Analgesic Effects of Transcutaneous Vagus Nerve Stimulation (VNS) in Healthy Volunteers

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Impact of VNS on pain: Preclinical data

- Electrical VNS *modulates nociception*. Effects depend upon vagal input to NTS and subsequent relays such as NRM and LC.

  Randich & Gebhart Brain Res Rev 17: 77-99, 1992

- VNS activates the *ascending* antinociceptive pathway from PAG onto VPM and the *descending antinociceptive system* acting on STN.

  Nishikawa et al., Brain Res 833: 108-11, 1999

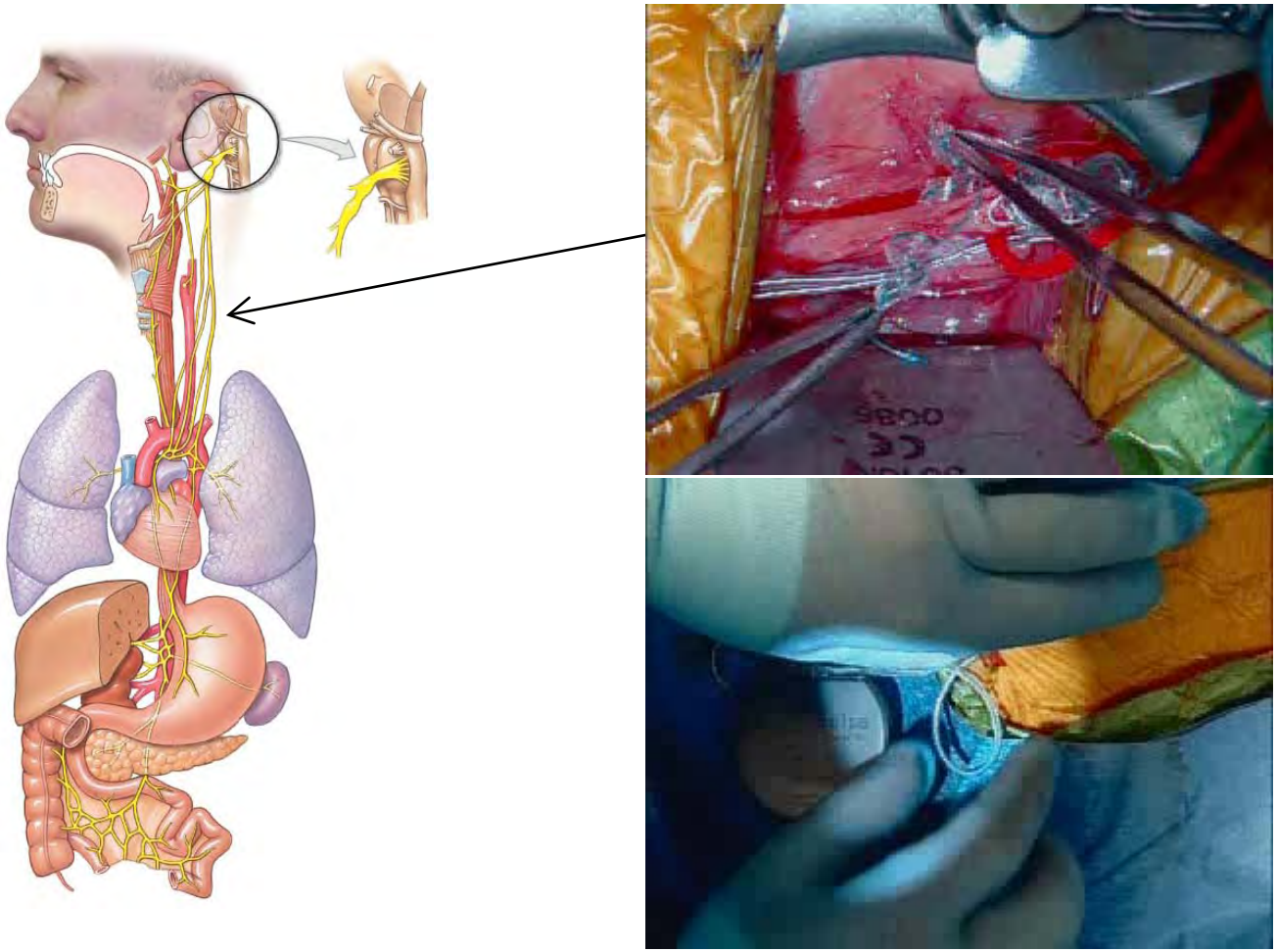
- VNS reduces duration of nociceptive *behavior* in the orofacial formalin pain model and the number of *Fos*-activated neurons in the STN.

  Bohotin et al., Pain 101: 3–12, 2003

- Decreased vagal activity by *vagotomy* aggravates both the severity and the time course of painful polyneuropathy.

  Weissman-Fogel et al., Pain 138: 153-62, 2008

Vagus Nerve Stimulation (VNS)



Martini & Nath, Anatomy and Physiology, 2010; Chang Gung Memorial Hospital

Impact of VNS on pain: Clinical data

- A prospective trial in drug-resistant *epilepsy* showed reduction of wind-up phenomenon and tonic pressure pain under invasive VNS.

