DYNAMIC EXPERIMENTAL PAIN MODELS: HOT NEWS OR BIG HYPE?

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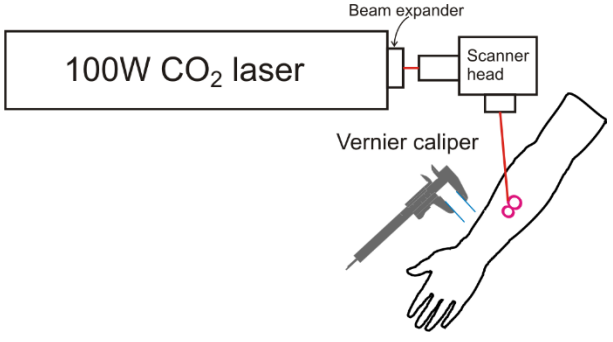
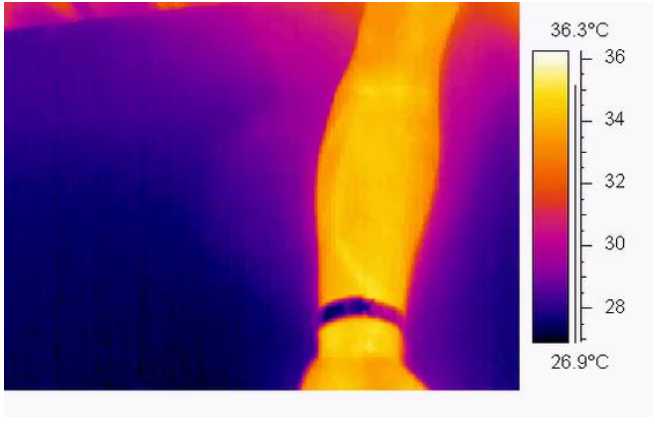
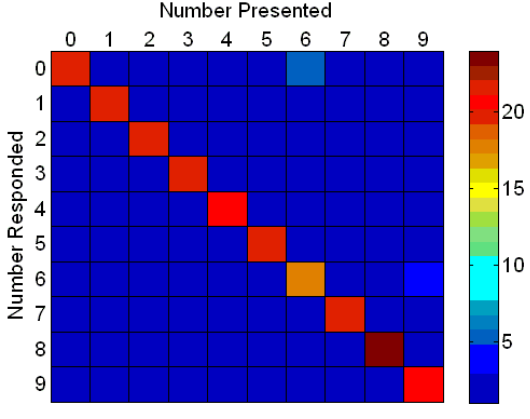
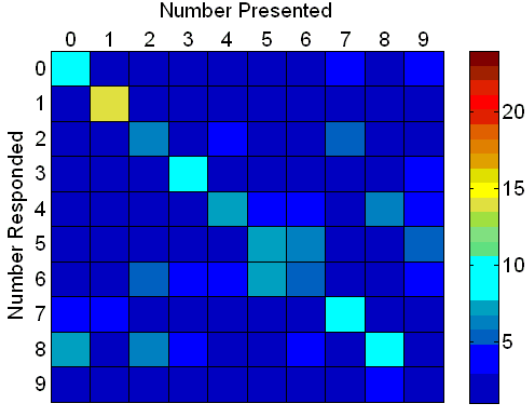
Dynamic experimental pain models

- Graphesthesia



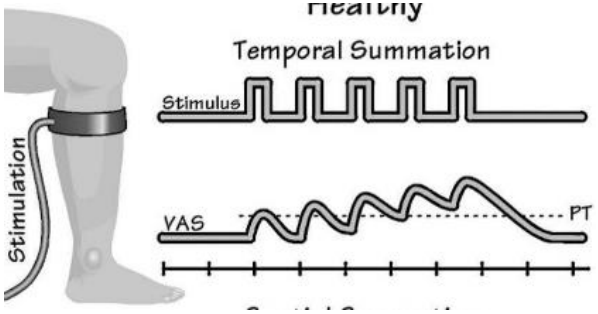


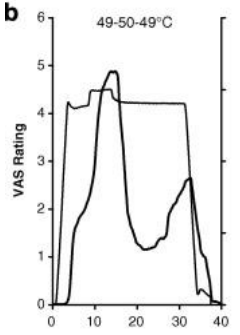


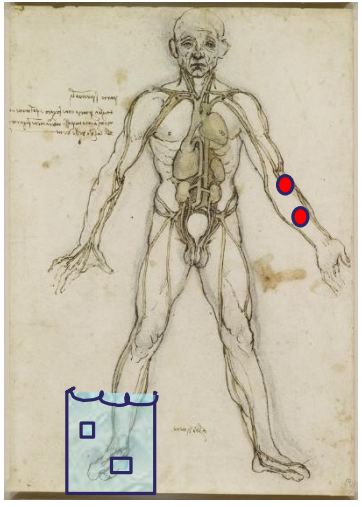


Dynamic experimental pain models

- Temporal models
  - Temporal Summation
  - Offset Analgesia
- Spatial models
  - Spatial summation
  - Lateral Inhibition
  - CPM

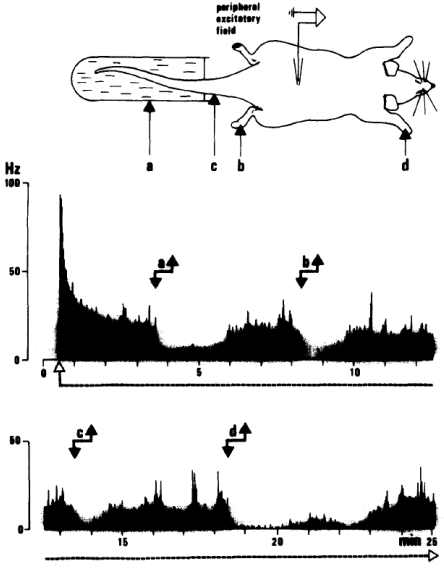




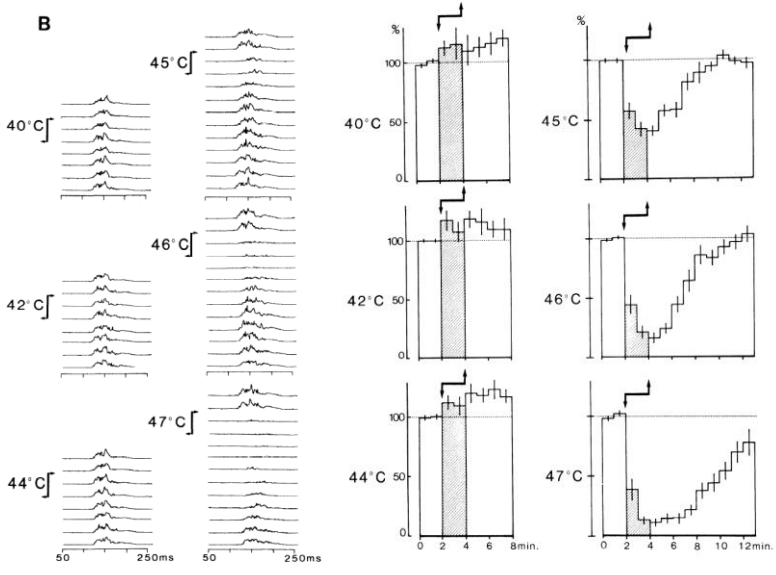


Conditioned Pain Modulation

- WDR neuron response attenuated by contralateral stimuli

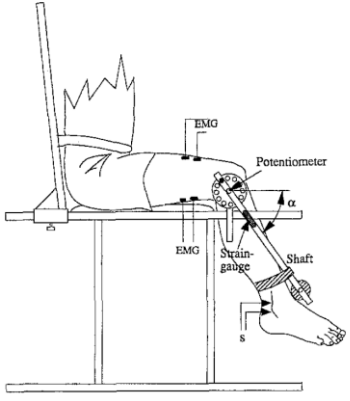


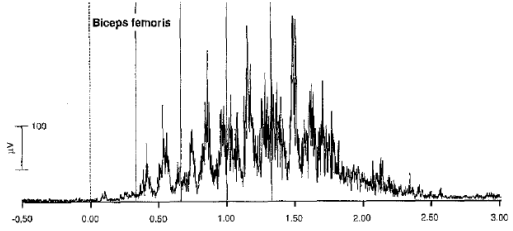
- Painful **hot** water attenuated the RIII reflex

