

## **Analgesic Effects of Transcutaneous Vagus Nerve Stimulation (136)**

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**Introduction:** Vagus nerve stimulation modulates nociception and pain processing in animal and human experimental studies. Due to the invasive procedure of vagus nerve stimulation, studies mainly involve patients suffering from both drug-resistant epilepsy and pain. The present study addressed the hypothesis that noninvasive, transcutaneous electrical stimulation of the auricular branch of the vagus nerve (t-VNS) alters pain processing.

**Methods:** Somatosensory processing was assessed by the quantitative sensory testing (QST) protocol with mechanical and thermal stimulation in 48 healthy volunteers in a randomized, controlled study. Each volunteer participated in two experimental sessions with or without (control) active t-VNS on different days in randomized order. In one session QST was performed before and during t-VNS on both hands. After baseline QST, t-VNS at the left ear was started with a nonpainful stimulus intensity using rectangular pulses.

**Results:** Statistical analysis revealed significant interactions between stimulation and side for the parameters mechanical pain sensitivity (MPS) and pressure pain threshold (PPT). MPS of the left hand was lower under t-VNS as compared to control session and the right side ( $P < .05$ ). PPT was higher under t-VNS as compared to control condition and the right side ( $P < .05$ ). Sustained application of painful heat for 5 min induced increased perception ratings under baseline conditions. Under t-VNS pain rating increase was significantly reduced as compared to control ( $P < .001$ ). All other QST parameters remained statistically unchanged.

**Conclusion:** Sensitivity to mechanically evoked pain on the ipsilateral hand was reduced. Besides flattening of the stimulus-response-function for superficial mechanical pain (MPS), increased PPT reveals suppression of deep muscle pain under t-VNS. Furthermore, temporal summation of noxious heat seems to be inhibited with t-VNS. The study shows alteration of mechanical and thermal pain processing in healthy volunteers. Future studies in chronic pain patients will address the potential analgesic effects of t-VNS.

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# Analgesic effects of transcutaneous vagus nerve stimulation

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## 1 Introduction

Stimulation of vagus nerve afferents has been shown to modulate nociception and pain processing in animal and human experimental studies (1,2). Due to the invasive procedure of vagus nerve stimulation (VNS), the vast majority of clinical studies investigated patients who primarily suffered from epilepsy or depression with concomitant pain diseases (3-5). However, in one case series VNS was implanted in order to treat chronic headache showing significant improvement in four out of six patients (6). A recently developed medical device allows for transcutaneous electrical stimulation of the auricular branch of the vagus nerve (t-VNS). The present study addresses the hypothesis that t-VNS alters pain processing.

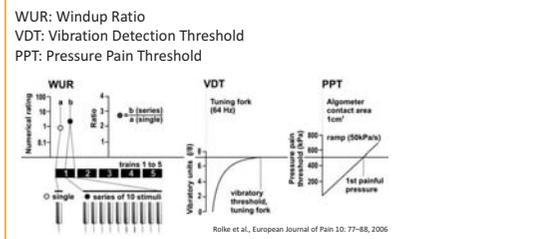
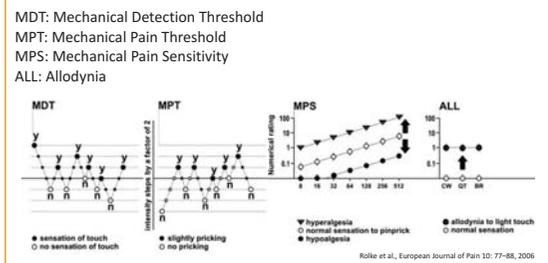
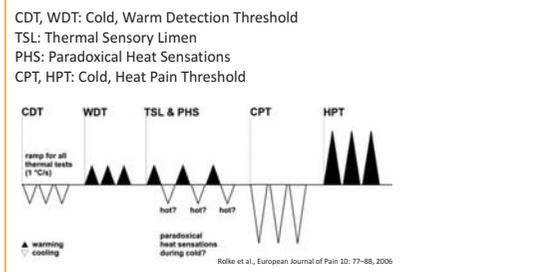
- (1) Bohotin et al., Pain 101: 3-12, 2003
- (2) Kirchner et al., Neurology 55: 1167-71, 2000
- (3) Broggi et al., Neurol Sci 31: S87-92, 2010
- (4) Multon & Schoenen, Acta Neurol Belg 105: 62-7, 2005
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- (6) Mauskop, Cephalalgia 25: 82-6, 2005

