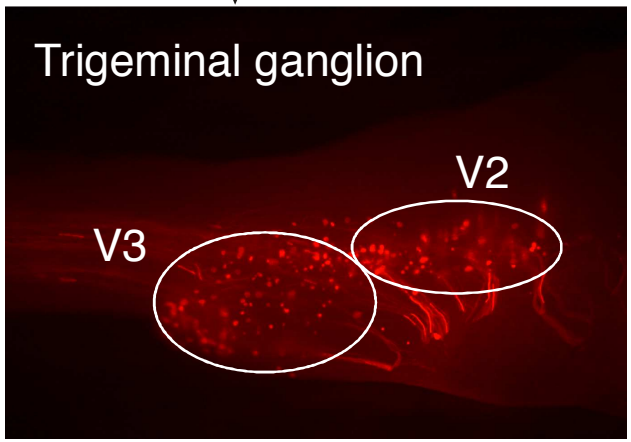
DiI











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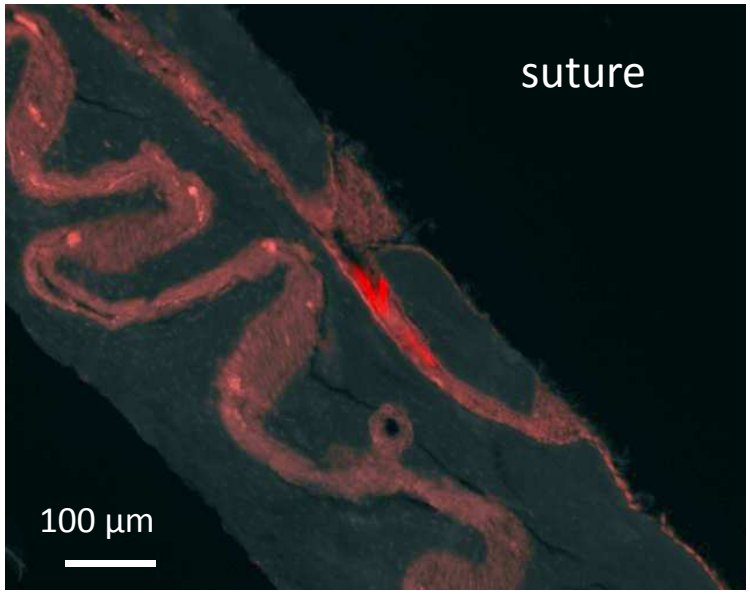
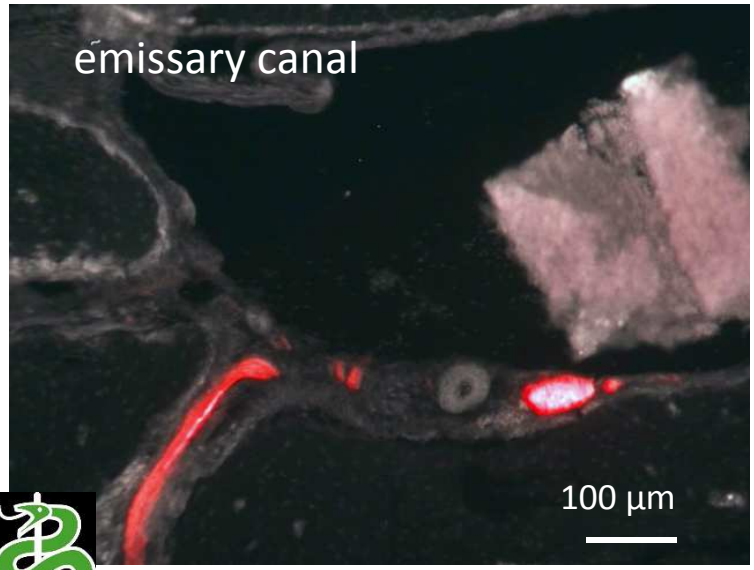
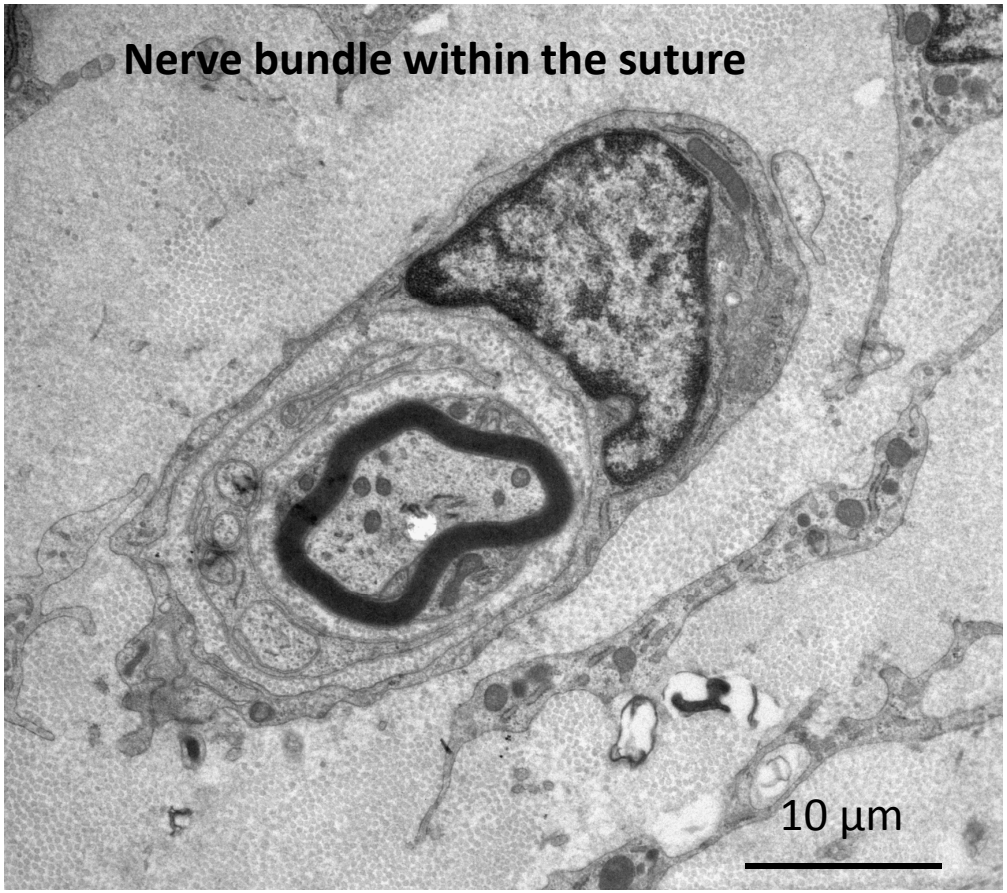
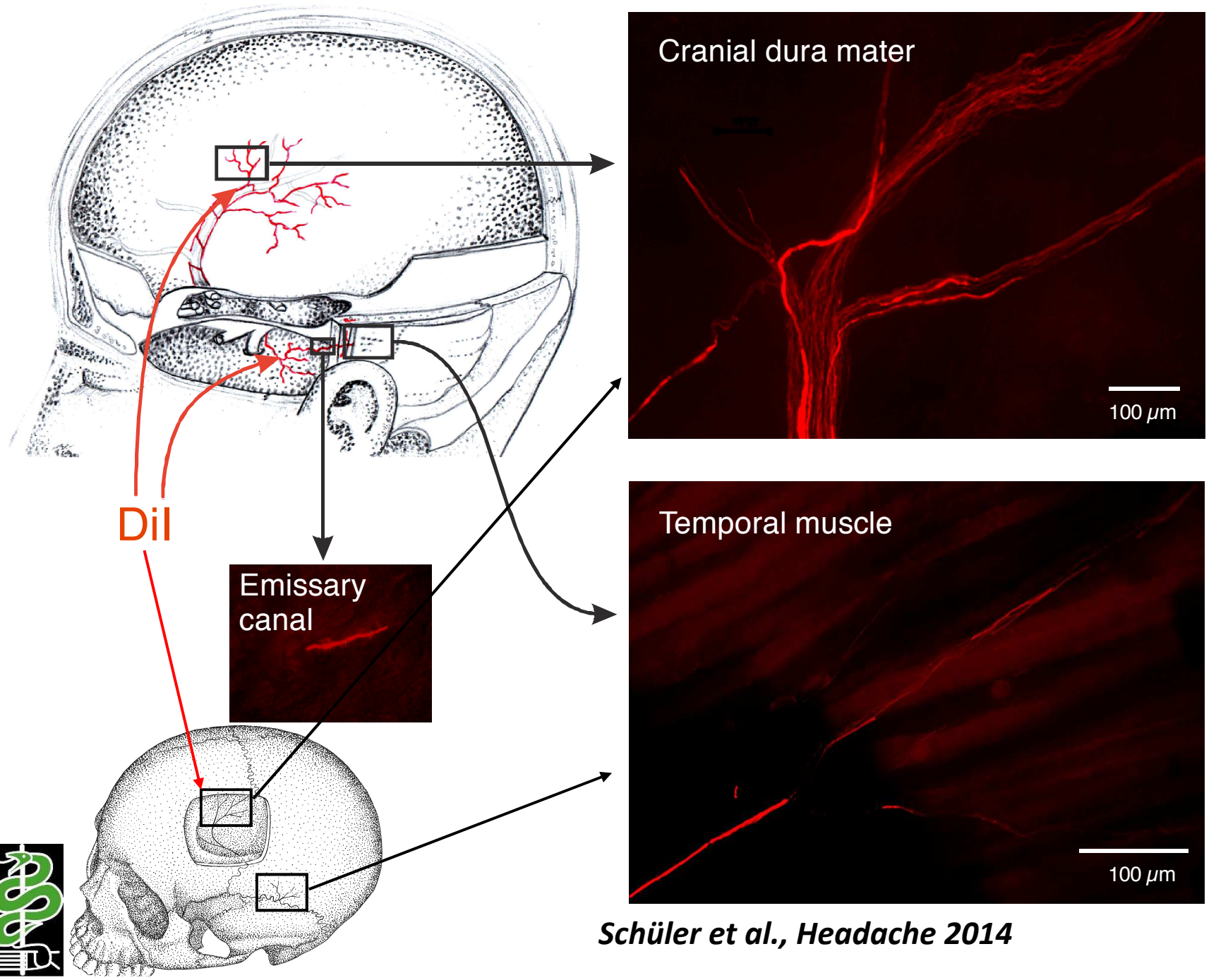
Passage of nerve fibers of the dura through skull sutures



