Source localization of the P300 event-related potential as a biomarker for the efficacy of vagus nerve stimulation in patients with epilepsy

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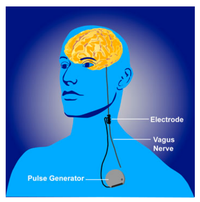
Introduction



± 50 million epileptic patients worldwide

± 33% not responsive to medication

Vagus Nervus Stimulation (VNS) is efficient alternative treatment for some patients [1]:

	# patients	seizure reduction
Responders (R)	1/3	> 50%
Non-responders (NR)	1/3	30 – 50%
Non-responders (NR)	1/3	< 30%

Problem:

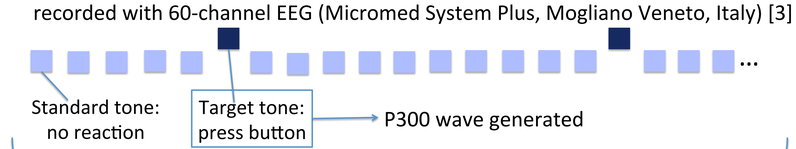
- Working mechanism unknown
- Unable to predict whether patient will benefit from VNS treatment or not before expensive and risky implantation

Goal: Investigate whether EEG source reconstruction can provide information on the working mechanism of VNS and whether a biomarker for the efficacy of VNS can be found

Data

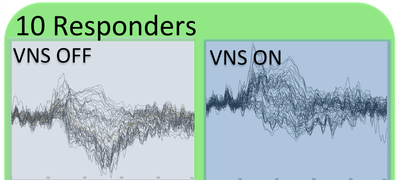
P300 component modulated by norepinephrine level in the brain, which is linked to the anti-epileptic effect of VNS [2].

20 VNS patients performed auditory oddball task
recorded with 60-channel EEG (Micromed System Plus, Mogliano Veneto, Italy) [3]



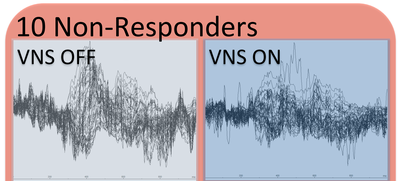
$Standard_{average}$-$Target_{average}$

10 Responders



6 with good quality MR image
4 with bad quality or no MR image

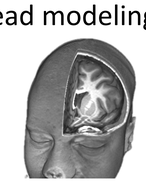
10 Non-Responders



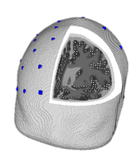
8 with good quality MR image
2 with bad quality or no MR image

Methods

Head modeling

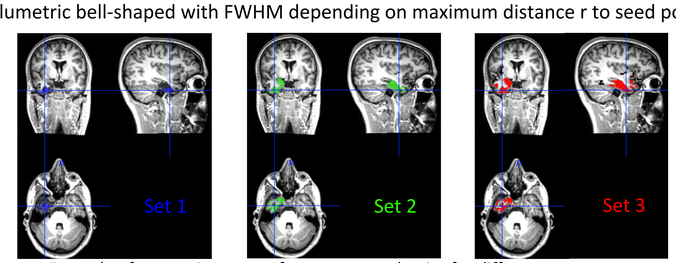


Good quality MR:
Individual 5-layered head model [4]
(scalp, skull, CSF, gray matter, white matter)
Bad or no MR:
Template 4-layered head model



Inversion: multiple sparse volumetric priors algorithm based on region growing in gray matter [5].
Source priors are volumetric bell-shaped with FWHM depending on maximum distance r to seed point and smoothing σ.

Set	r	σ
1	6 mm	0.6
2	7 mm	0.7
3	7 mm	0.8



Example of one region grown from same seed point for different parameters

Results

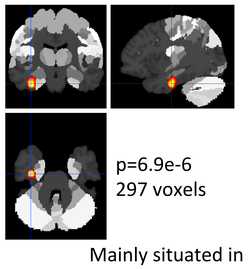
Statistical analysis: 2nd level analysis in SPM (flexible factorial design, t-tests, p-values FWE corrected, on cluster level)
Priors set 1: no significant clusters > 15 voxels

Main effect of group

What is the difference in brain activity between R and NR, independent of VNS OFF or ON?

