

Alteration of pain processing by transcutaneous vagus nerve stimulation

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Vagus nerve stimulation in awake rats reduces formalin-induced nociceptive behavior and fos-immunoreactivity in trigeminal nucleus caudalis

- 4 experimental groups
 - Left cervical vagus nerve stimulation (VNS)
 - Formalin injection into left vibrissal pad
 - VNS and formalin injection
 - Sham VNS

Experimental groups	Fos- Immunoreactive neurons			Pain behaviour Cumulative time (sec)	
	Ipsilateral	Contralateral	Delta (ipsi-contral)	Early phase (0–6 min)	Late phase (6–45 min)
Group 1 VNS only	20.4 ± 5.7	8.8 ± 3.6	11.7 ± 6	n.a.	n.a.
Group 2 Formalin only	68.9 ± 17.6	7.3 ± 4.9	61.6 ± 15.9	38.8 ± 4.1	449.7 ± 74.4
Group 3 VNS + Formalin	45.8 ± 14.4	14.6 ± 3.5	31.3 ± 15	1.5 ± 2* (ANE = 96.1%)	176.7 ± 11.2* (ANE = 60.7%)
Group 4 Sham VNS	5.9 ± 1	3.7 ± 0.8	2.2 ± 1.2	n.a	n.a.

➤ VNS inhibits sensory neurons in the brainstem and pain-related behavior on the ipsilateral side.

Left vagus nerve stimulation suppresses experimentally-induced pain

- 2 experimental groups
 - 10 patients with drug resistant epilepsy
 - 12 healthy, age-matched volunteers
- Experimentally-induced pain (hand)
 - Mechanical impact: pain threshold, wind-up
 - Tonic pressure (pinch)
- No effect on mechanical pain threshold.
- Reduction of wind-up.
- Reduction of tonic pressure pain.
- Results suggest influence of VNS on central pain processing.

Transcutaneous vagus nerve stimulation (t-VNS)

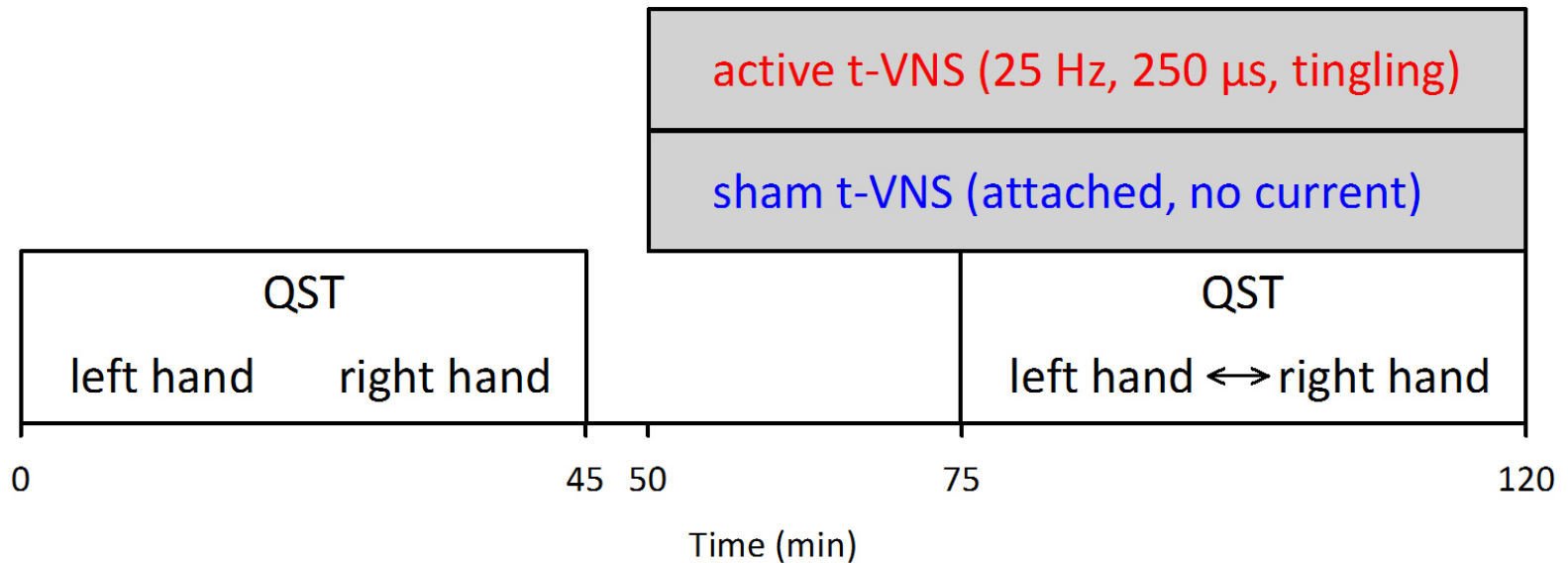


Auricular branch of vagus nerve supplies the concha as shown by:

