

# Transcutaneous vagus nerve stimulation has no impact on the pupillary light reflex in healthy volunteers



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## 1 Introduction

Transcutaneous vagus nerve stimulation (t-VNS) is a new treatment option in drug-resistant epilepsy, depression and pain. t-VNS bases upon the topographic anatomy of the auricular branch of the vagus nerve in the concha of the human ear in order to gain non-invasive access to the vagal system [1]. Stimulation of the vagus nerve is known to activate the nucleus of the solitary tract [2] and, subsequently, the locus coeruleus which is involved in the modulation of the pupil diameter [3]. Vagus nerve stimulation in rodents evoked pupil dilation [4]. The present study addresses the possible impact of t-VNS on the pupillary light reflex (PLR) in man. It was hypothesized that t-VNS does not elicit persistent changes of the pupilomotor function.

(1) Ellrich, European Neurological Review 6: 2-4, 2011  
 (2) Henry, Neurology 59: 3-14, 2002  
 (3) Samuels and Szabadi, Current Neuropharmacology 6: 254-85, 2008  
 (4) Blanca and Komisaruk, Brain Research 1177: 29-36, 2007

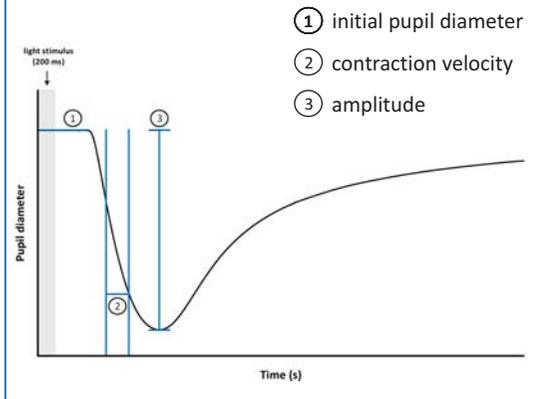
## 2 Methods

- Randomized, single-blinded, crossover study
- 33 healthy volunteers: 16♀, 17♂, 24.8 ± 5.3 years
- **Transcutaneous vagus nerve stimulation, t-VNS**
  - applied to skin afferents of the auricular branch of the vagus nerve in left ear's cymba conchae.
  - electrical, rectangular pulses (250 µs duration).
  - intensity above detection threshold and below pain threshold evoking tingling sensations.
- 3 randomized sessions with varying conditioning stimulations on different days:
  - active t-VNS (25 Hz)
  - active control (1 Hz)
  - sham (no t-VNS)



### Assessment of the left pupillary light reflex, PLR

- Compact Integrated Pupillograph (CIP, AMTech, Germany)
- elicit PLR by a 200 ms light stimulus followed by a 4 s PLR recording.
- main outcome parameters:
  - ① initial pupil diameter
  - ② contraction velocity
  - ③ amplitude

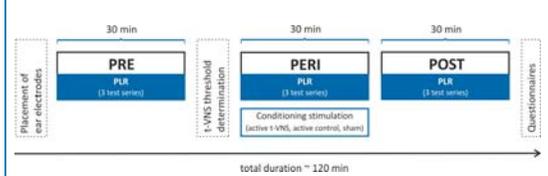


### Questionnaires

1. Sensation and comfort scale: Evaluation of perception by a set of adjectives describing possible sensations related to conditioning stimulation on a scale from 1 (no fit) to 4 (perfect fit). Provides information about the quality of t-VNS and, additionally, of the blinding.
2. Screening for autonomic symptoms: Reporting whether specific autonomic symptoms decreased (-1), remained unchanged (0) or increased (+1) during conditioning stimulation.

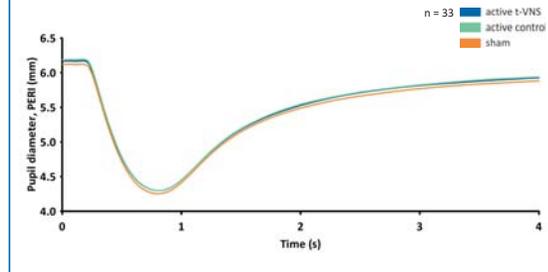
### Experimental session design

- 5 PLR measurements in one test series
- 3 test series each during PRE, PERI and POST

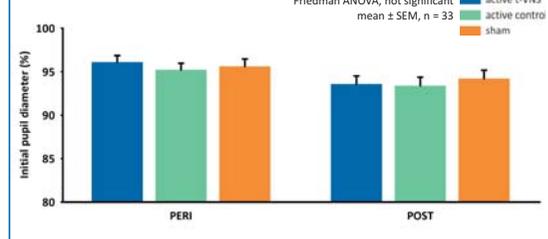


## 3 Results

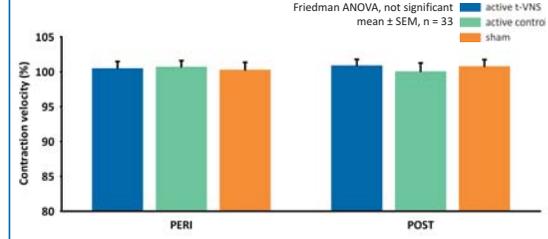
### PLR did not change during conditioning stimulation



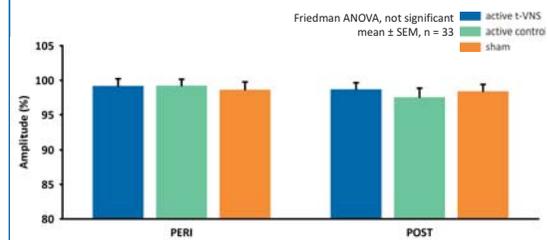
### No difference in initial pupil diameter



### No difference in contraction velocity



### No difference in amplitude



## Safety of t-VNS

- No serious adverse events occurred.
- Most frequent adverse events (AEs) related to t-VNS were palpitation, dysesthesia and dizziness.
- All AEs ended immediately or shortly after termination of conditioning stimulation.

## t-VNS sensation

- Volunteers felt active t-VNS as primarily tingling.
- Tingling, itching and pricking showed to be significant in describing the sensation during active stimulation as compared to sham.
- Volunteers stated to feel active t-VNS significantly more itching than during active control or sham.

sensation	active t-VNS	active control	sham
tingling***	2.9 ± 1.0	2.5 ± 1.1	1.9 ± 0.9
itching***	2.6 ± 1.1	1.4 ± 0.7	1.3 ± 0.5
pricking**	2.1 ± 1.2	2.0 ± 1.1	1.5 ± 0.8

Friedman ANOVA, \*\* p<0.01, \*\*\* p<0.001, n = 33

- 26 of the 33 volunteers (79%) indicated to receive electrical stimulation during sham session confirming the blinding to be effective.

## 4 Summary & Conclusions

- Invasive VNS in rodents evokes pupil dilation.
- t-VNS has no impact on the PLR in man.
- t-VNS does not affect the pupil accommodation ability.
- Side effects concerning the pupilomotor function during t-VNS are considered as unlikely.
- t-VNS is a safe treatment alternative in drug-resistant epilepsy, depression and pain.

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