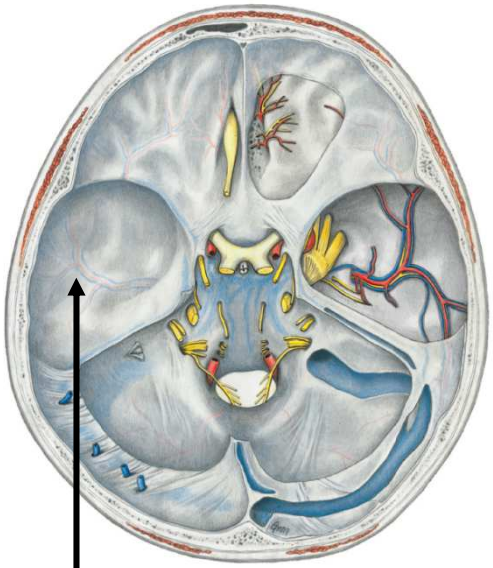


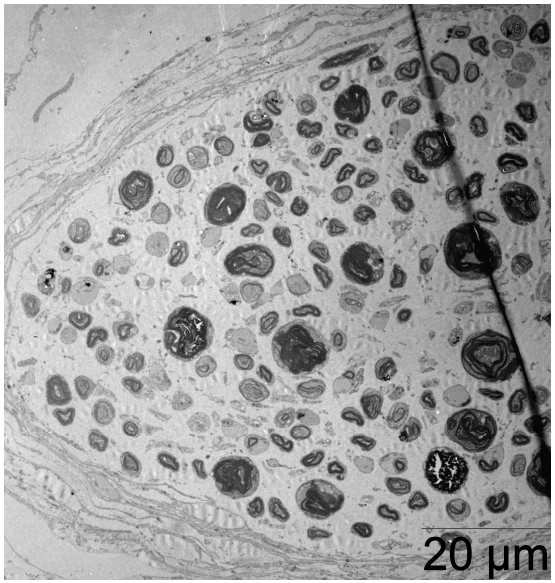


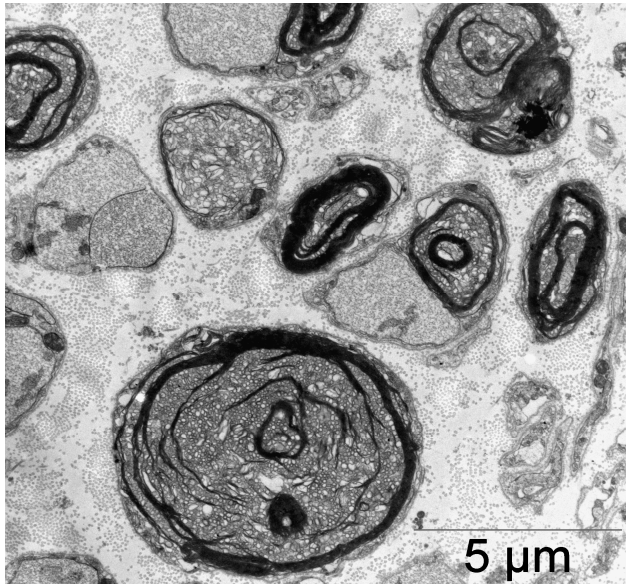


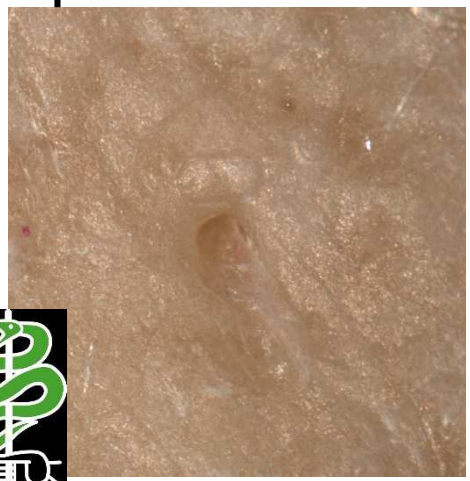
Schüler et al., Headache 2014

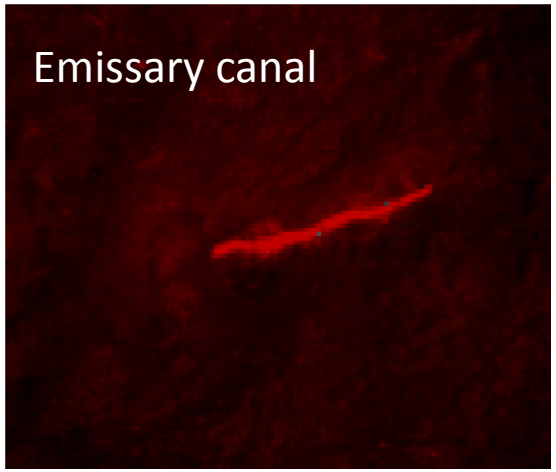
Anterograde tracing and EM of human N. spinosus branches