- Neuroanatomical study in human ears (Peuker & Filler, Clin Anat 15: 35-7, 2002)
- Intracranial section of the vagus nerve in man (Fay, J Neurol Psychopathol 8: 110-23, 1927)
- Isolated vagus nerve palsy with herpes zoster (Ohashi et al., Rinsho Shinkeigaku 34: 928-9, 1994)
- Auricular syncope (Thakar et al., J Laryngol Otol 122: 1115-7, 2008)
- Gastroauricular phenomenon (Engel, Arch Psychiat Nervenkr 227: 271-7, 1979)
- Referred, auricular pain secondary to lung neoplasms (Eross et al., Cephalalgia 23:2-5, 2003)

t-VNS affects pain processing in man – Study design

- Randomized, controlled, crossover study (ClinicalTrials.gov Identifier: NCT01174498)
- 48 healthy volunteers: 24 female, 24 male, 23.3±2.1 years
- 2 sessions with or w/o active t-VNS in randomized order
- Quantitative Sensory Testing (QST) on left and right hand dorsum



t-VNS affects pain processing in man – Results

- Increased pressure pain threshold (PPT) on left hand during t-VNS
2-way ANOVA: interaction between stimulation and side, $p < 0.05$ (sham vs. t-VNS: 402 vs. 432 kPa)



Pressure gauge device

t-VNS affects pain processing in man – Results

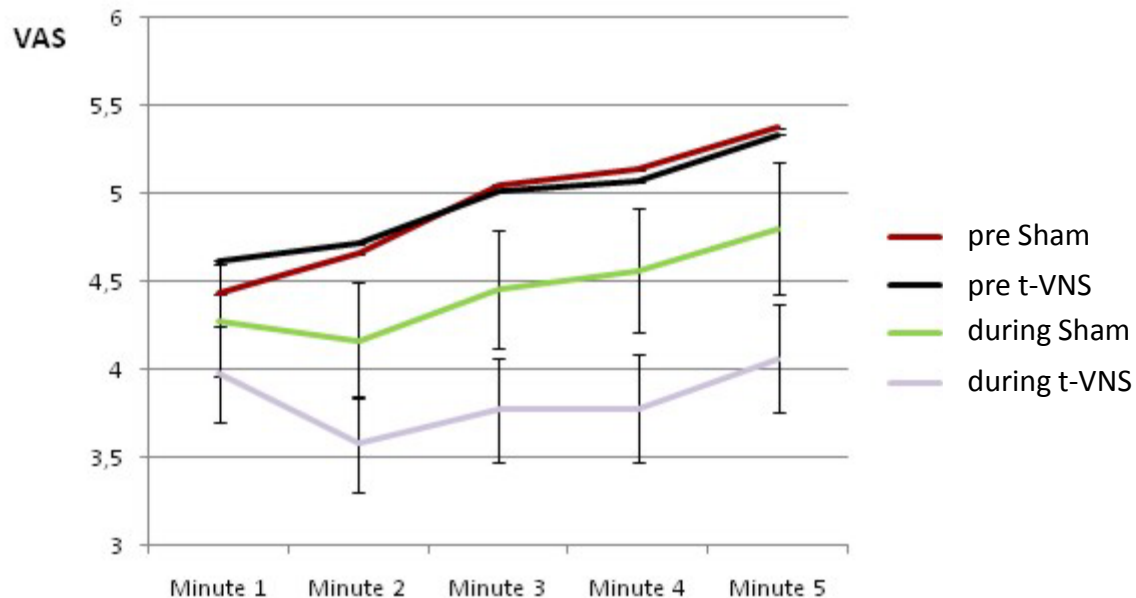
- Increased pressure pain threshold (PPT) on left hand during t-VNS
2-way ANOVA: interaction between stimulation and side, $p < 0.05$ (sham vs. t-VNS: 402 vs. 432 kPa)
- Reduced mechanical pain sensitivity (stimulus-response function)
2-way ANOVA: interaction between stimulation and side, $p < 0.05$ (sham vs. t-VNS: 3.2 vs. 2.1)



Pinprick stimulator

t-VNS affects pain processing in man – Results

- Increased pressure pain threshold (PPT) on left hand during t-VNS
2-way ANOVA: interaction between stimulation and side, $p < 0.05$ (sham vs. t-VNS: 402 vs. 432 kPa)
- Reduced mechanical pain sensitivity (stimulus-response function)
2-way ANOVA: interaction between stimulation and side, $p < 0.05$ (sham vs. t-VNS: 3.2 vs. 2.1)
- Reduced sensitivity for sustained heat pain
ANOVA: stimulation $p < 0.001$, time $p < 0.0001$



Summary and Conclusion

- VNS in rats inhibits sensory neurons in the brainstem and pain-related behavior on the ipsilateral side.
- VNS in epilepsy patients inhibits wind-up and tonic pressure pain. Spinal or even supraspinal mechanisms may be involved.

- t-VNS inhibits deep muscle pain processing on the ipsilateral side.
- t-VNS flattens the stimulus-response function of pinprick pain.
- t-VNS reduces temporal summation of noxious heat.

- t-VNS affects pain processing but does not interfere with innocuous somatosensory processing.
- t-VNS seems to activate CNS mechanisms of pain modulation.
- Future studies will address potential analgesic effects in patients.