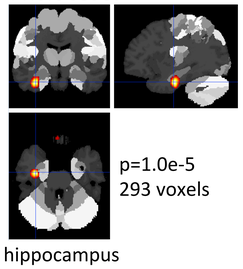
R > NR

Priors set 2:



p=6.9e-6
297 voxels

Priors set 3:

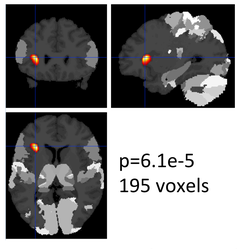


p=1.0e-5
293 voxels

Mainly situated in the left hippocampus

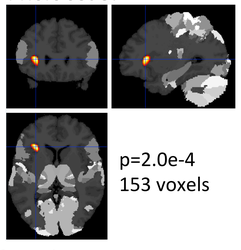
NR > R

Priors set 2:



p=6.1e-5
195 voxels

Priors set 3:



p=2.0e-4
153 voxels

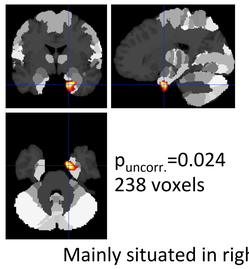
Mainly situated in the left insula

Main effect of VNS

What is the difference in brain activity when VNS is applied or not, independent of the patient being R of NR?

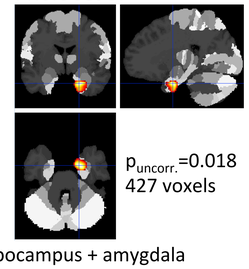
ON > OFF

Priors set 2:



$p_{uncorr.}$=0.024
238 voxels

Priors set 3:

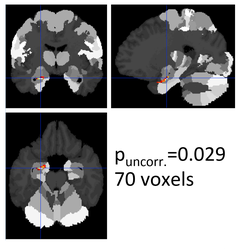


$p_{uncorr.}$=0.018
427 voxels

Mainly situated in right hippocampus + amygdala

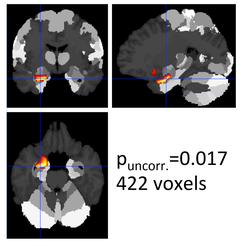
OFF > ON

Priors set 2:



$p_{uncorr.}$=0.029
70 voxels

Priors set 3:



$p_{uncorr.}$=0.017
422 voxels

Mainly situated in left amygdala and hippocampus [6]

Interaction group x VNS

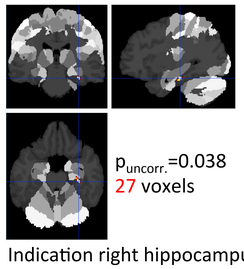
What is the difference between R and NR when looking at the difference in both groups for VNS OFF and ON?

R_{ON}-R_{OFF} > NR_{ON}-NR_{OFF}

Priors set 2:

No significant clusters

Priors set 3:

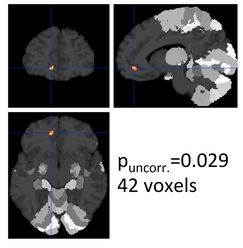


$p_{uncorr.}$=0.038
27 voxels

Indication right hippocampus

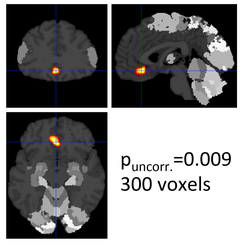
NR_{ON}-NR_{OFF} > R_{ON}-R_{OFF}

Priors set 2:



$p_{uncorr.}$=0.029
42 voxels

Priors set 3:



$p_{uncorr.}$=0.009
300 voxels

Left middle orbital gyrus

Conclusion

Priors should be chosen large enough to find significant overlapping brain activity due to intersubject variability.

Significant differences in brain activity for responders vs. non responders were found, indicating a possible biomarker for the efficacy of VNS.

Significant differences in brain activity were also found for VNS off vs on, providing information on the working mechanism of VNS.

The group x VNS test can serve as a biomarker for VNS and provides insights on the working mechanism of VNS, but the significance of the tests should be increased (more subjects, even larger priors, …).

Although more research is needed, we showed the potential of EEG source reconstruction in the research on VNS.

References

[1] P. Boon, et al. "Vagus nerve stimulation for refractory epilepsy." Seizure 10.6 (2001): 448-455.
[2] R. Raedt, et al. "Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model." Journal of neurochemistry 117.3 (2011): 461-469.
[3] L. De Taeye, et al. "The P3 Event-Related Potential is a Biomarker for the Efficacy of Vagus Nerve Stimulation in Patients with Epilepsy." Neurotherapeutics (2014): 1-11.
[4] G. Strobbe, et al. "Bayesian model selection of template forward models for EEG source reconstruction." NeuroImage 93 (2014): 11-22.
[5] G. Strobbe, et al. "Multiple sparse volumetric priors for distributed EEG source reconstruction." NeuroImage (2014).
[6] T.R. Henry, et al. "Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: I. Acute effects at high and low levels of stimulation." Epilepsia 39.9 (1998): 983-990.