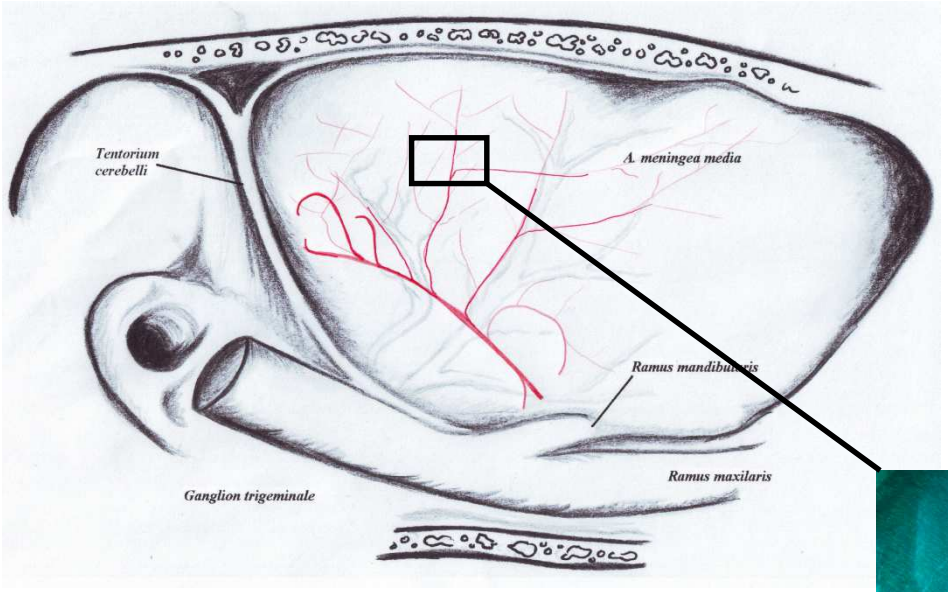






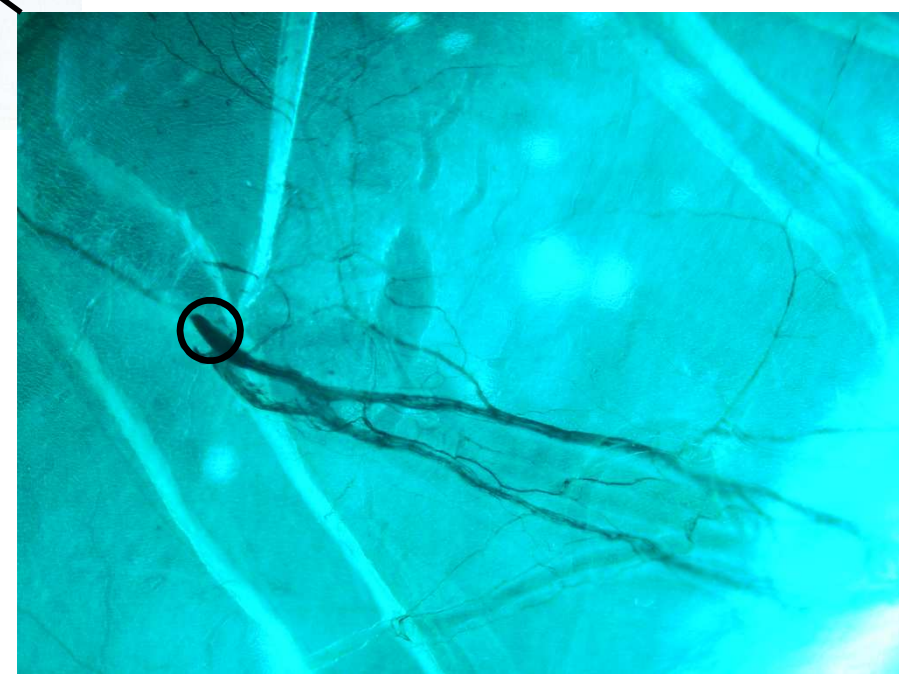
Schüler et al., Headache 2014

Retrograde tracing of extra-cranial afferents in vivo

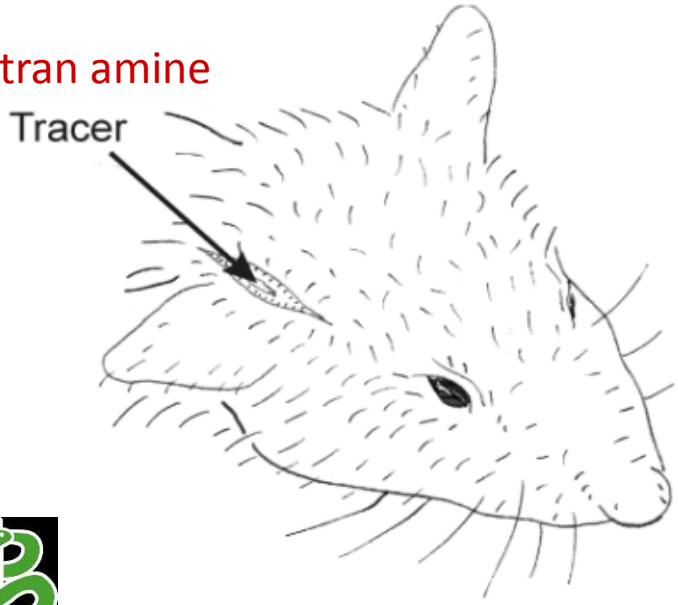


- Tracer: dextran amine-crystals, fluorescent markered, hydrophilic
- Application: as crystals under the muscle
- Transport in living cells: 2 mm/h
- Incubation: 48 h in physiol. solution