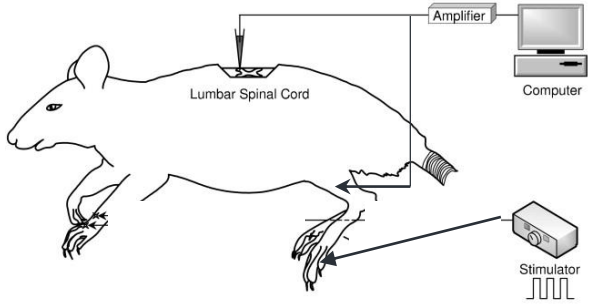


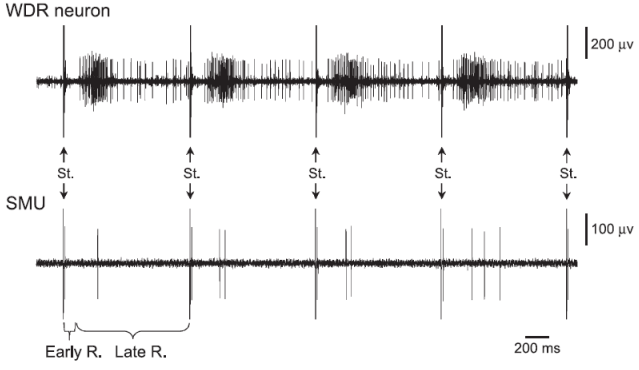
Willer et al. J Neurophys. 1989, 62(5)
Cadden et al. Brain research 1983, 275p1-11

Temporal summation



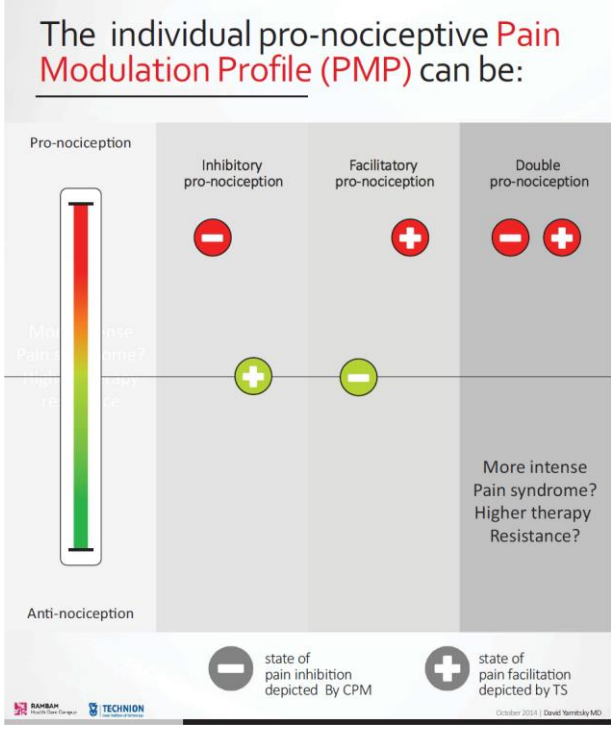


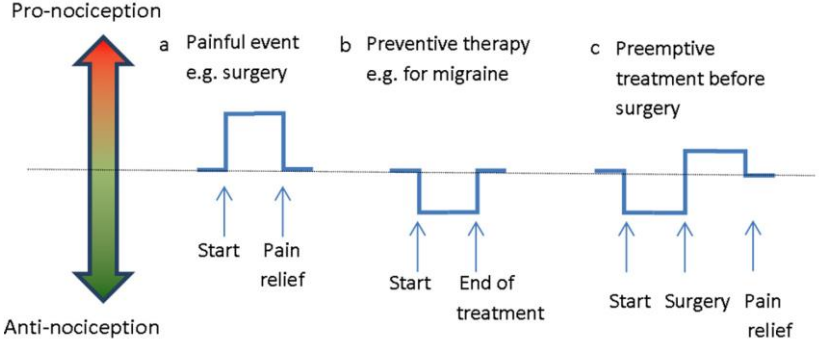




Arendt-Nielsen Eur J Appl Physiol. 1994, 68:266-273
You et al. Brain Research 2004 110-119

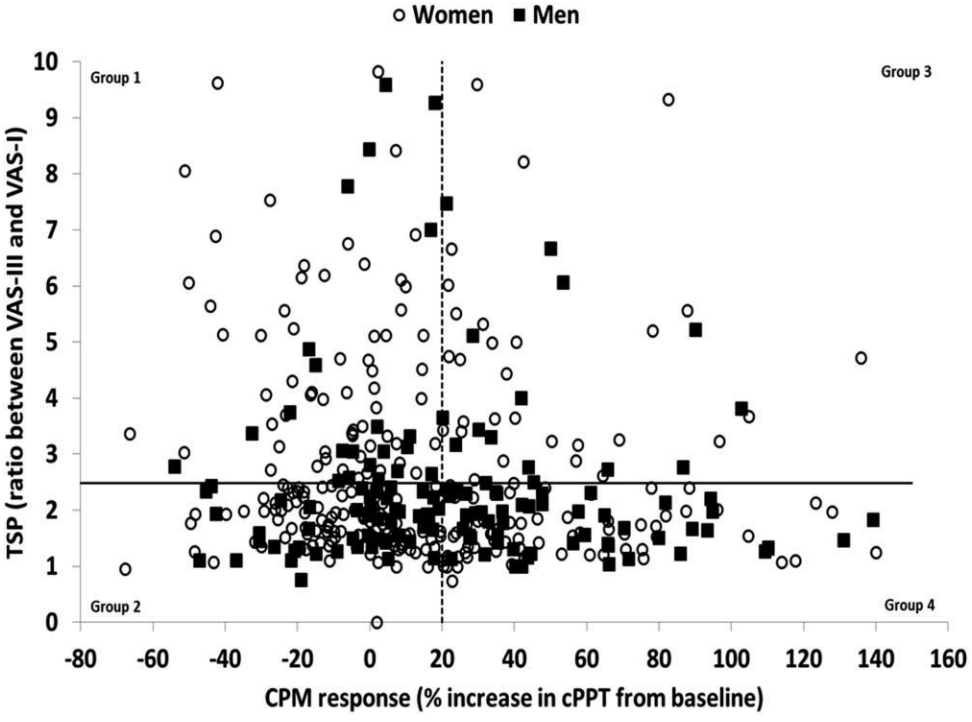
Pain Modulatory Profile





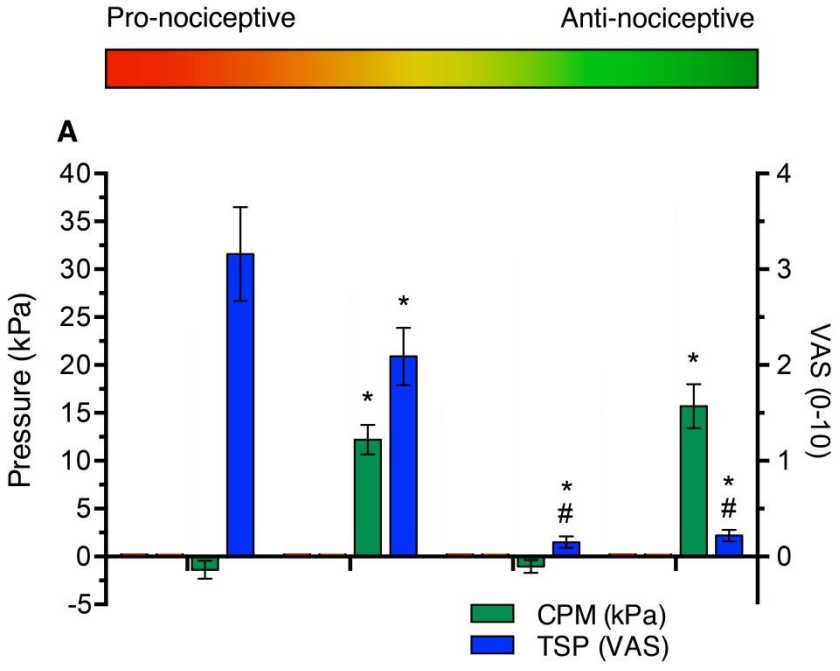
Yarnetsky, Pain, 2015, 156(4)

Classifying chronic pain patients?



Vaegter and Graven-Nielsen, 2016

Predictive value of CPM and TS?