  Kirchner et al., Neurology 55: 1167-71, 2000

- A retrospective study in epilepsy patients with VNS identified 10 *migraineurs*. Eight had a reduction of monthly frequency of ≥50%.

  Lenaerts et al., Cephalagia 28: 392-5, 2008

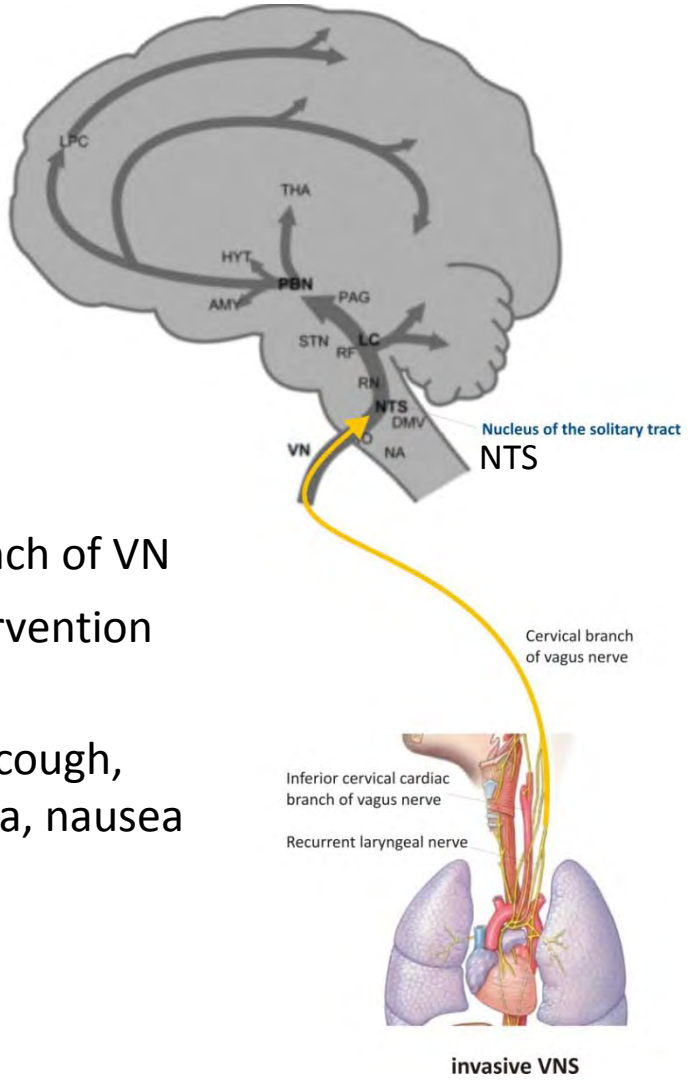
- Drug-resistant chronic cluster *headache* or migraine significantly improved in 4 out of 6 patients under invasive VNS.

  Mauskop, Cephalalgia 25: 82-6, 2005

- 5 out of 11 patients with *fibromyalgia* attained efficacy criteria with VNS. 2 patients no longer met widespread pain or tenderness criteria.

  Lange et al., Pain Med 12: 1406-13, 2011

VNS – Mode of action



invasive VNS

- Cervical branch of VN
- Surgical intervention
- Side effects:
  hoarseness, cough,
  pain, dyspnea, nausea

Cerebral activation

↑

Brainstem projection

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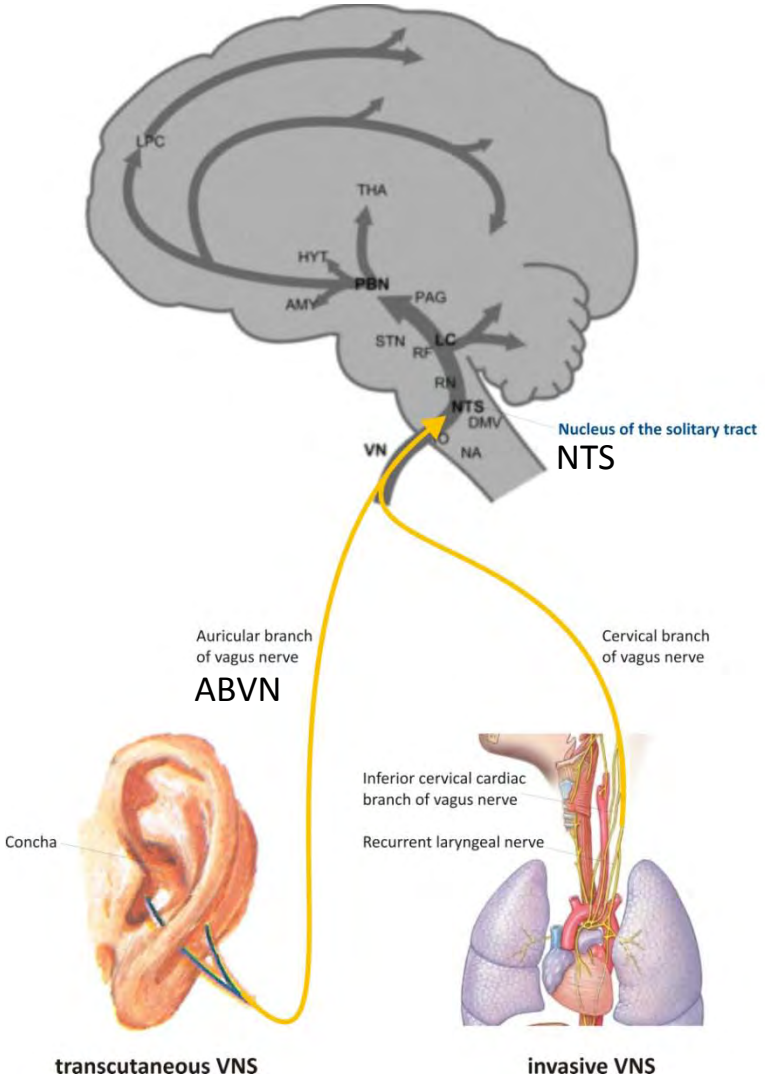
Site of stimulation