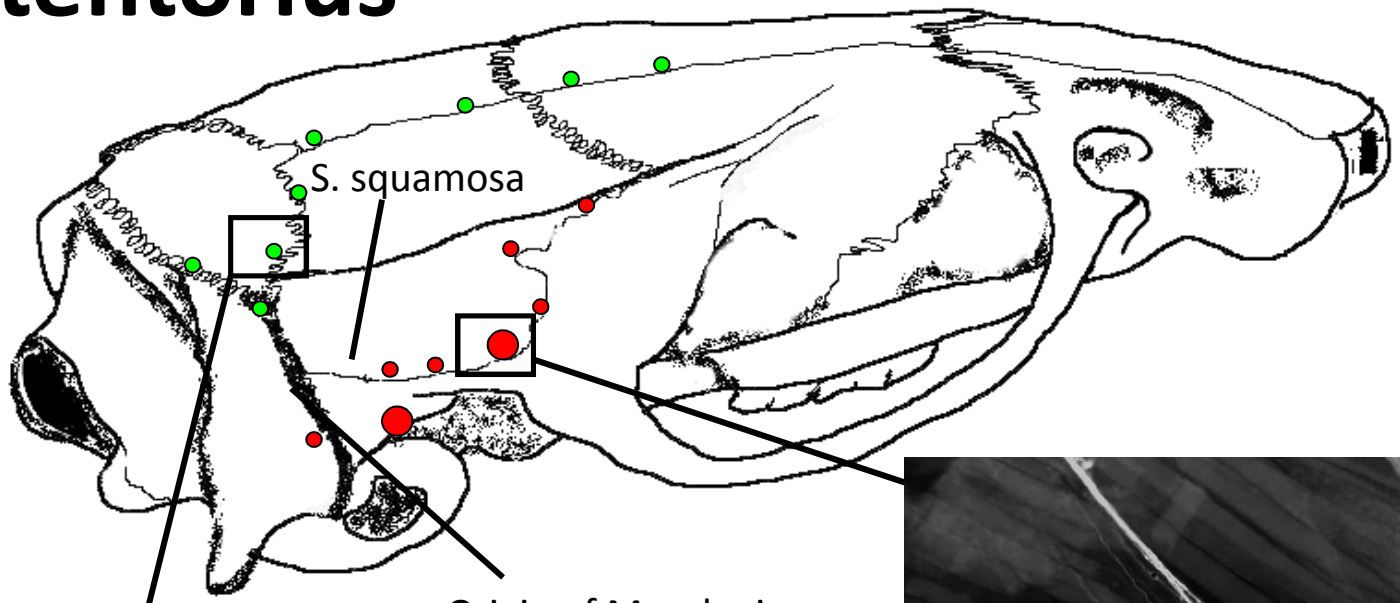
© M Schueler, M Dux

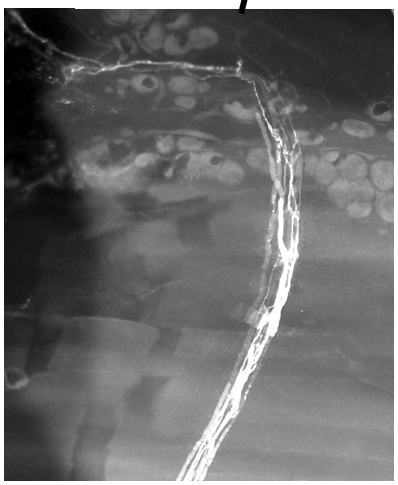


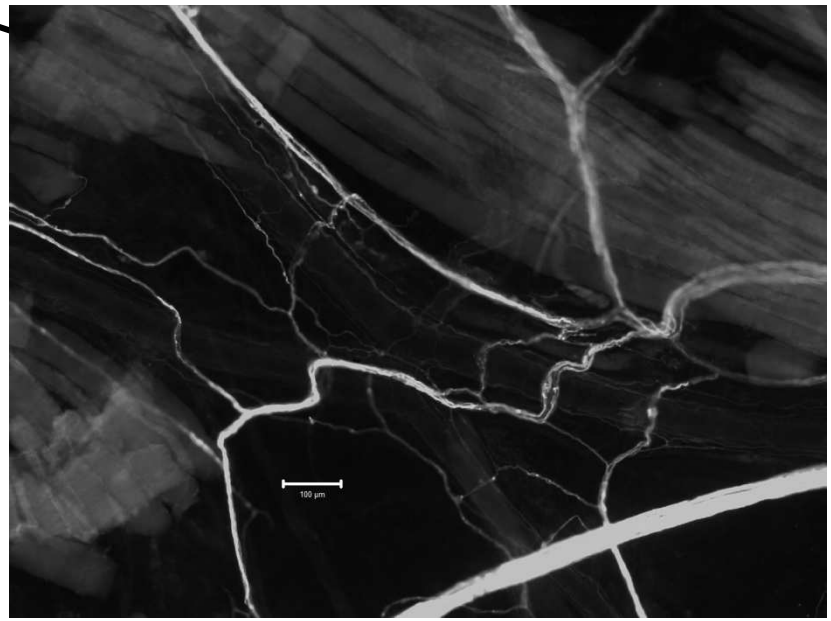
dextran amine



Extra-cranial branches of N. spinosus and N. tentorius





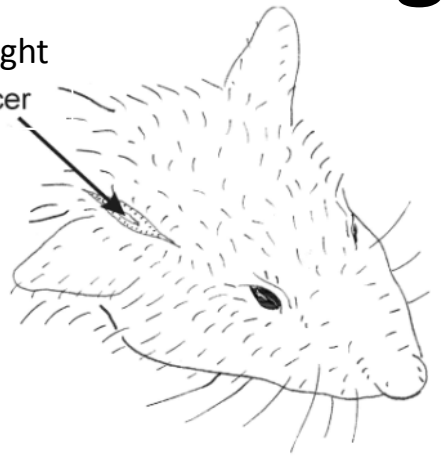


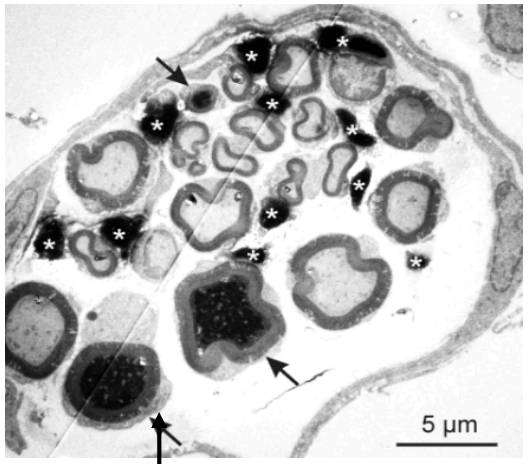
Nervus tentorius

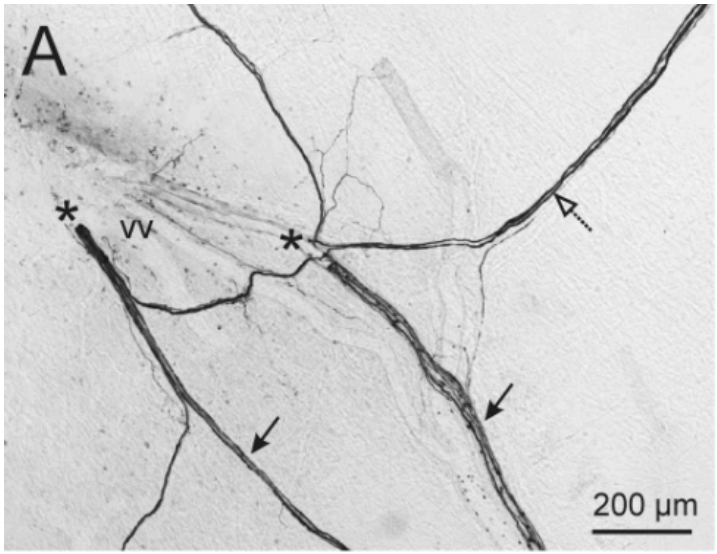
Nervus spinosus

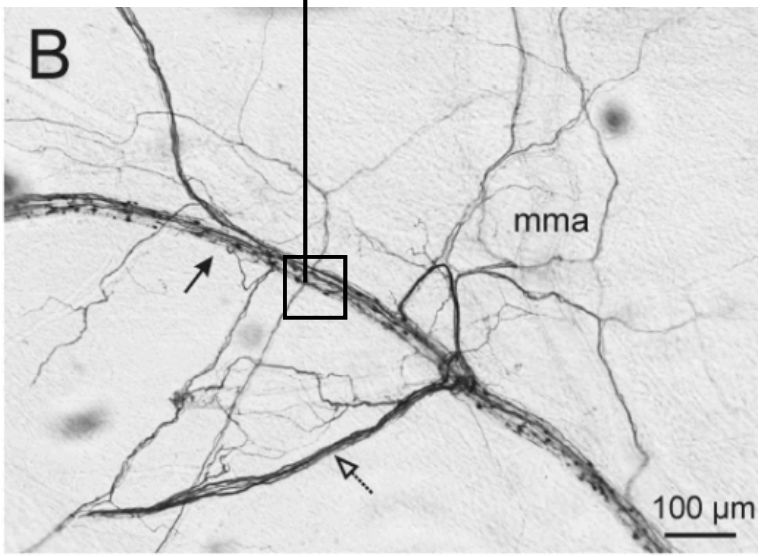
Retrograde tracing extra-cranial afferents

