BOLD fMRI clusters during transcutaneous vagus nerve stimulation (t-VNS) vary with frequency and pulse width

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Introduction

Non-invasive transcutaneous vagus nerve stimulation (t-VNS®) has been established as a reliable method to stimulate vagus nerve associated brain areas. Using BOLD fMRI, it could be demonstrated that t-VNS® was able to specifically activate higher order relay nuclei of vagal afferent pathways. Within this study BOLD cluster activations end effects on psychophysical parameters (rating, heart rate and heart rate variability) are analyzed. Sets of four different pulse frequencies combined with three different pulse widths are tested to assess parameter specific t-VNS® brain effects.

Questions which were addressed:

- Does perception of stimuli differ as a function of frequency / pulse width?
- Do frequency / pulse changes interact with psychophysical parameter?
- Do fMRI activated areas change with stimulus frequency / pulse width?

Material and Methods

Subjects and Stimulation

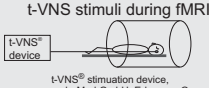
- 14 subjects - 7 males, 7 female (27.8 ± 2.3 years, mean ± SD)
- Transcutaneous electrical non-painful stimulation of Nervus vagus at the inner side of the tragus
- Individual threshold determination for each subject

Experimental protocol

experimental setup:

A) Psychophysical session
threshold detection
t-VNS stimuli with recording of rating, heart rate, -variabilty

B) fMRI session (12 subjects: 5m/7f)
t-VNS stimuli during fMRI



t-VNS® stimuation device, cerboMed GmbH, Erlangen, Germany

Psychophysical and fMRI - protocol setup:

Transcutaneous application of 12 different electric stimuli S1-S12 (table 1) in a random block design (table 2). Each stimulus is repeated 3 times and presented for 30 sec, interleaved with a 30 sec baseline condition

pulse width [µs] \ frequency [Hz]	10	25	50	100
130	S1	S2	S3	S4
250	S5	S6	S7	S8
500	S9	S10	S11	S12

Table 1: stimulation matrix.

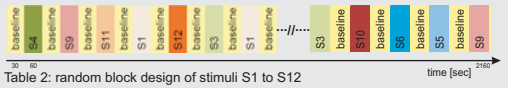


Table 2: random block design of stimuli S1 to S12

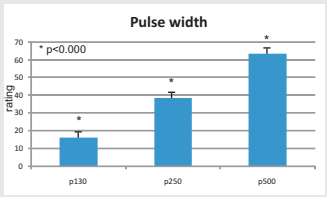
Data evaluation

- Standard pre-processing of the EPI data with „BrainVoyager QX® (Version1.10, Brain Innovations, Netherlands, brainvoyager.com)
- Coregistration of fMRI-data to individual 3D-MPRAGE data and further transformation to Talairach space
- GLM multi study with z-transformation and high statistical significance of activated clusters by $p_{cortex} < 0.005$ and $p_{brainstem} < 0.05$
- Anatomical assignment of activated areas by averaged brain analysis with "Talairach Daemon" and with standard anatomical atlas
- Psychophysical data sampling with PowerLab ADInstruments and Chart HRV Module and Chart ECG Analysis
- Statistical evaluation of psychophysical data with STATISTICA
- GLM-Model of ANOVA repeated measure with 3 factors
- Post hoc test LSD (least signif. diff.) on significant ANOVA results

Psychophysical results

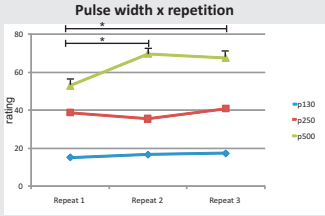
Rating - Visual Analog Scale (VAS):

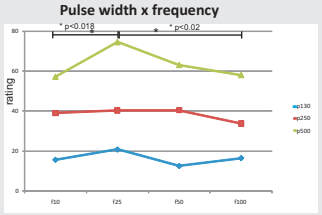
All subjects rated the perception of the stimulus on a VAS:
0 = VAS ... no perception of stimulus
0 < VAS < max ... perception of stimulus present but not unpleasant
max = VAS ... perception of stimulus unpleasant



Rating scores from VAS differ significantly with the three different pulse widths analyzed with a ANOVA repeated measure design. A pulse width of 500µs showed highest rating of the subjects.

A post hoc test on the significant repeated factor leads to a significantly increased perception of the stimulus with a pulse width of 500µs with the second and third repetition.

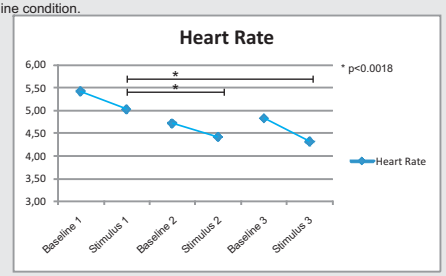




A post hoc test on the increased frequency at 25Hz leads to a significantly increased perception of the stimulus with a pulse width of 500µs compared to 10Hz or 100Hz.