Petersen et al., 2016

Danmarks Grundforskningsfond
Danish National Research Foundation

CNAP
Center for Neuroplasticity and Pain

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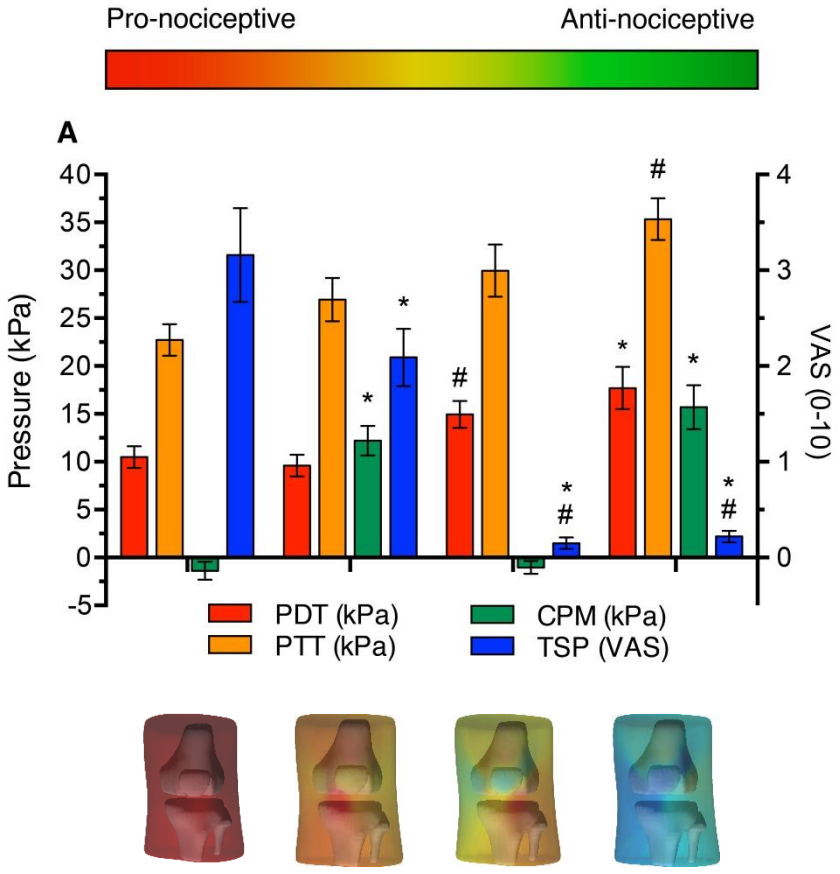

Petersen et al., 2016

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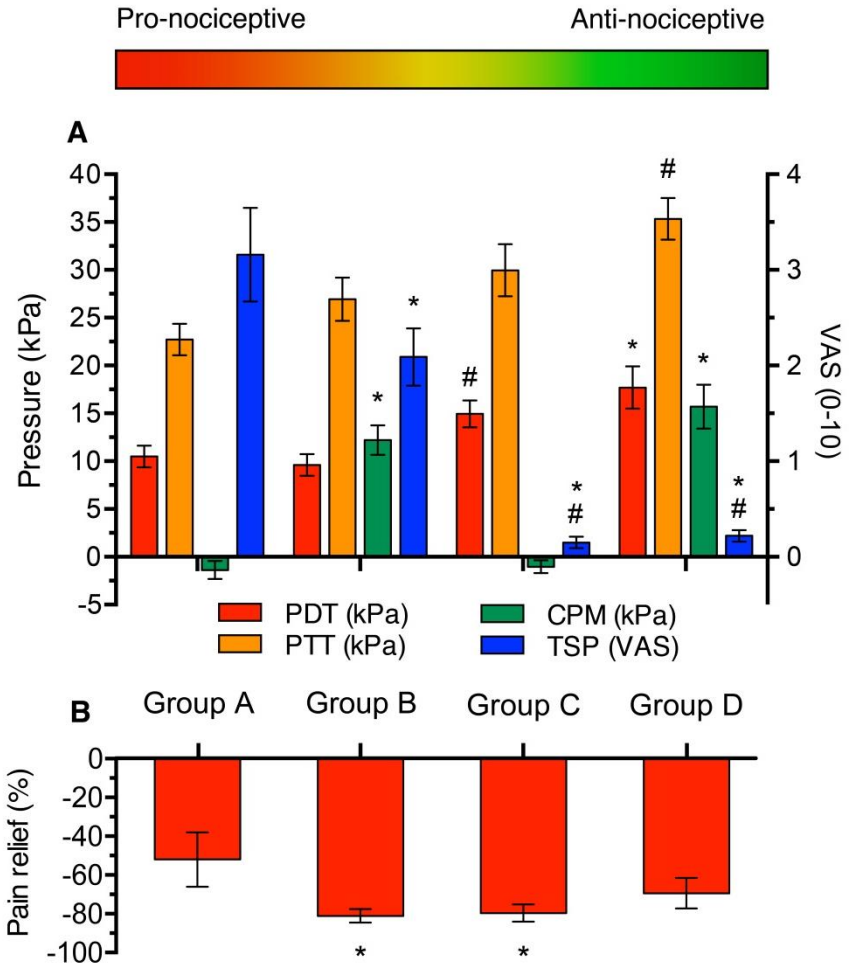
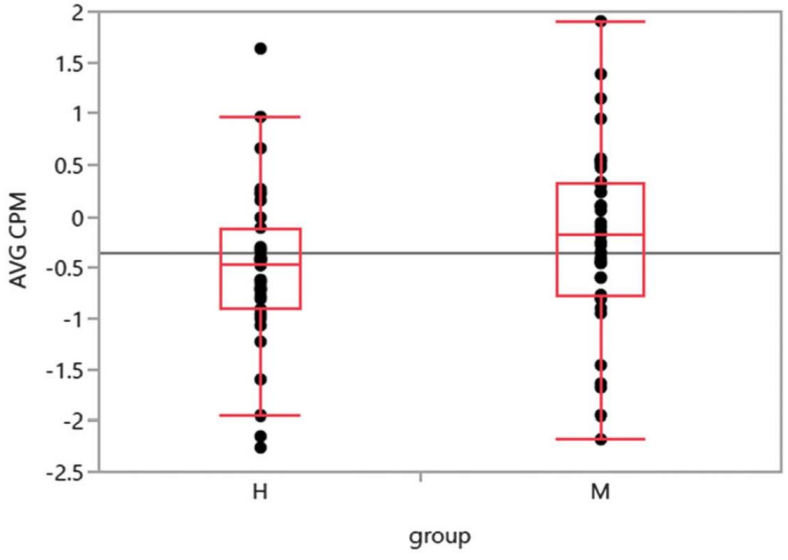
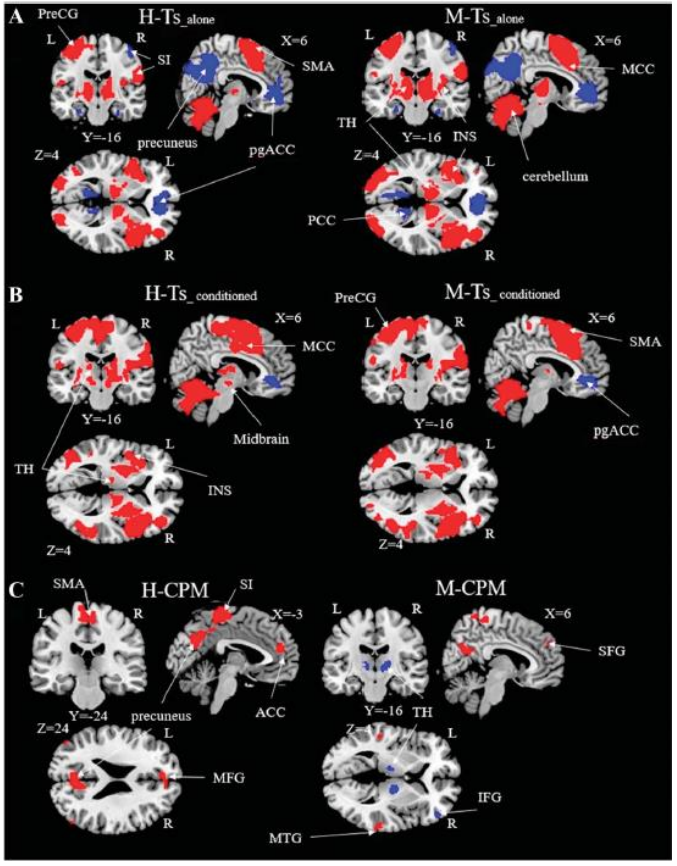