Martini & Nath, Anatomy and Physiology, 2010; Beekwilder & Beems, J Clin Neurophysiol 27: 130-8, 2010

transcutaneous VNS (t-VNS)



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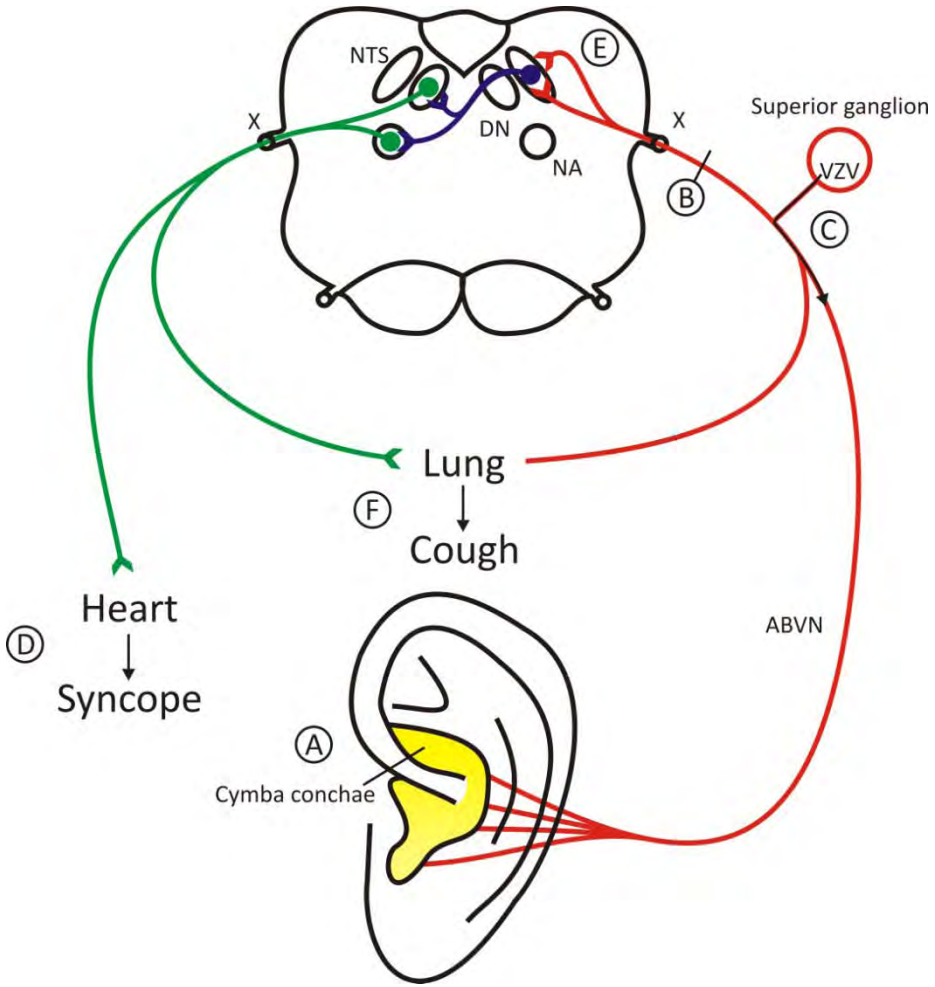
transcutaneous VNS: Site of stimulation



A) ABVN exclusively supplies the cymba conchae.
Peuker & Filler, Clin Anat 15: 35–7, 2002

B) Complete anesthesia of concha after section of vagus nerve.
Fay, J Neurol Psychopathol 8: 110–23, 1927

C) Herpetic vesicles in concha due to herpes zoster of vagus nerve.
Ohashi et al., Rinsho Shinkeigaku 34: 928–9. 1994