## 2 Methods

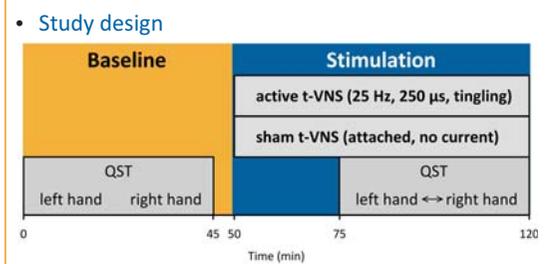
- Randomized, controlled, crossover study
- 48 healthy volunteers: 24 ♀, 24 ♂, 23.3 ± 2.1 years
- 2 randomized sessions with active or sham t-VNS on different days
- **Conditioning stimulation:**  
**Transcutaneous vagus nerve stimulation, t-VNS**
  - applied to skin afferents of the auricular branch of the vagus nerve in left ear's concha
  - electrical, rectangular pulses (250 μs duration)
  - 25 Hz stimulation frequency
  - intensity above detection threshold and below pain threshold evoking tingling sensations



- Test stimulation: Quantitative Sensory Testing, QST on left and right hand dorsum

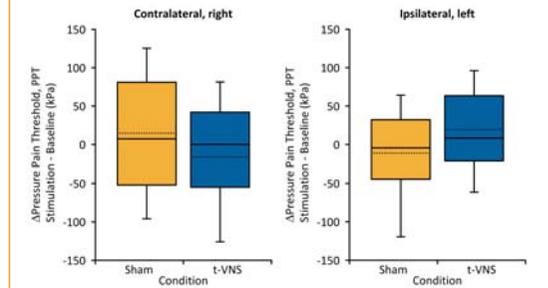


Tonic Heat Pain (THP): Contact heat pulse with a saw tooth shape started from 0.5°C below individual HPT and increased to 0.5°C above HPT with 25 pulses per min. During the stimulation period of 5 min volunteers rated pain perception on a numerical rating scale (0 to 10) every 20 seconds.

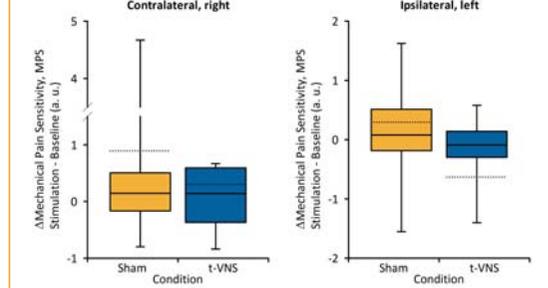


## 3 Results

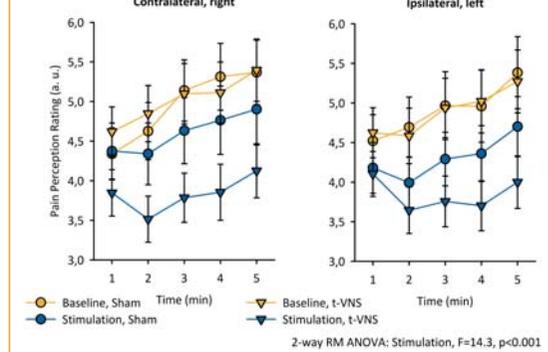
Ipsilateral PPT increased under active t-VNS.



Ipsilateral MPS decreased under active t-VNS.



Reduced THP under t-VNS.



Non-painful QST parameters remained unchanged.

Parameter	Stimulation	Interaction Stimulation*Side
CDT	F=0.01, n.s.	F=0.05, n.s.
WDT	F=0.05, n.s.	F=0.10, n.s.
TSL	F=1.71, n.s.	F=0.03, n.s.
MDT	F=1.96, n.s.	F=0.75, n.s.

2-way RM ANOVA, n.s.: not significant

## 4 Summary & Conclusions

- Invasive VNS in rats inhibits sensory neurons in the brainstem and pain-related behavior. Fos-immuno-reactivity in the brainstem decreased on the ipsilateral side.
- Invasive VNS in epilepsy patients inhibits wind-up and tonic pressure pain. Spinal or even supraspinal mechanisms are suggested to be involved.
- t-VNS inhibits deep muscle pain processing on the ipsilateral side (PPT).
- t-VNS reduces mechanical pain sensitivity (MPS).
- t-VNS reduces temporal summation of noxious heat (THP).
- t-VNS affects pain processing but does not interfere with innocuous somatosensory processing.
- t-VNS is suggested to activate CNS mechanisms of pain modulation.
- Future studies will address potential analgesic effects in patients.

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