Petersen et al., 2016

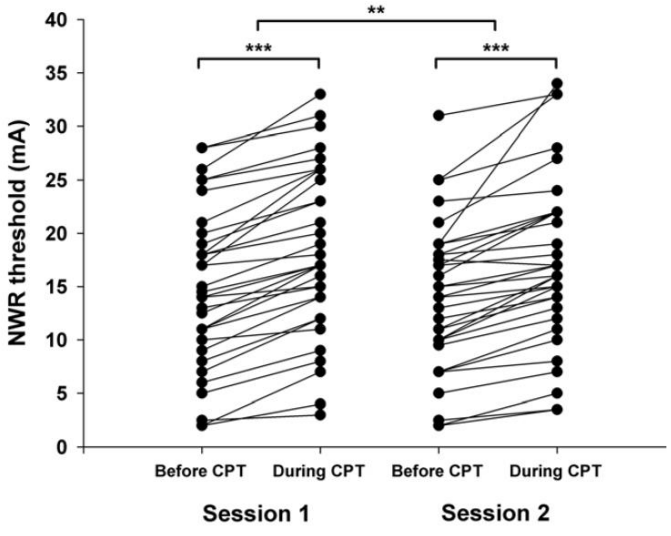
CPM in attack-free migraineurs





Kisler et al. Pain 2018 159(12)

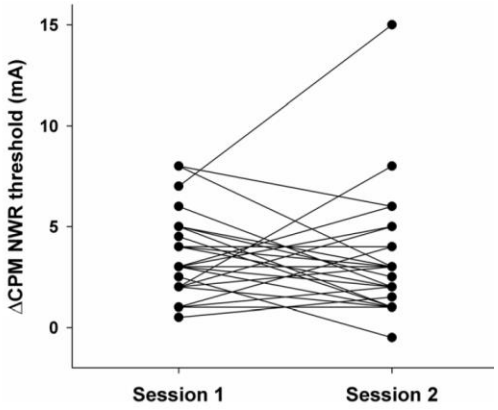
Reliability of CPM

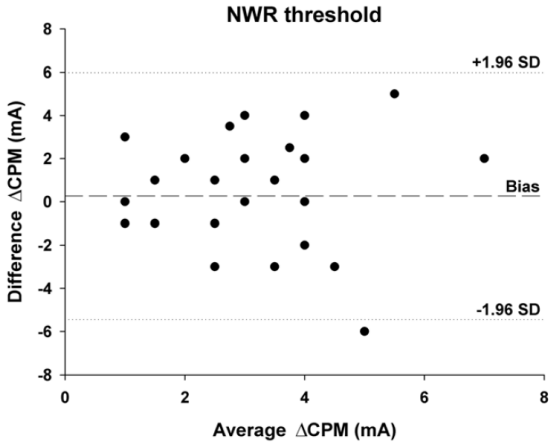


Assessment measure	Bland-Altman analysis Bias (lower LoA – upper LoA)		CV (95% confidence intervals)		ICC (95% confidence intervals)	
	Before CPT	During CPT	Before CPT	During CPT	Before CPT	During CPT
NWR threshold (mA)	0.8	1.1	12.6%	11.5%	0.93	0.94
	(−4.1–5.7)	(−3.6–5.8)	(8.9%–15.4%)	(8.1%–14.2%)	(0.87–0.97)	(0.88–0.97)

Manresa PLOS ONE 2014, 9(6)

Reliability of CPM





Assessment measure	Bland-Altman analysis - Bias	CV	ICC
	(lower LoA – upper LoA)	(95% confidence intervals)	(95% confidence intervals)
	ΔCPM	ΔCPM	ΔCPM
NWR threshold (mA)	0.3	64.1%	0.26
	(−5.4–6.0)	(39.1%–81.8%)	(0–0.55)

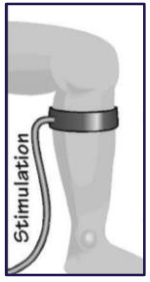
Manresa PLOS ONE 2014, 9(6)

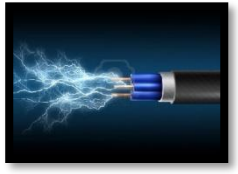
Reliability of CPM

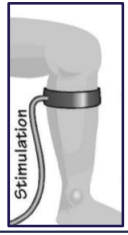
Percentage of return to normal ΔCPM values	NWR threshold	
	N_c	N_p
100%	6	8
75%	10	14
50%	23	31
25%	93	124

Manresa PLOS ONE 2014, 9(6)

Reliability of CPM



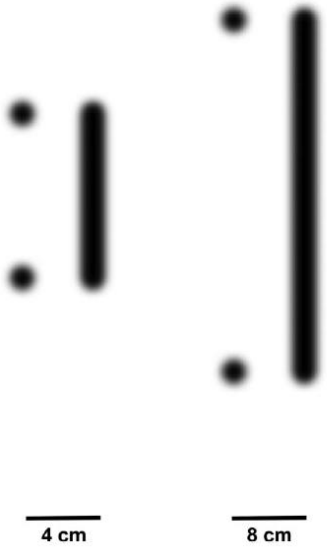


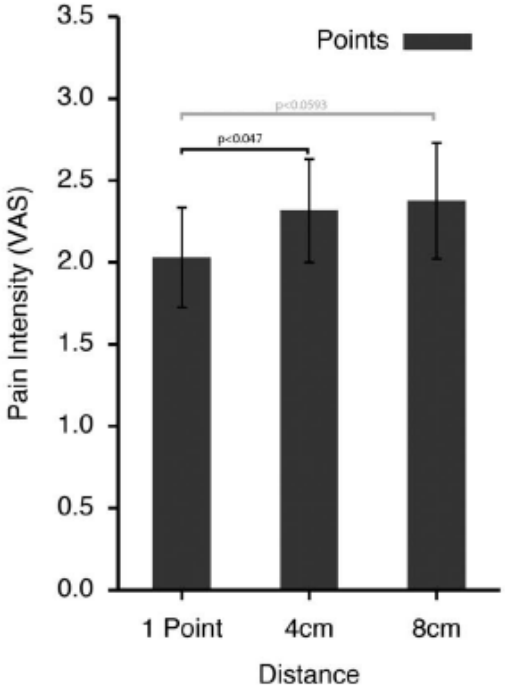


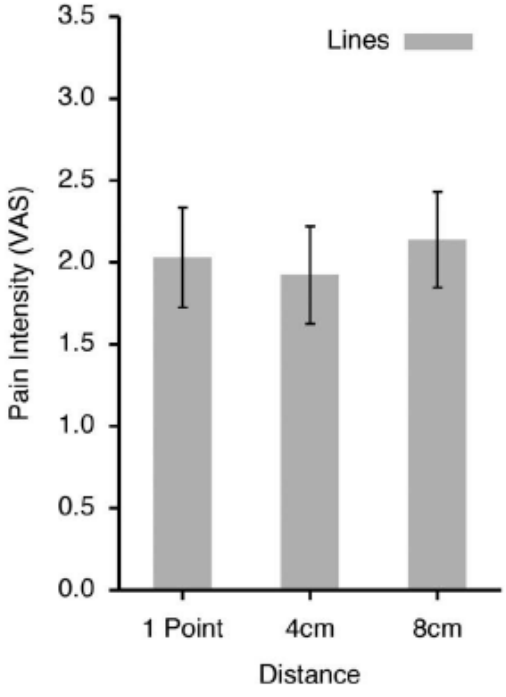
	Electrical		Heat		Handheld		Cuff PDT		Cuff PTT	
cs	CPT	Cuff	CPT	Cuff	CPT	Cuff	CPT	Cuff	CPT	Cuff
ICC (3,1)	0.09	0.12	0.10	0.48	0.49	0.04	0.44	0.53	0.51	0.14
95% CI	[−0.30, 0.45]	[−0.27, 0.48]	[−0.29, 0.46]	[0.12, 0.73]	[0.13, 0.73]	[−0.35, 0.41]	[0.08, 0.71]	[0.18, 0.76]	[0.16, 0.75]	[−0.25, 0.49]
CV [%]	105.7	503.9	78.5	442.7	63.6	125.3	107.6	143.1	127.3	295.2
Nc	23	534	13	412	9	33	24	43	34	183
Np	26	609	14	784	17	34	44	91	69	213