D) Auricular syncope triggered by mechanical stimulation of concha.
Thakar et al., J Laryngol Otol 122: 1115–7, 2008

E) Referred otalgia with non-metastatic lung cancer.
Eross et al., Cephalalgia 23: 2–5, 2003

F) Ear-cough reflex.
Tekdemir et al., Surg Radiol Anat 20: 253–7, 1998

Ellrich, European Neurological Review 6: 262–4, 2011

transcutaneous VNS (t-VNS)

Hypothesis: t-VNS alters pain perception in man

Two trials in healthy volunteers:

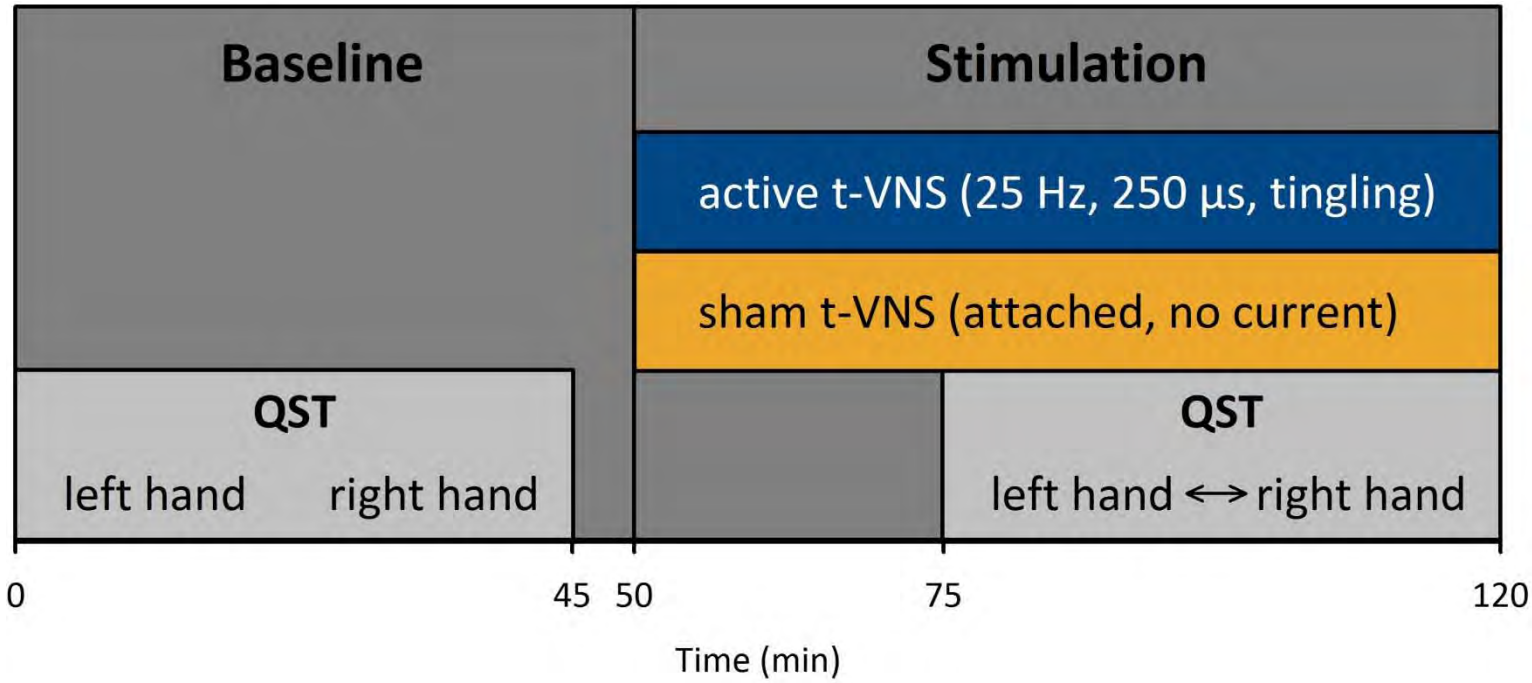
1. Randomized, crossover, two arms
   n=48, left-sided t-VNS
   complete quantitative sensory testing (QST) protocol

2. Randomized, controlled, crossover, three arms
   n=49, left-sided and right-sided t-VNS
   selected QST tests

Impact of t-VNS on pain: 1st trial

Study design

- 2 randomized sessions with active or sham t-VNS on different days
- Volunteers: n=48 (24 ♀, 24 ♂), 23.3±2.1 years
- Psychophysics: standard QST protocol plus tonic heat pain