Rating - Visual Analog Scale (VAS):

The analysis of the heart rate showed a significant effect with repetition as *factor*. Baseline versus stimulus has no significant effect, none the less there is a tendency of a decrease of the heart rate during stimulation condition compared to baseline condition.

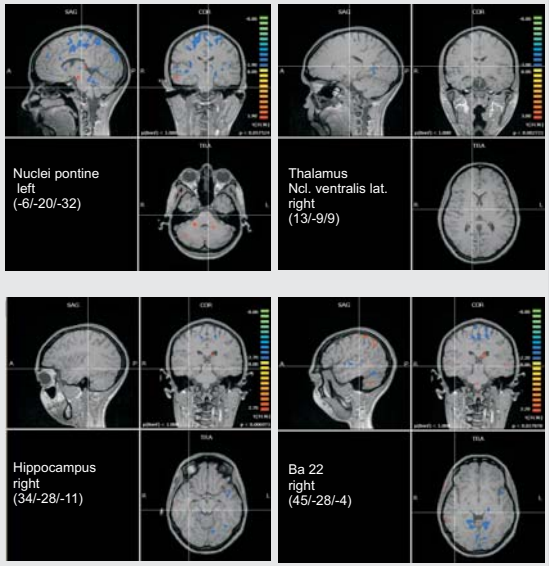


Heart Rate Variability - HRV, RMSSD, pNN50

The still ongoing analysis of HRV parameters (HF, RMSSD and pNN50) showes so far no significant differences between stimulus and baseline condition..

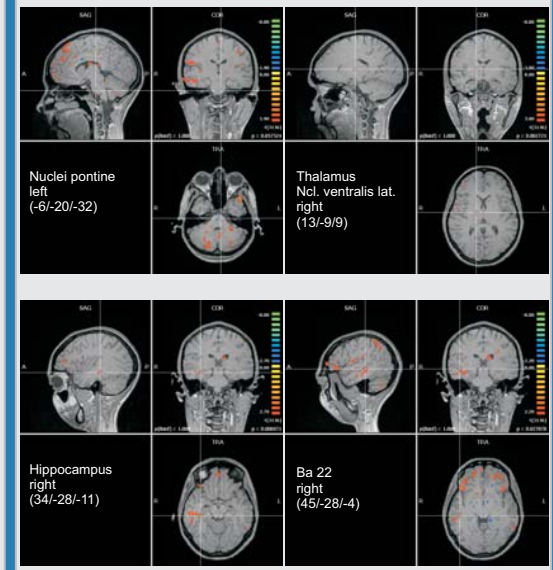
fMRI results

Stimulus S2 - frequency 25 Hz, pulse width 130µs

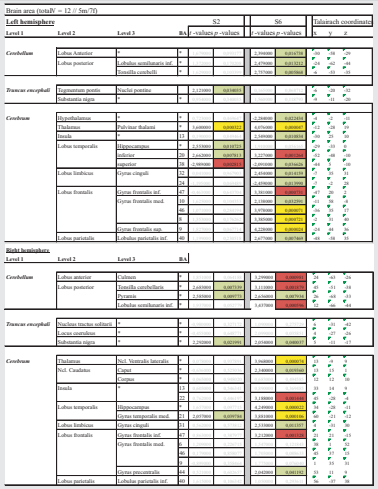


fMRI results

Stimulus S6 - frequency 25 Hz, pulse width 250µs



fMRI results



Conclusions & Answers

- **The sophisticated matrix study design is feasible to be used in psychophysical and fMRI projects.**
- **Does perception of stimuli differ as a function of frequency / pulse width? => Individual setting specific intensity perception does not correlate with autonomic responses.**
- **Do frequency / pulse changes interact with psychophysical parameter? => t-VNS slightly decreases heart rate during stimulation as vagal response, although no adverse effects were detected during stimulation session neither during fMRI nor psychophysical testing. All tested parameters in the matrix are considered to be safe in clinical and non-clinical settings.**
- **Do fRMI activated areas change with stimulus frequency / pulse width? => To date, parameter specific dependency was detected in psychophysical experiments and the fMRI results comparing stimulus S2 to stimulus S6. Further evaluation of stimuli settings is work in process.**

Literature

Dietrich S, Smith J, Scherzinger C, Hoffmann-Preiß K, Freitag T, Eisenkolb A, Ringler R. A novel transcutaneous vagus nerve stimulation leads to brainstem activations measured by functional MRI. Biomed Tech 2008;53(3):104-111.

Acknowledgement | Supported by cerboMed GmbH, Germany, Grant Ft002

Society for Neuroscience, 39th Annual Meeting, 2009, Chicago

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