Imai, Somatosensory & Motor Research, 33:3-4, 169-177

Lateral Inhibition vs Spatial Summation

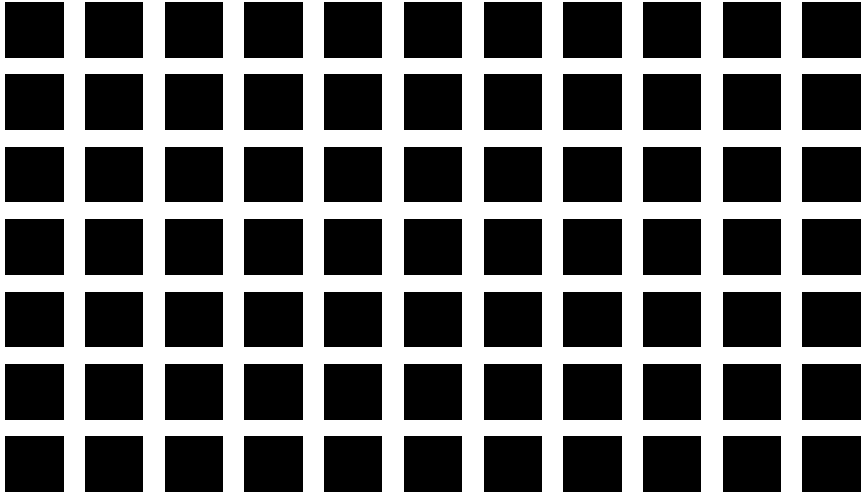


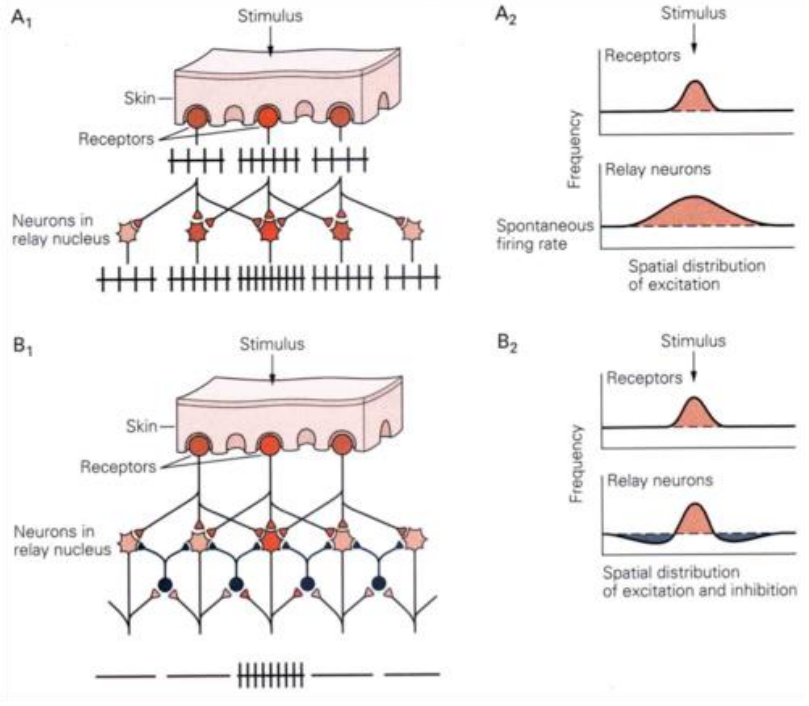




Quevedo et al. Pain 2017, 158(6)

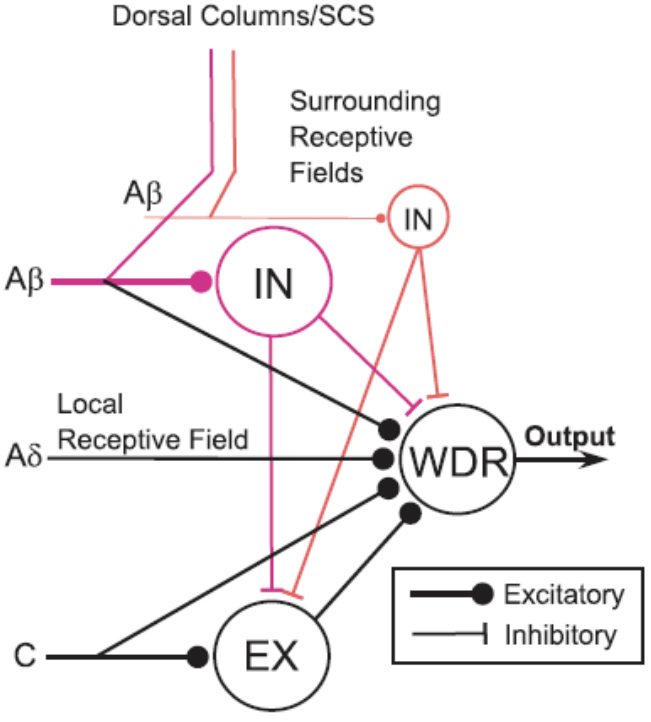
Lateral Inhibition





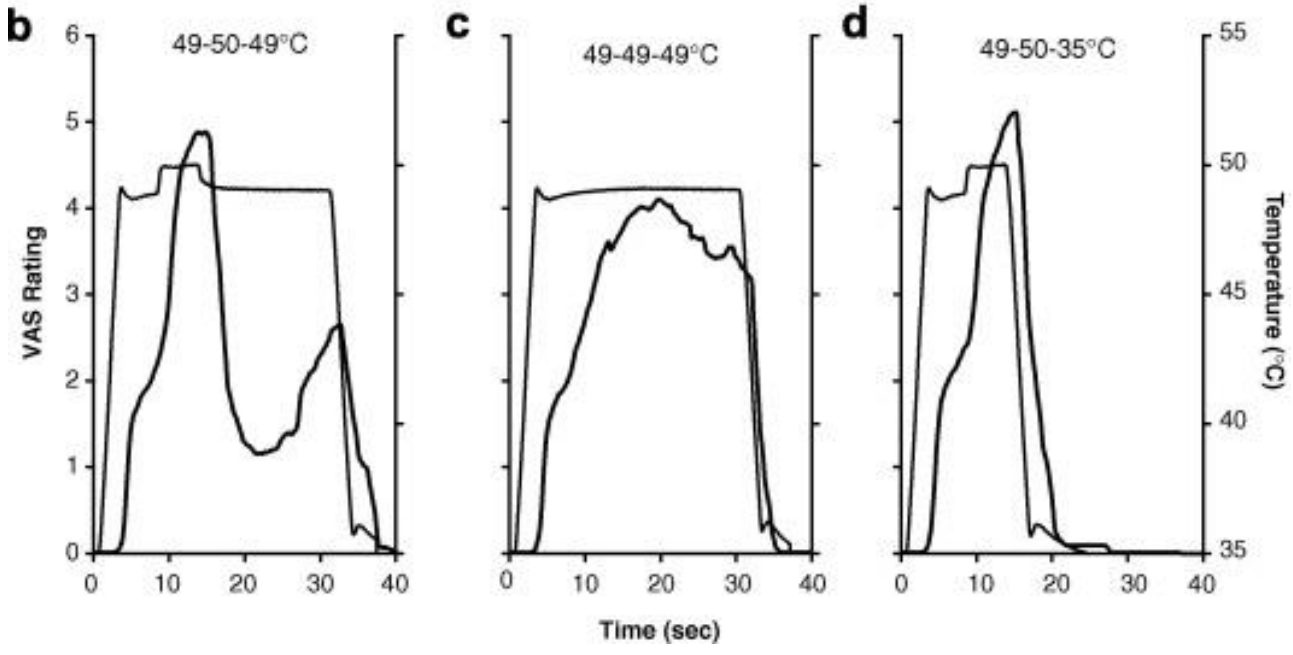
Computer model of dorsal horn neurons during SCS

- If the GABAergic inhibitions are reduced, SCS looses its effect.