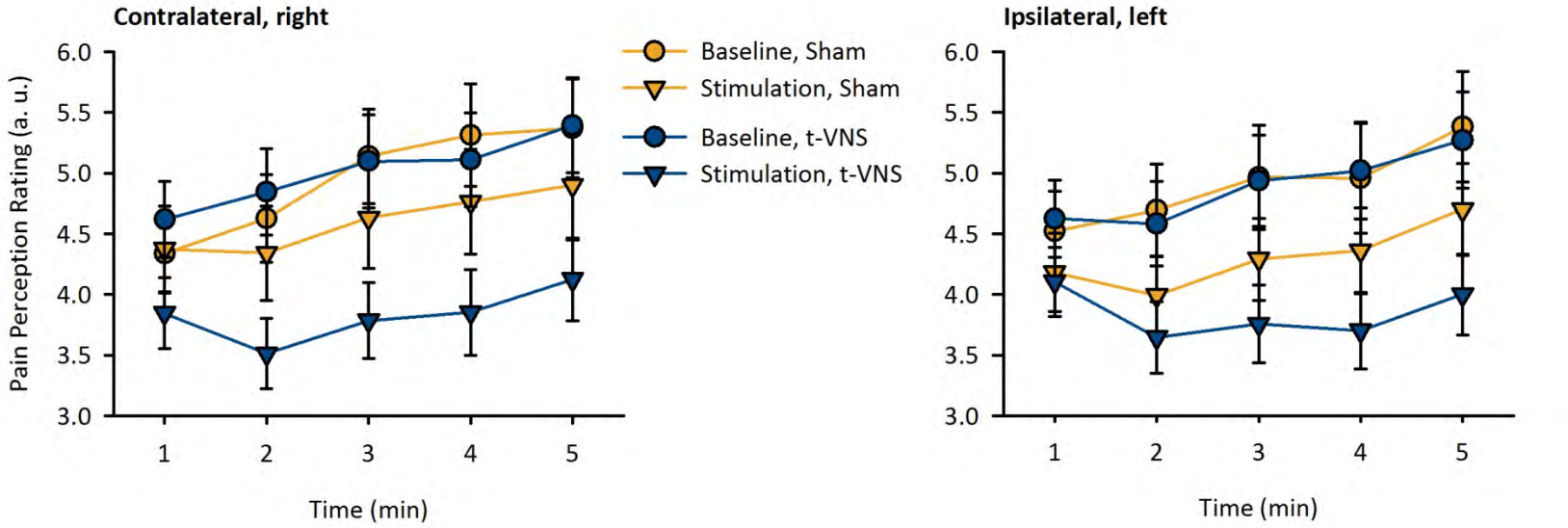


Busch et al., Brain Stimul 2012, Epub ahead of print

Impact of t-VNS on pain: 1st trial

Results

- Pressure Pain Threshold (PPT): Stimulation × Side: $p<0.05$, $F=4.6$
- Mechanical Pain Threshold (MPT): Stimulation × Side $p<0.01$, $F=7.7$
- Mechanical Pain Sensitivity (MPS): Stimulation × Side $p<0.05$, $F=6.6$
- Tonic Heat Pain (THP): Stimulation $p<0.001$, $F=14.3$



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Impact of t-VNS on pain: 1st trial

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- Tonic Heat Pain (THP): Stimulation $p<0.001$, $F=14.3$

- Thresholds of innocuous mechanical stimuli remained unchanged.
- Thermal thresholds remained unchanged.