Low molecular weight dextran amine Tracer





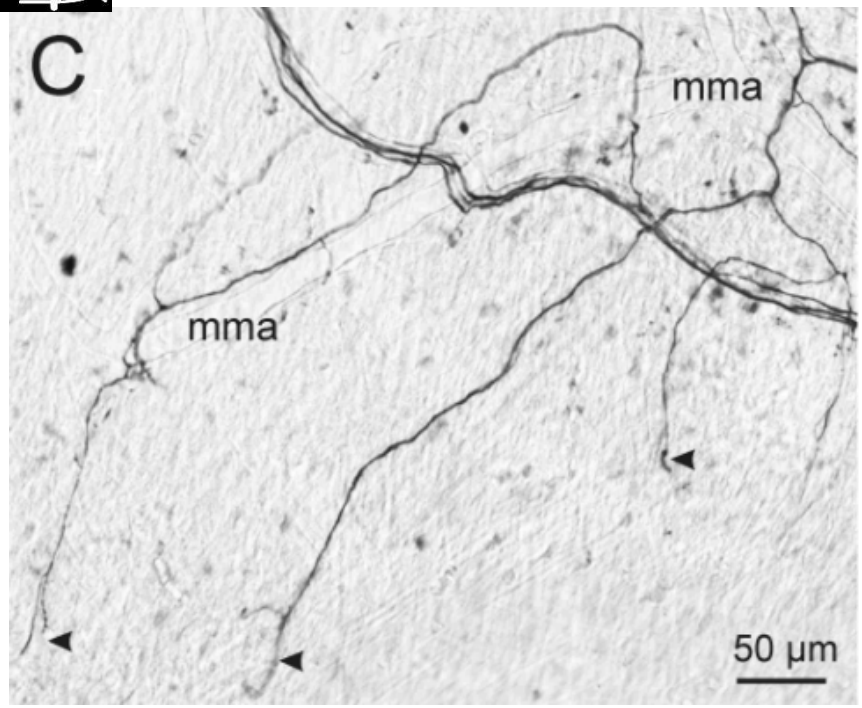


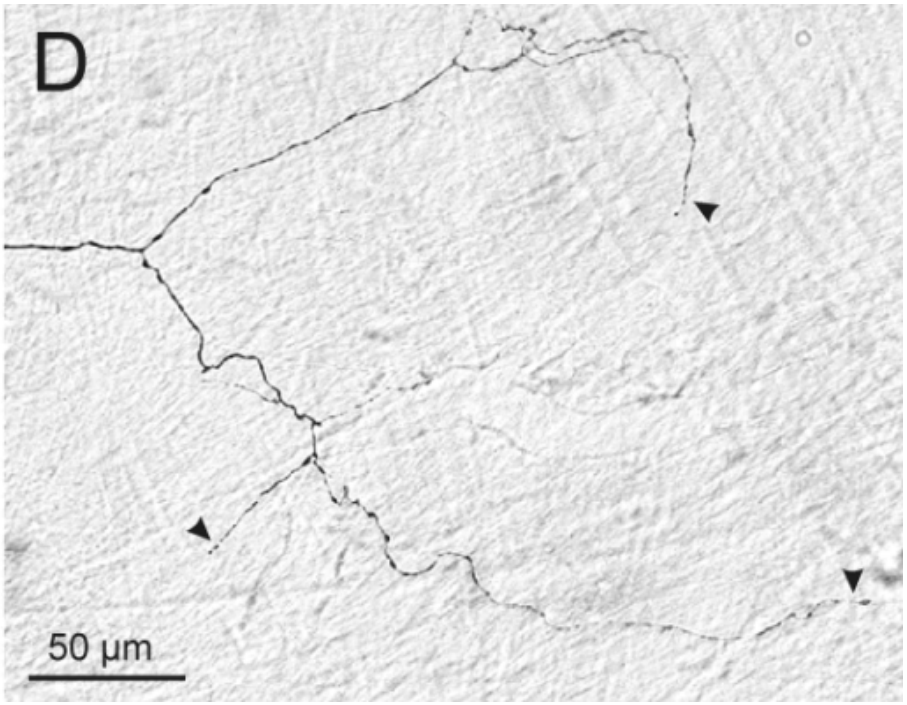


(A) Two bundles of retrograde labeled nerve fibers (arrows) are disconnected at the site of their entrance along emissary venous vessels (vv) through the skull into the dura mater. Collateral nerve fibers branching off from the retrograde labeled nerve fiber bundles run in rostral direction (blank ar).

(B) Bundle of retrograde labeled nerve fibers (arrow) approaching the middle meningeal artery (mma; visible by its meandering course) gives off (in anterograde direction labeled) nerve fiber bundles (blank arrow) and multiple collateral fibers.

Intra-cranial branches of N. spinosus after retrograde tracing



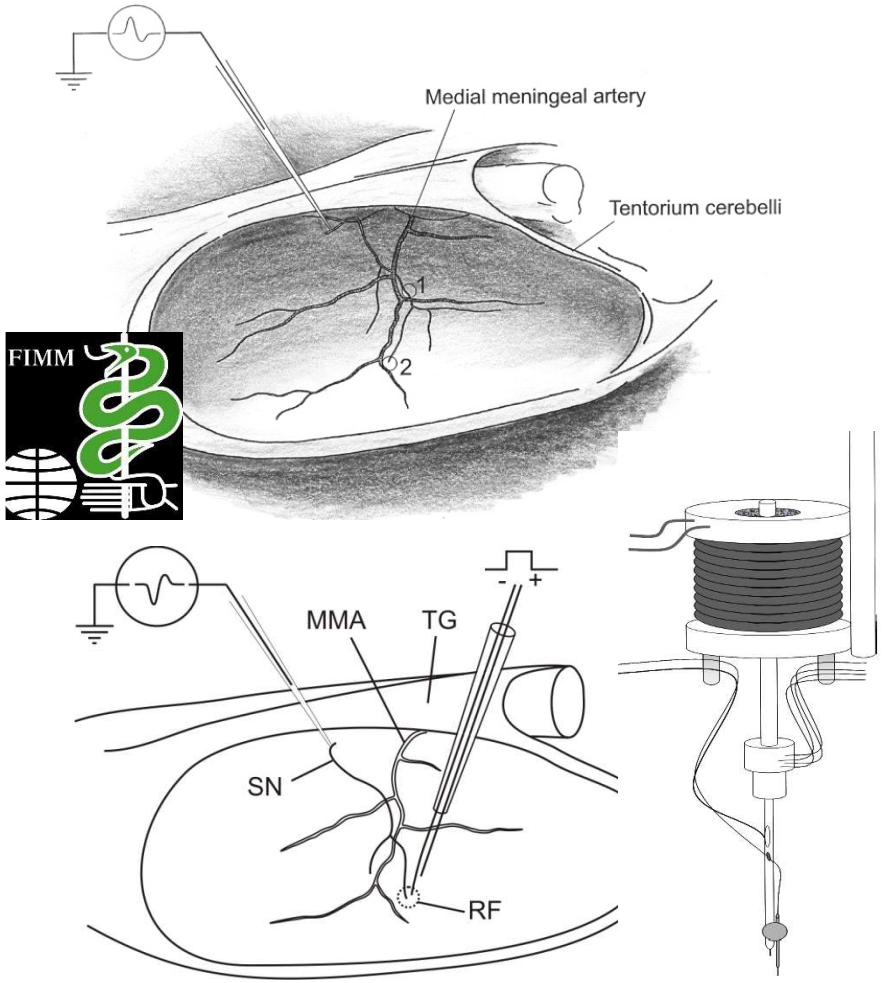


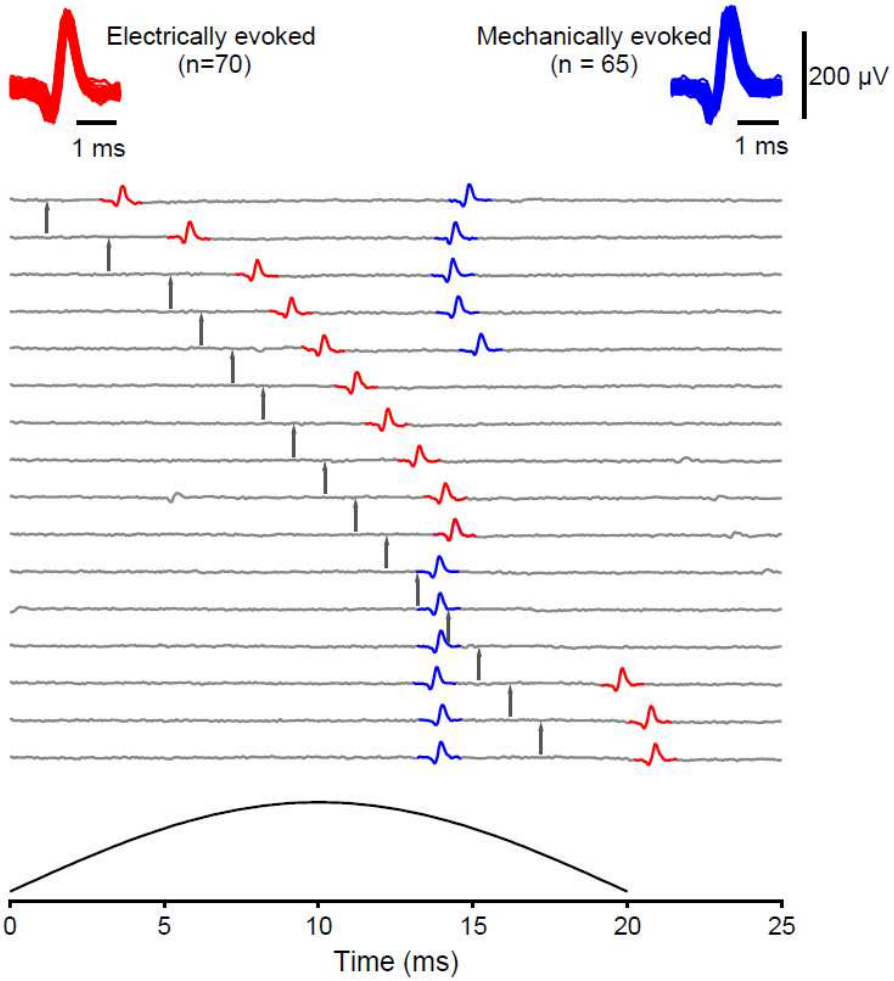
(C) Labeled nerve fiber bundles and single fibers accompanying and crossing branches of the mma; some of them form terminals in dural connective tissue (arrowheads).