J Neurophysiol • doi:10.1152/jn.00254.2014 • www.jn.org

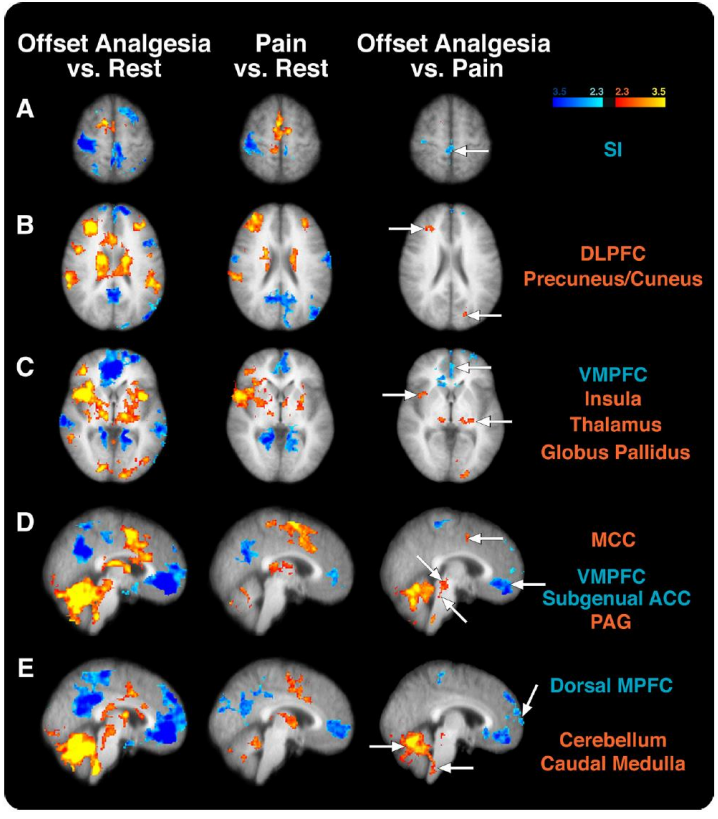
Offset Analgesia – The basic concept

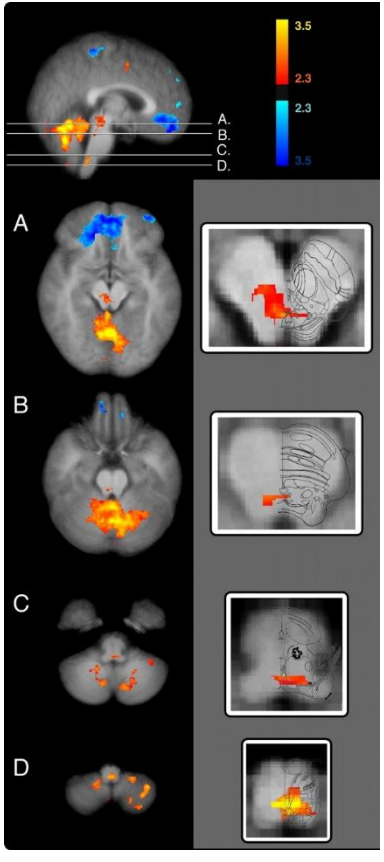


Yelle et al. Pain 134 (2008) 174-186

Offset Analgesia

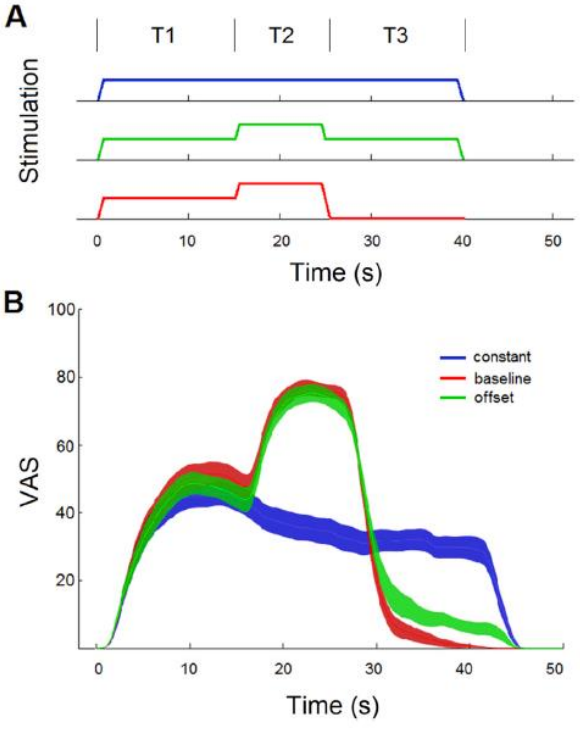
Activity in areas related to descending inhibition of pain is activated during offset analgesia compared to constant pain.

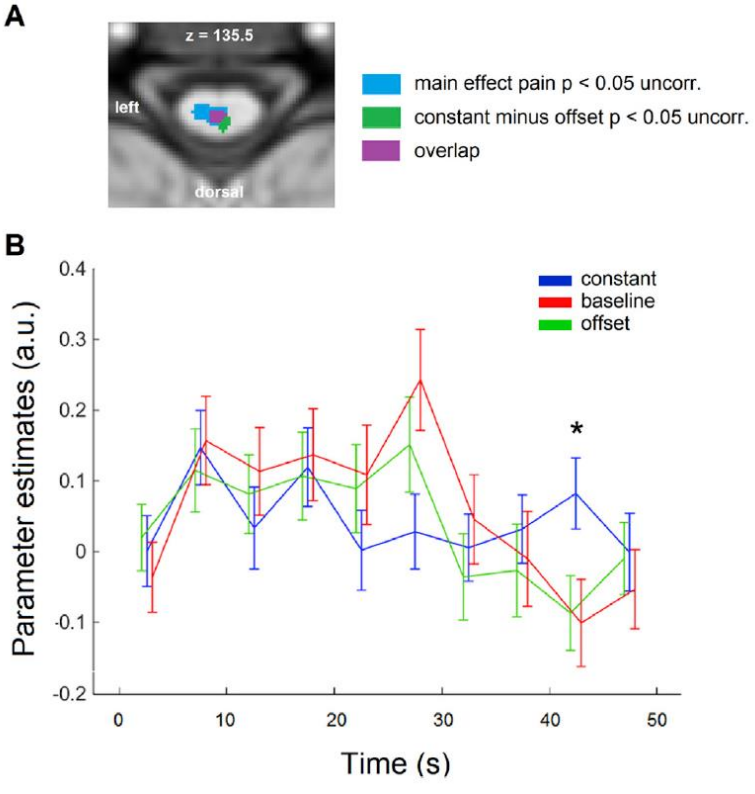




Yelle et al. J Neuroscience 29(33) (2009)