Busch et al., Brain Stimul 2012, Epub ahead of print

Impact of t-VNS on pain: 1st trial

Summary and Conclusions

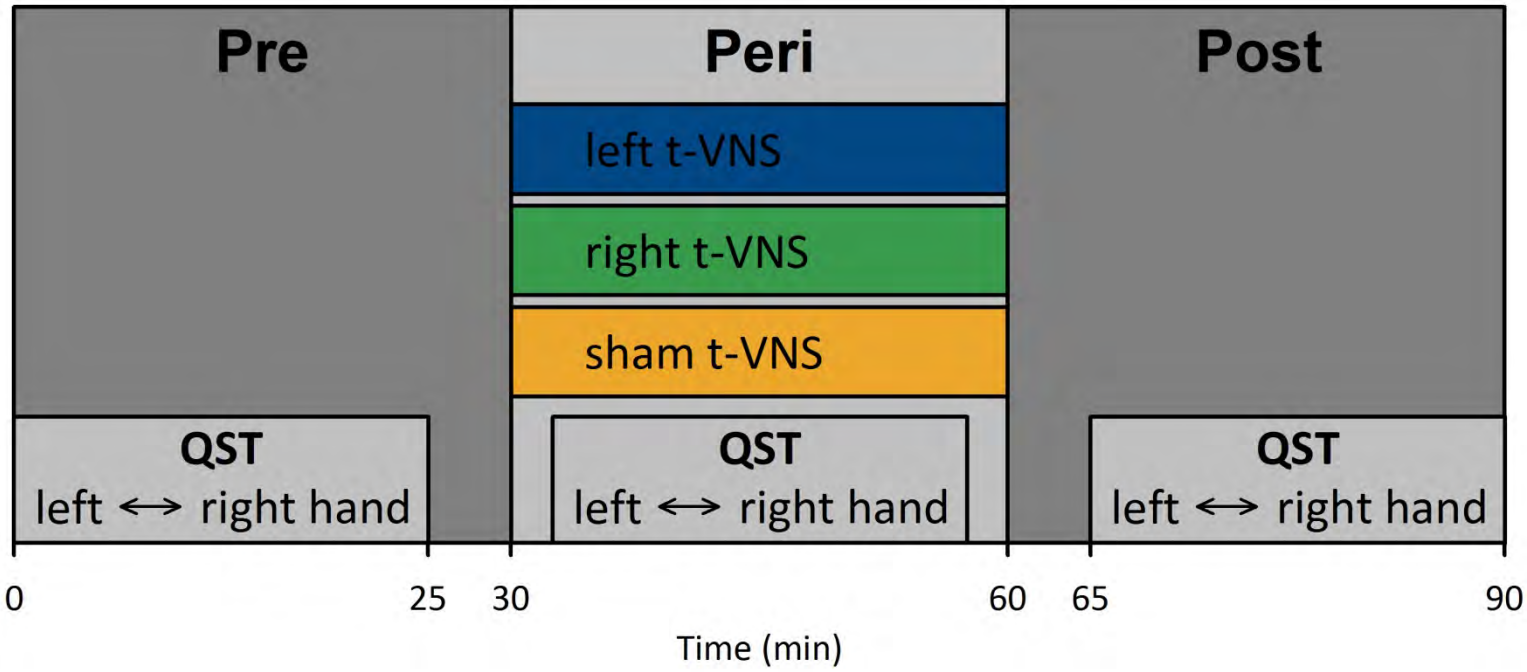
- PPT: Decrease of deep tissue pain.
- MPT, MPS: Decrease of nociception for mechanical pain stimuli.
- Selective effect on noxious parameters without any alteration of non-painful processing.
- Analgesic effects of t-VNS as shown by QST parameters PPT, MPT, and MPS. Evidence for lateralization on ipsilateral side.
- Reduced temporal summation of noxious tonic heat on both sides.

Busch et al., Brain Stimul 2012, Epub ahead of print

Impact of t-VNS on pain: 2nd trial

Study design

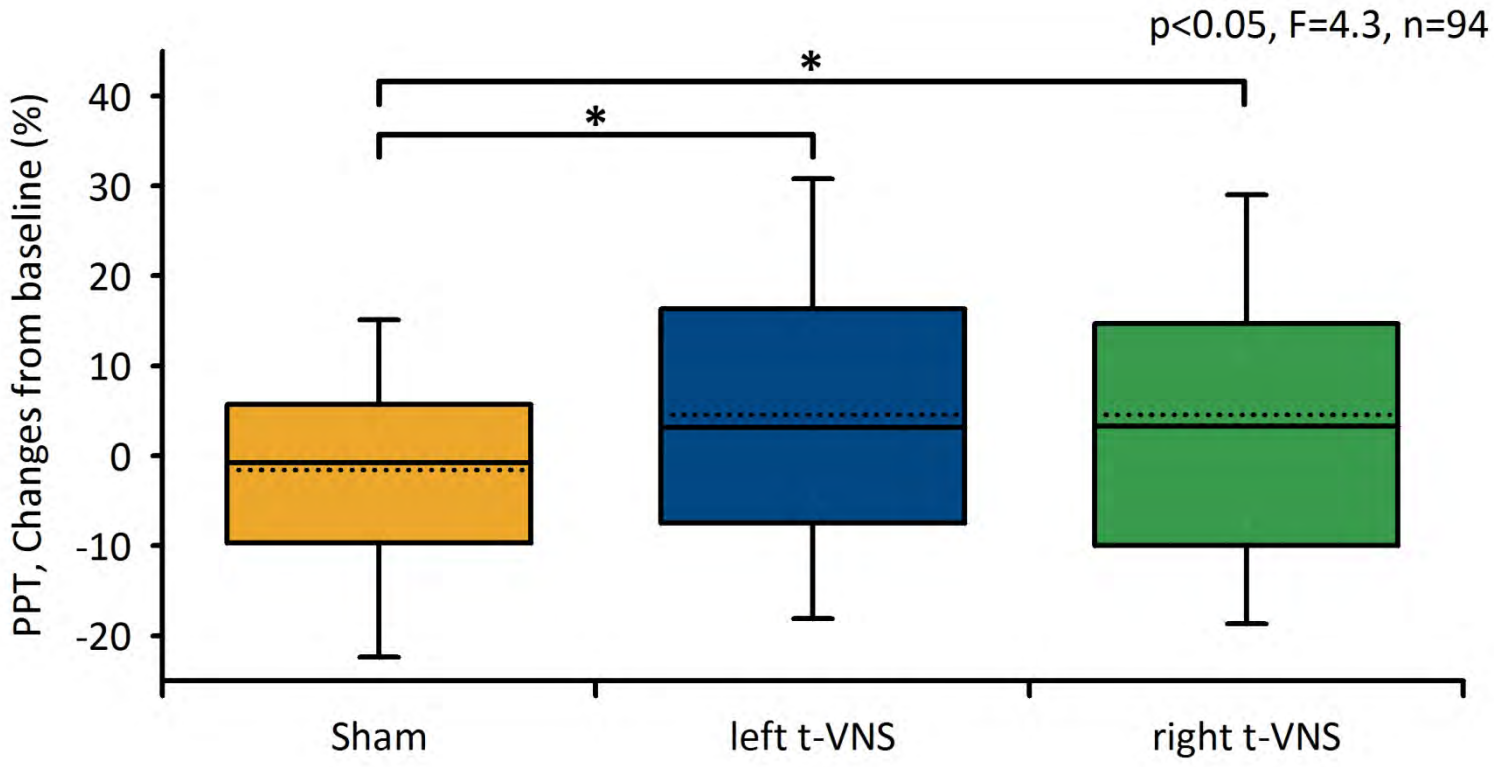
- 3 randomized sessions with active or sham t-VNS on different days
- Volunteers: n=49 (25 ♀, 24 ♂), 23.4±4.2 years
- QST parameter: PPT, MPT, MPS