(D) Fine-labeled collateral fiber forming several terminals (arrowheads) in the dural connective tissue.

Extracranial projections of meningeal afferents and their impact on meningeal nociception and headache. PAIN 154 (2013) 1622–1631

Lead of meningeal afferents in a half-skull preparation



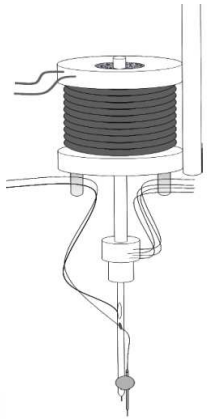


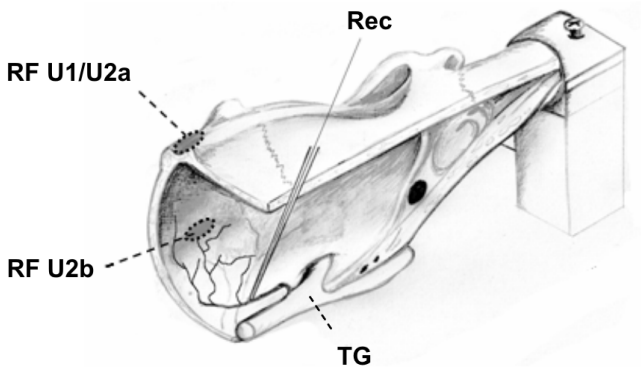
R. De Col et al. J.Physiol. 2012

Action potential responses to mechanical and electrical stimulation can be shown to arise from a single axon by exploiting the phenomena of refractoriness. The time of electrical stimulation is indicated by an arrow. The profile of mechanical stimulation is shown in the bottom. The action potential response to mechanical stimulation occurs approximately 14–15 ms after onset of the mechanical stimulus. The latency of the response to electrical stimulation is approximately 2 ms. Electrical stimulation in the period 8–12 ms after the onset of mechanical stimulation produces electrically evoked action potential, the absolute refractory period prevents an action potential to mech. stimulation.

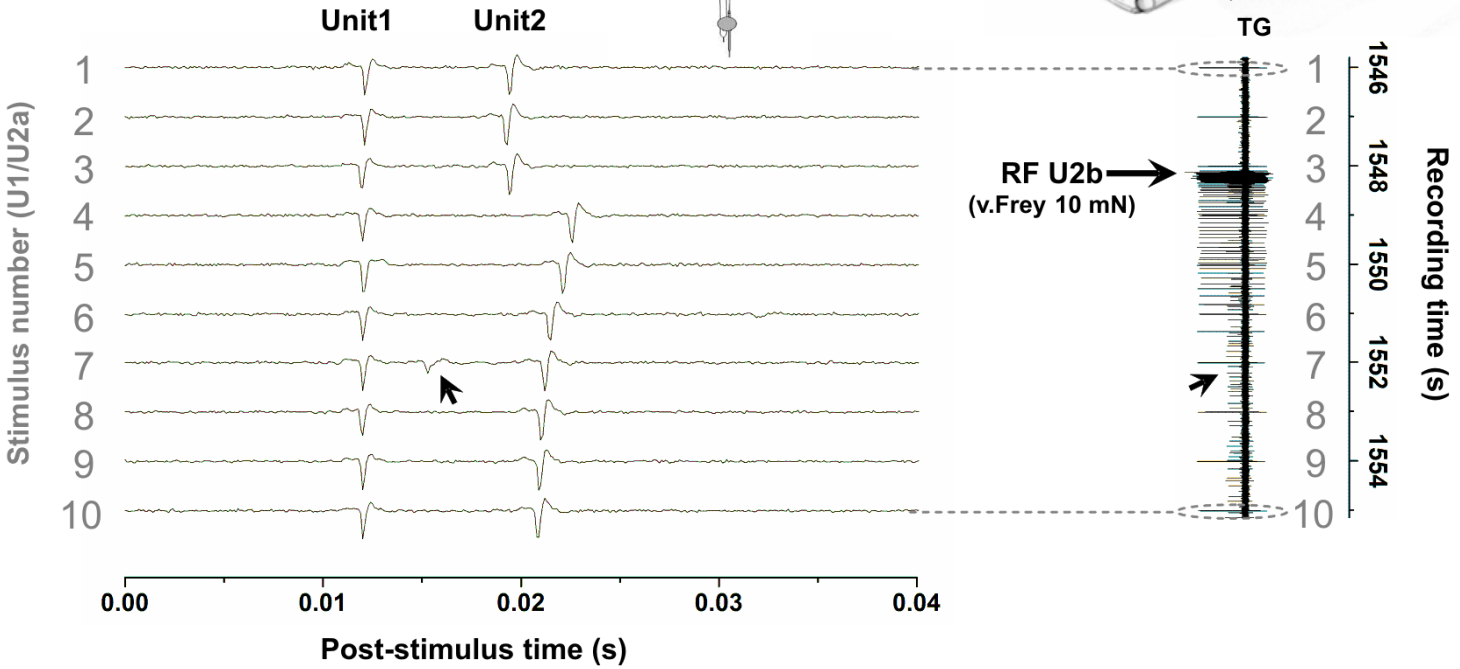
Lead of intra- and extra-cranial collaterals of meningeal afferents