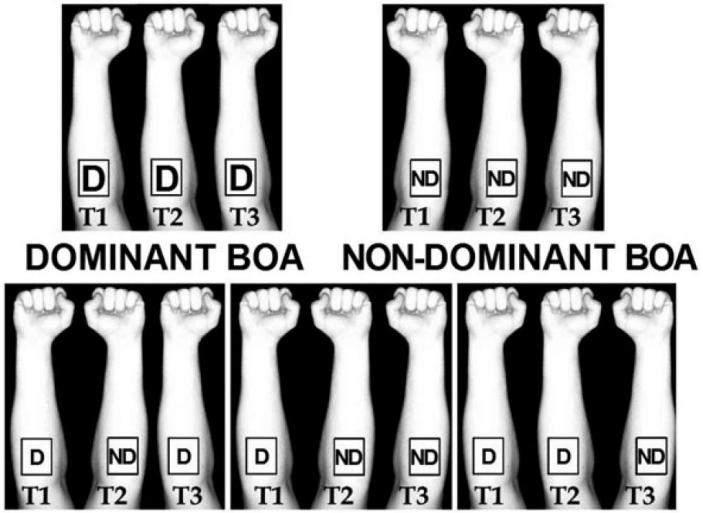
Spinal involvement

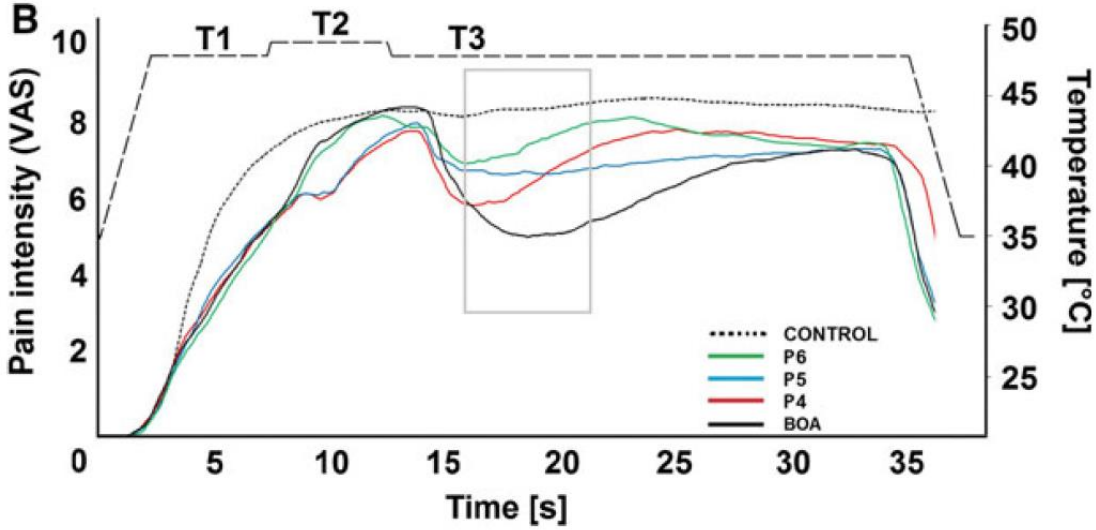




Sprenger et al. NeuroImage 183 (2018) 788–799

Offset Analgesia – A central or peripheral phenomenon





Ligato et al. Eur J Pain 22 (2018) 142-149

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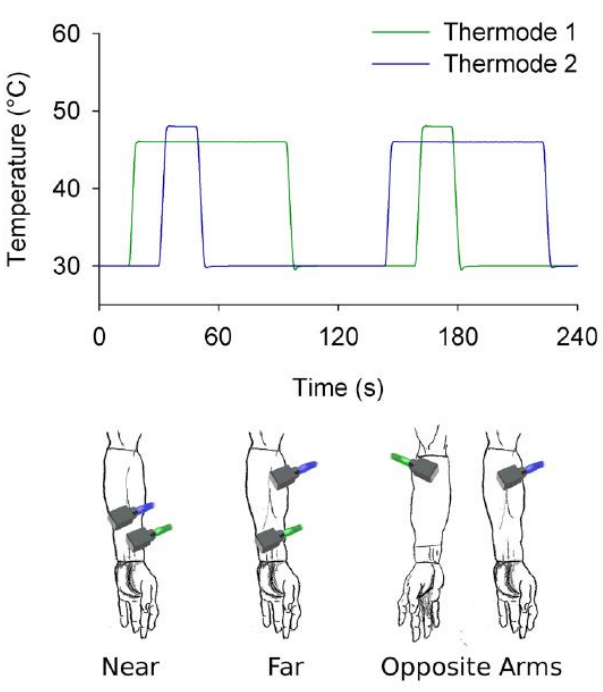

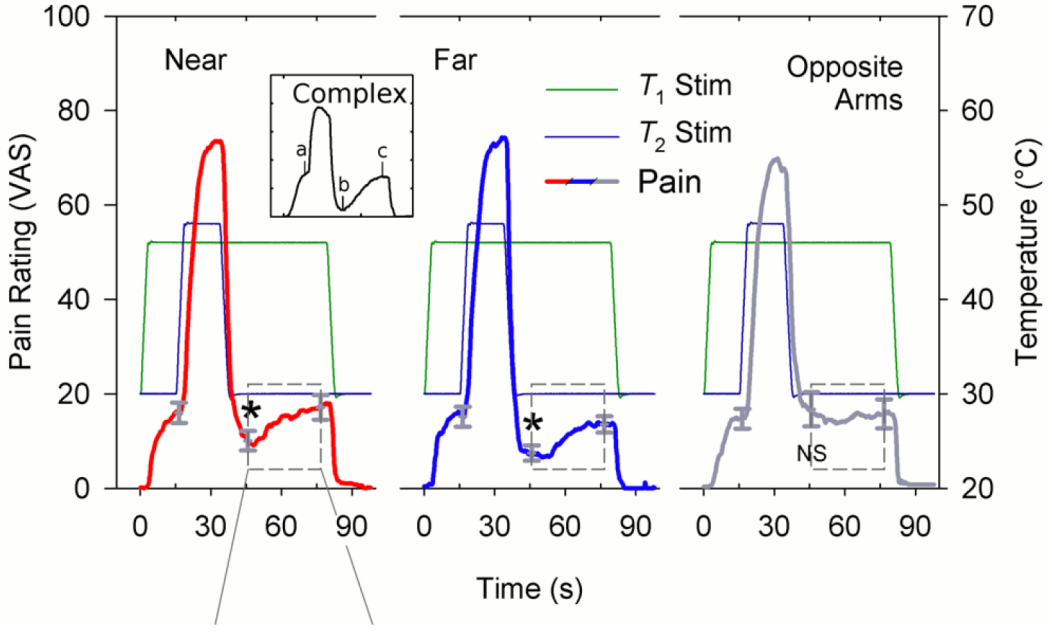

Petre, et al. Scientific Report 2017, 7p3894

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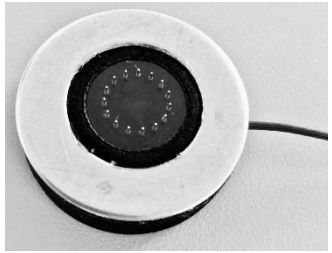
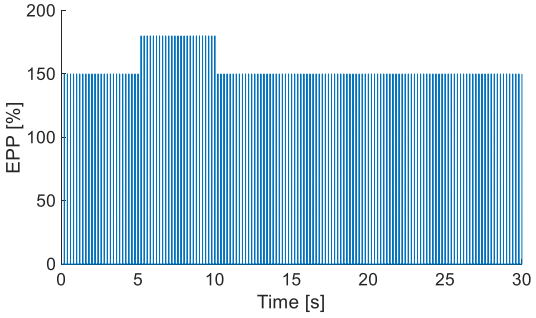
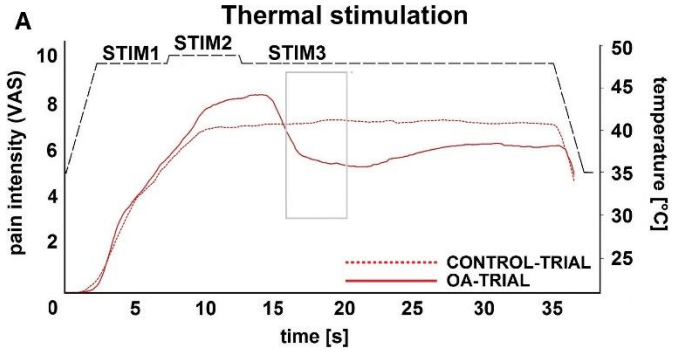
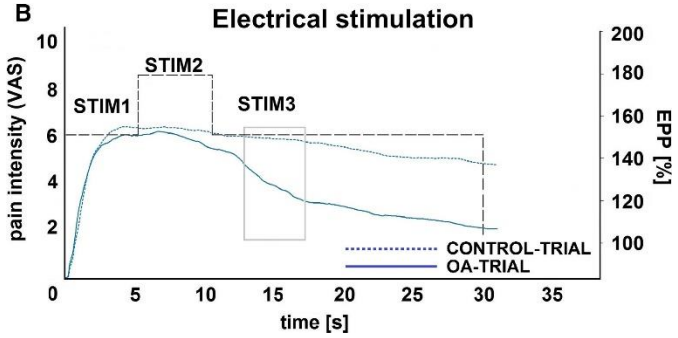
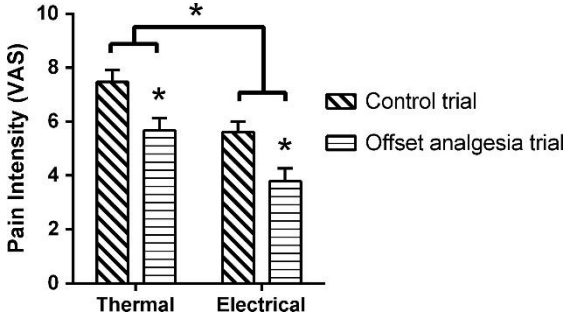
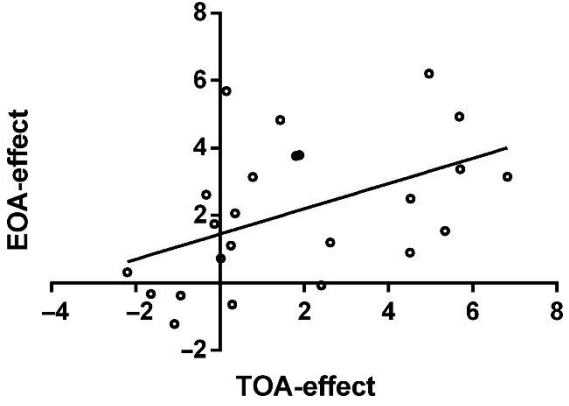