Impact of t-VNS on pain: 2nd trial

Results

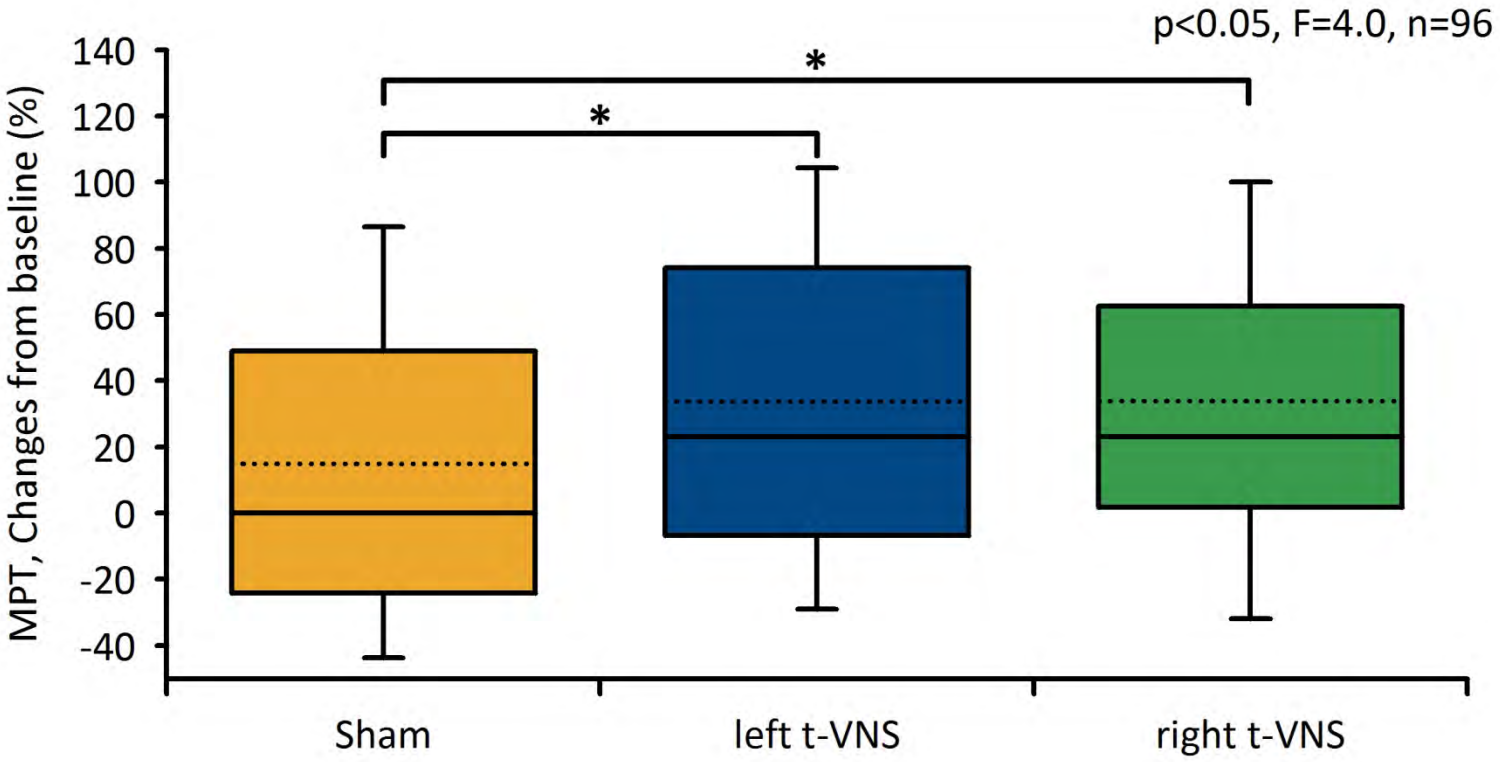
- Pressure Pain Threshold (PPT)