M. Schueler et al., Pain 2013





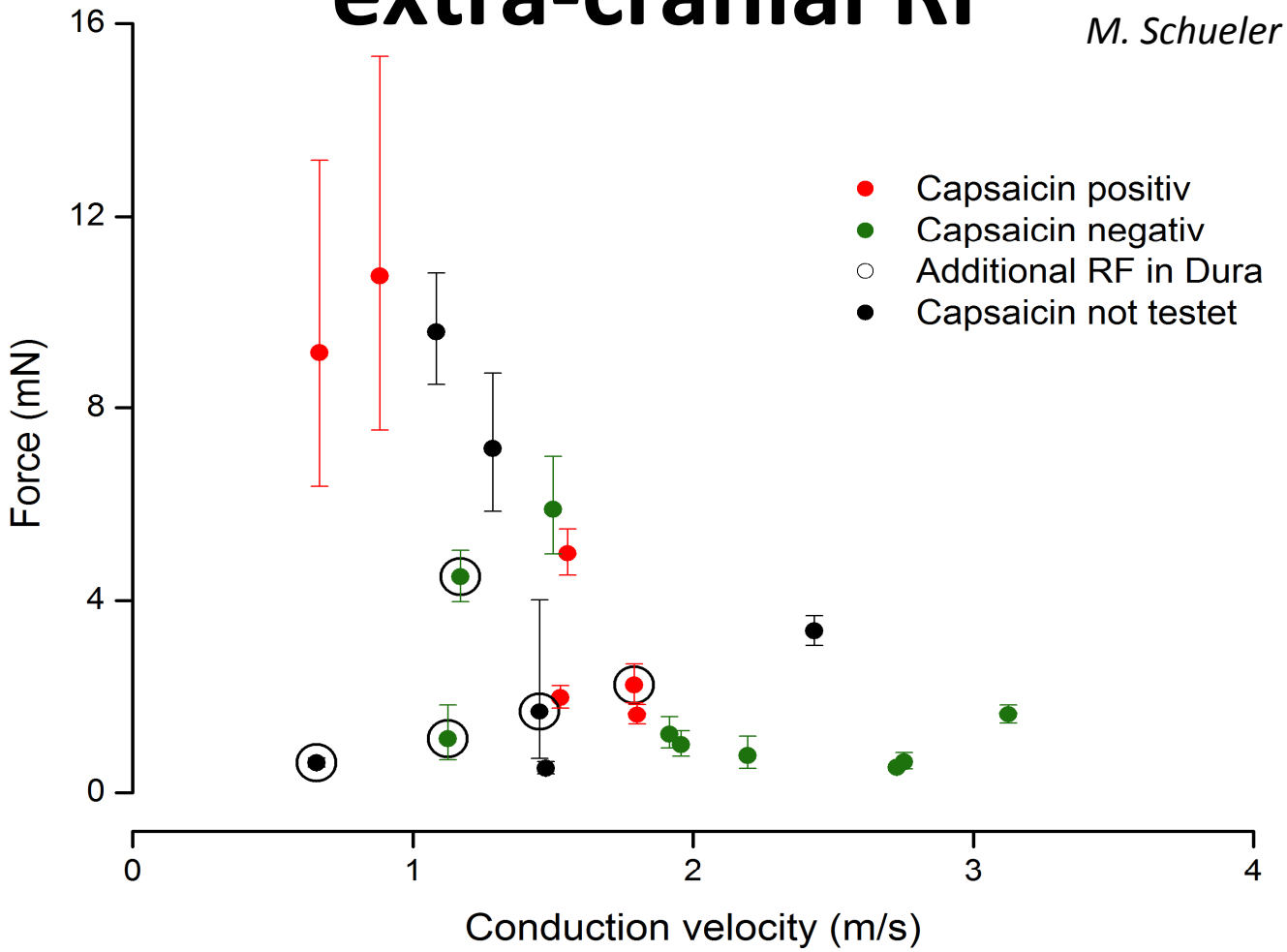
Marking technique



Repetitive short mechanical stimuli at intervals of 1 s applied to the periosteal receptive field generated 2 action potentials (Unit 1 and Unit 2) with characteristic latencies (about 12 and 20 ms post-stimulus). Stimulation of the dural receptive field with a von Frey filament (10 mN) between the periosteal stimulus 3 and 4 caused a burst of action potentials (right panel, horizontal arrow) and a selective increase in latency of Unit 2 (left panel, declined arrow) indicative for an additional activation of exactly this unit (‘‘marking’’).

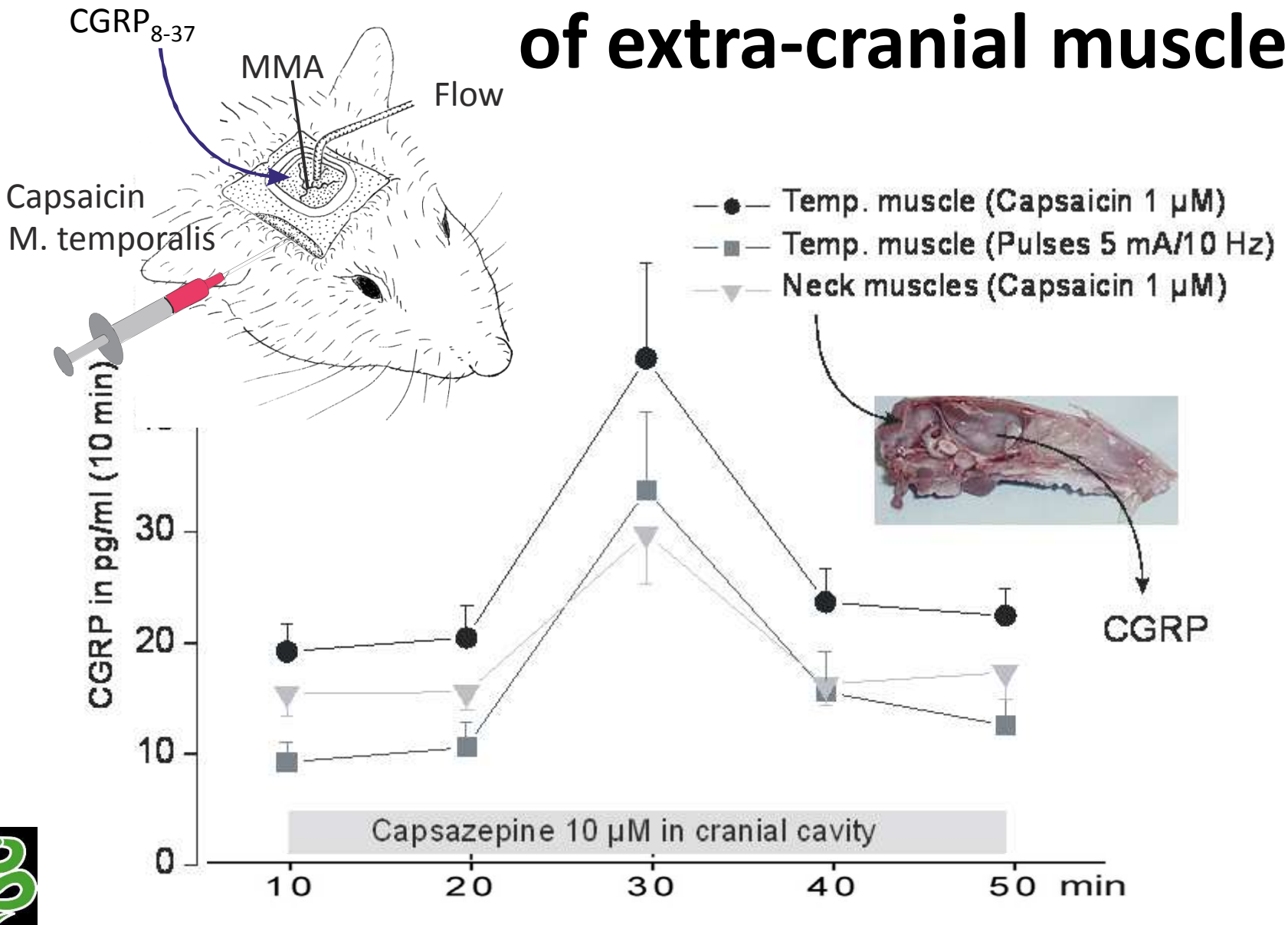
Properties of meningeal afferents with extra-cranial RF