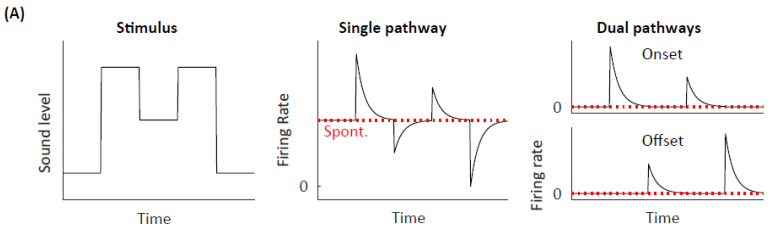


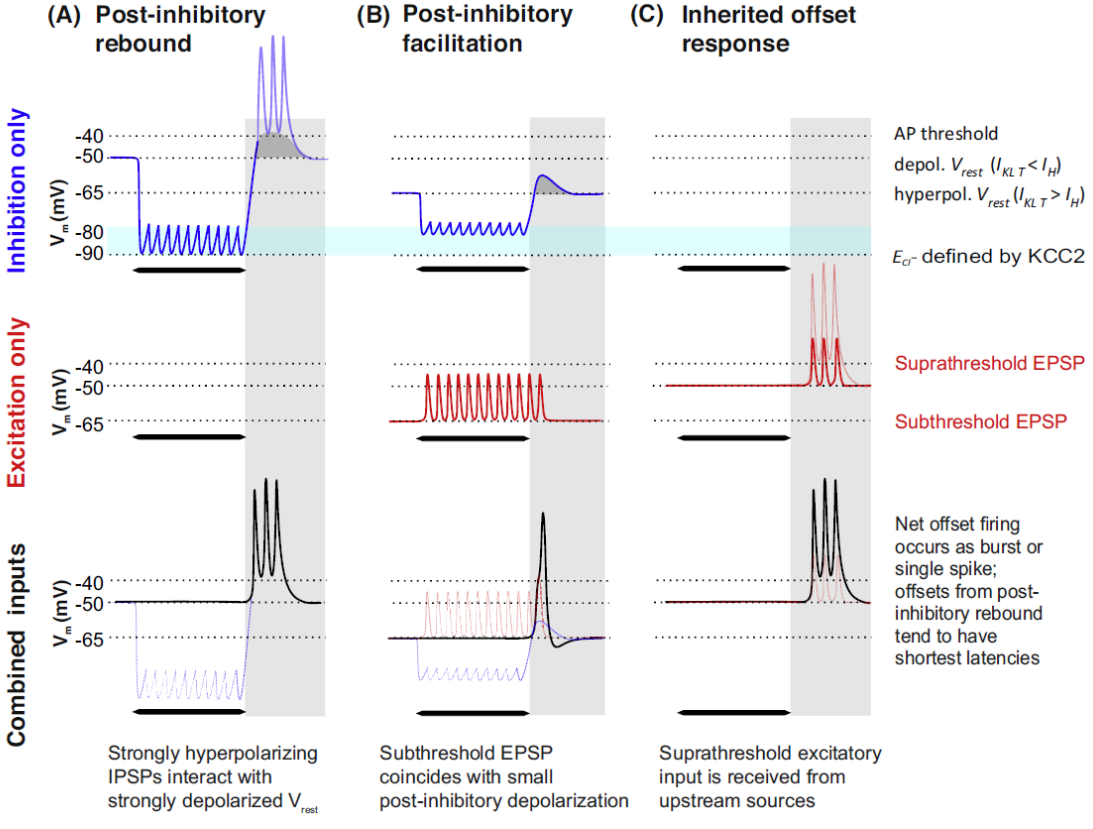


Pedersen et al. Eur J Pain 22 (2018) 1678-1684

How is pain offset coded?
- an idea from the auditory system

- Different pathways are activated during on- and off-set of sounds



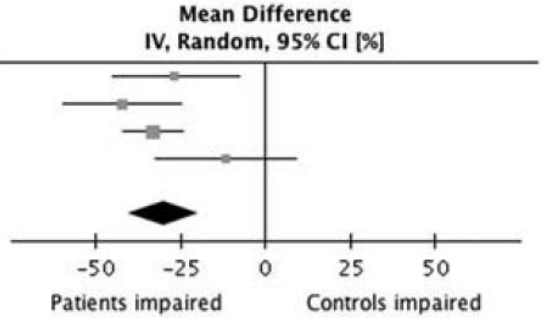


Kopp-Scheinpflug et al. Trends in Neuroscience

Offset Analgesia – reduced in chronic pain patients

Study or Subgroup	chronic pain Mean [%]	SD [%]	Total	healthy control Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]
Kobinata et al. [40]	35.3	24.9	12	61.8	21.7	12	20.1%	-26.50 [-45.19, -7.81]
Niesters et al. [22]	56	28	10	98	3	10	21.9%	-42.00 [-59.45, -24.55]
Oudejans et al. [49]	65	26	34	98	5	34	40.5%	-33.00 [-41.90, -24.10]
Zhang et al. [53]	27.8	28.7	17	39.4	32.7	17	17.5%	-11.60 [-32.28, 9.08]
Total (95% CI)			**73**			**73**	**100.0%**	**-29.92 [-40.30, -19.53]**

Heterogeneity: $Tau^2 = 48.72$; $Chi^2 = 5.32$, df = 3 (P = 0.15); $I^2 = 44\%$
Test for overall effect: Z = 5.65 (P < 0.00001)

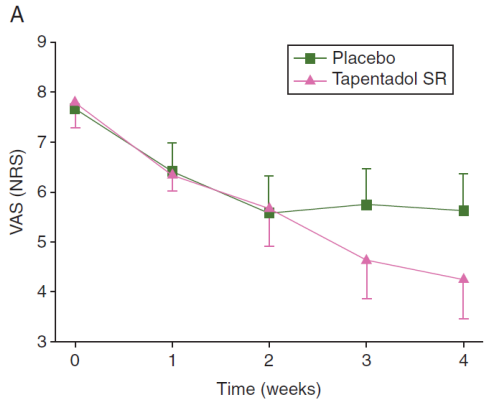


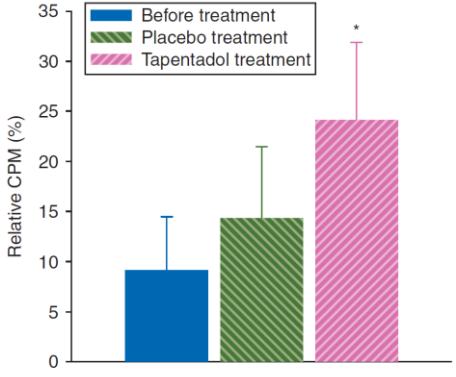
Kobinata: Chronic pain patients
Niesters: Neuropathic pain patients
Oudejans: Fibromyalgia
Zhang: “Patients with chronic pain”

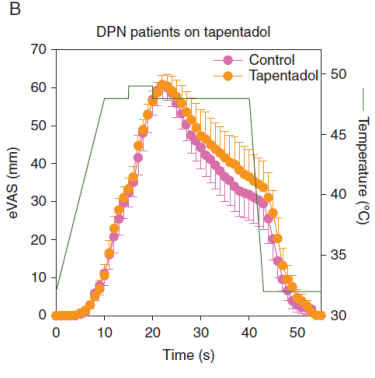
Szikszay et al. C.J.Pain 35(2), pp. 189-204

Tapentadol – OA and CPM

- Patients: Twenty-four patients with painful diabetic polyneuropathy (DPN)
- Treatment: 4 of Tapentadol
  - activates the μ-opioid receptor
  - inhibits norepinephrine reuptake
- Before treatment: no CPM or OA responses







Niester et al (2014) B.J. Anaesthesia 113(1): 148–56


THANK YOU FOR YOUR ATTENTION
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