Impact of t-VNS on pain: 2nd trial

Results

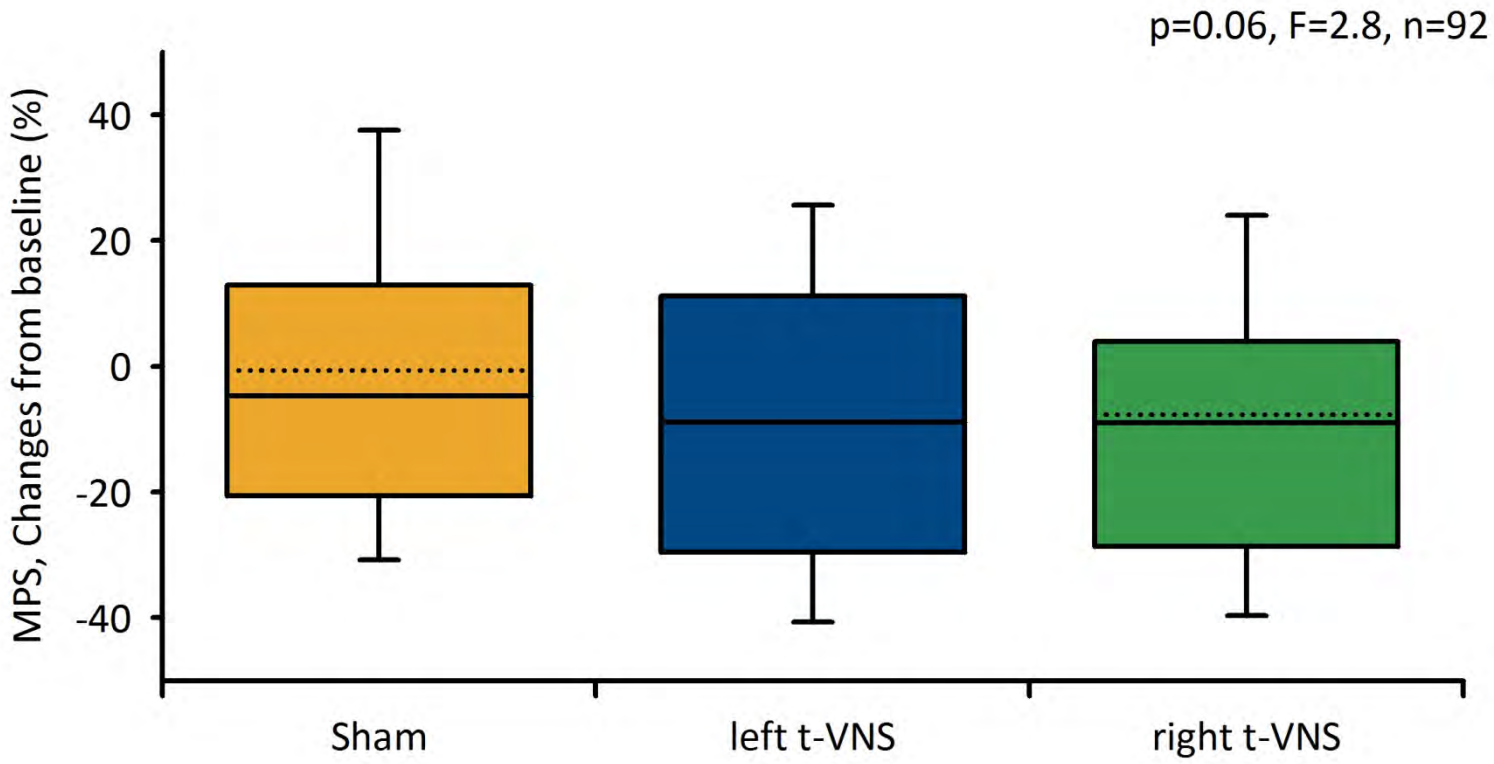
- Mechanical Pain Threshold (MPT)



Impact of t-VNS on pain: 2nd trial

Results

- Mechanical Pain Sensitivity (MPS)



Impact of t-VNS on pain: 2nd trial

Summary and Conclusions

- PPT: Decrease of deep tissue pain processing on both sides.
- MPT: Decrease of nociception for mechanical pain stimuli on both sides.
- MPS: Tendency to reduction.
- No indication of lateralized analgesic effect of t-VNS.

Impact of t-VNS on pain: Clinical trials

- **Evoked pain analgesia in chronic pelvic pain patients using respiratory-gated auricular vagal afferent nerve stimulation**
  Napadow et al., Pain Medicine 13: 777–89, 2012
  - 15 patients with chronic pelvic pain due to endometriosis
  - Invasive auricular stimulation at left cymba conchae or ear lobe

- **Transcutaneous vagus nerve stimulation for the treatment of chronic migraine**
  German Clinical Trials Register: DRKS00003681
  - Randomized controlled trial in 98 patients with chronic migraine
  - Transcutaneous VNS of the left cymba conchae

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Transcutaneous Vagus Nerve Stimulation

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