M. Schueler et al., Pain 2013



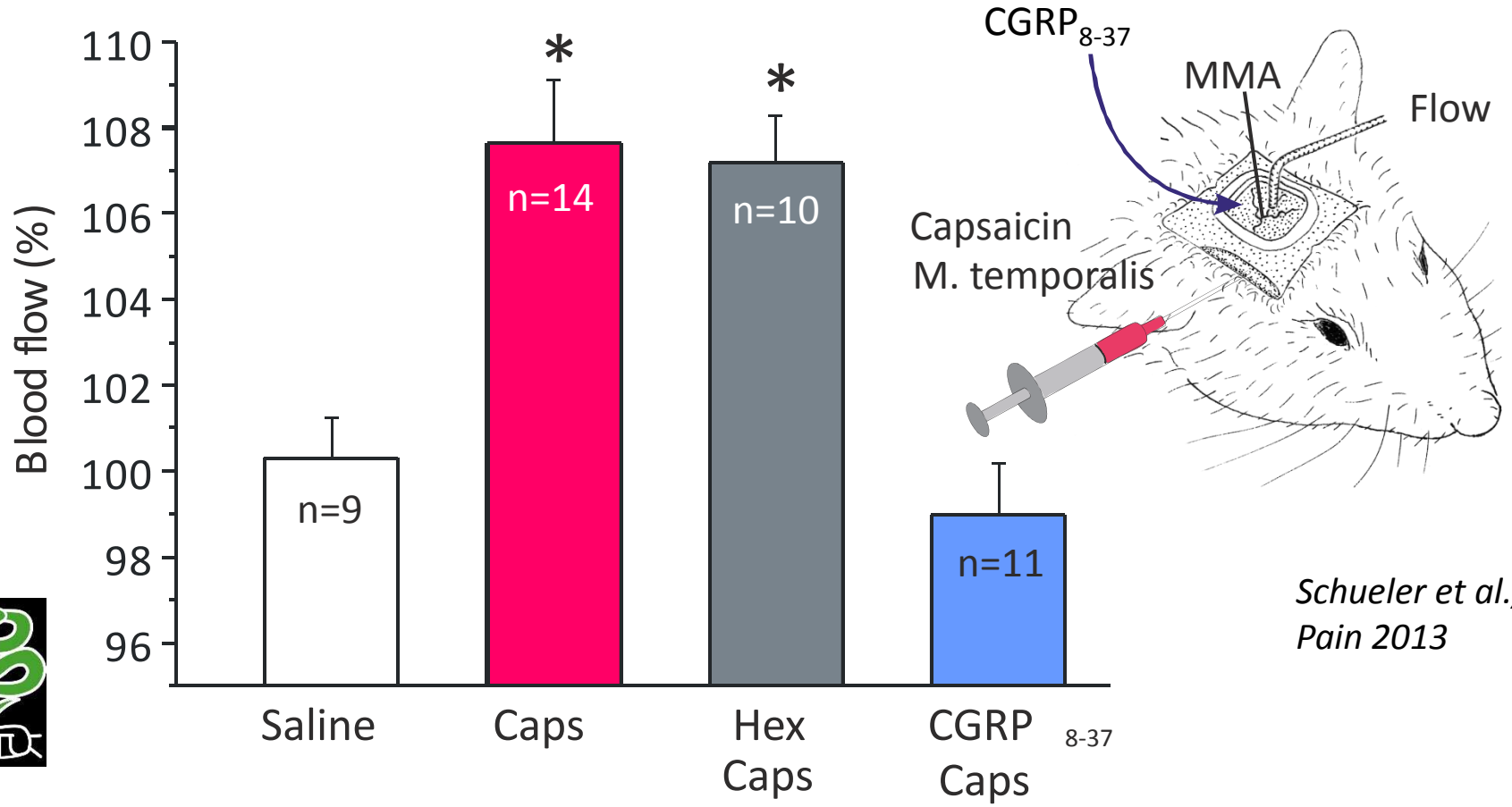
Sample of 23 units with their conduction velocities and mechanical thresholds to mechanical stimulation of their extracranial (periosteal) receptive fields. Error bars represent forces between 10% and 90% response probability. Six of 15 units tested responded to capsaicin (Capsaicin positive) and 9 were unresponsive (Capsaicin negative). Five units had an additional mechanosensitive receptive field in the dura evidenced by ‘‘marking’’.

CGRP- release from dura by stimulation of extra-cranial muscles



M. Schueler et al., Pain 2013

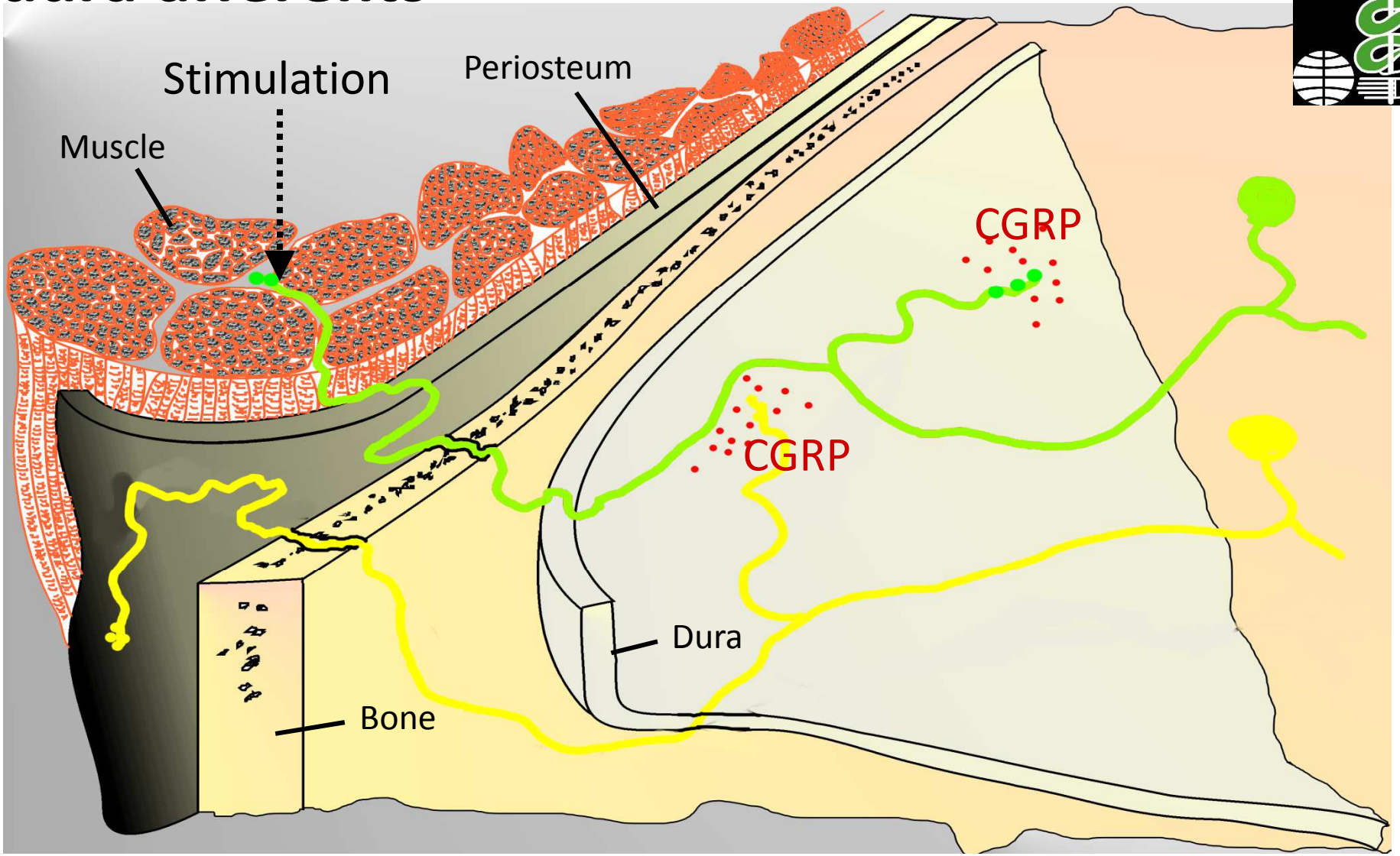
Increase of dura blood flow by stimulation of temporal muscle



Schueler et al., Pain 2013

Meningeal blood flow is increased after injection of capsaicin (Caps) into the ipsilateral temporal muscle. The increase is not influenced by intravenous pre-administration of hexamethonium (Hex), but blocked by local pre-application of the CGRP antagonist CGRP8–37, indicating that it was caused by the vasodilatory action of CGRP released from meningeal collaterals of afferent fibers innervating the temporal muscle.

Axonal reflex by extra-cranial stimulation of dura afferents



R. De Col in Schueler et al.: Innervation of rat and human dura mater and pericranial tissues in the parieto-temporal region by meningeal afferents. Headache. 2014; 54:996-1009

Summary of important results – part I

- Nerve fibers of the dura leave the skull through sutures alongside emissary venous canals and then innervate periosteum and extra-cranial muscles.
- Meningeal nerve fibers may have intra- and extra-cranial receptive fields.
- Noxic stimulation of peri-cranial muscles releases CGRP into the dura and increases the meningeal blood flow.
- Noxic stimulation of peri-cranial muscles (i.e. by ATP) activates neurons in the spinal trigeminal nucleus with meningeal and muscular receptive fields.
- Local anesthesia of peri-cranial muscles reduces the activity of secondary neurons that have afferent information from muscles and dura .
- Therapy of headache – can in case of involvement of peri-cranial muscles be possible by reduction of tonic afferents information from these muscles.
- This may be the explanation for known therapeutic results by manual techniques to the cranium – like myofascial release to the peri-cranial muscles.