Functional connectivity profile in VNS responders: a retrospective fMRI study

V. Joris[1,2], E. Van Boxstael[3], A. Berger[2], L. Dricot[2], R. El Tahry[2,3]
[1]Dept of Neurosurgery, Cliniques universitaires Saint-Luc, Brussels, Belgium
[2]Institute of NeuroScience (IoNS), Université Catholique de Louvain, Brussels, Belgium
[3]Dept of Neurology, Cliniques universitaires Saint-Luc, Brussels, Belgium

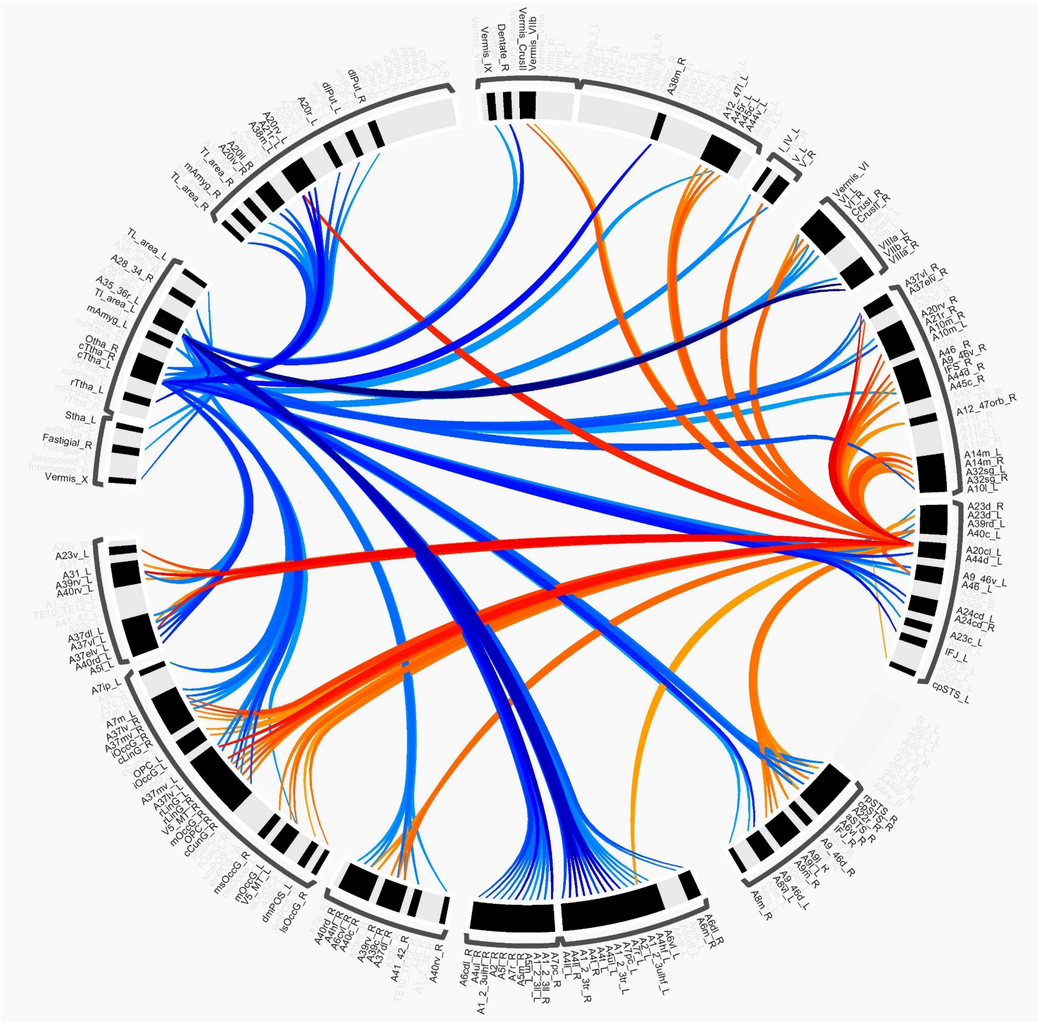

Fig. 1. Functional connectivity analysis (280 ROI)

Introduction

Vagus nerve stimulation (VNS) can be used as adjunctive therapy in patients with drug resistant epilepsy, allowing a reduction in seizure frequency of >50% in approximately 50% of patients, and up to 9% seizure freedom (1). Response to VNS is highly variable between patients and biomarkers allowing for the pre-implantation identification of responders versus non-responders are still lacking. Network-based connectivity is a promising, individual and non-invasive marker to answer these questions (2).

The aim of the present study was to identify markers of VNS response and unravel its mechanism of action through functional connectivity (FC) analysis.

Methods

Patients implanted with a VNS device were included retrospectively. Resting-state functional magnetic resonance imaging (rs-fMRI) was performed. We used BrainVoyager and a customized Matlab code to calculate cross-correlations between the average time-course signals of the rs-data, extracted from 280 regions (3,4) (Fig. 1.). We performed connectome-based predictive modeling (CPM) to find a model to predict the relationship between brain and success of VNS using cross-validation (5).

19 patients	
M/F ratio	8/11
Age	37 yo (19-62)
Epilepsy duration	13 y (2-36)
Implantation time	6 y (0.5-19)
Epilepsy onset	
Generalized	2
Multifocal	13
Focal	4
VNS response	
Responder	6
Partial responder	4
Non responder	9

Results

CPM revealed that the correlation between the predicted and actual success of implant was 0.28 (corrected for age and sex). The prediction significance of this correlation, based on 2.000 permutations, resulted in a p value of 0.07.

Although not significant, trends toward reduced FC was found in patients demonstrating higher therapeutic efficacy compared to non-responders. Nodes with the highest degree, corresponding to the regions with most different FC between responders and non responders where the left nucleus accumbens, the left amygdala, the left dorso-lateral and left ventro-lateral thalamus, all showing decreased connectivity, mainly with the right hemisphere (Fig. 2.). The first positive node (increased connectivity) was in the left temporo-basal region.

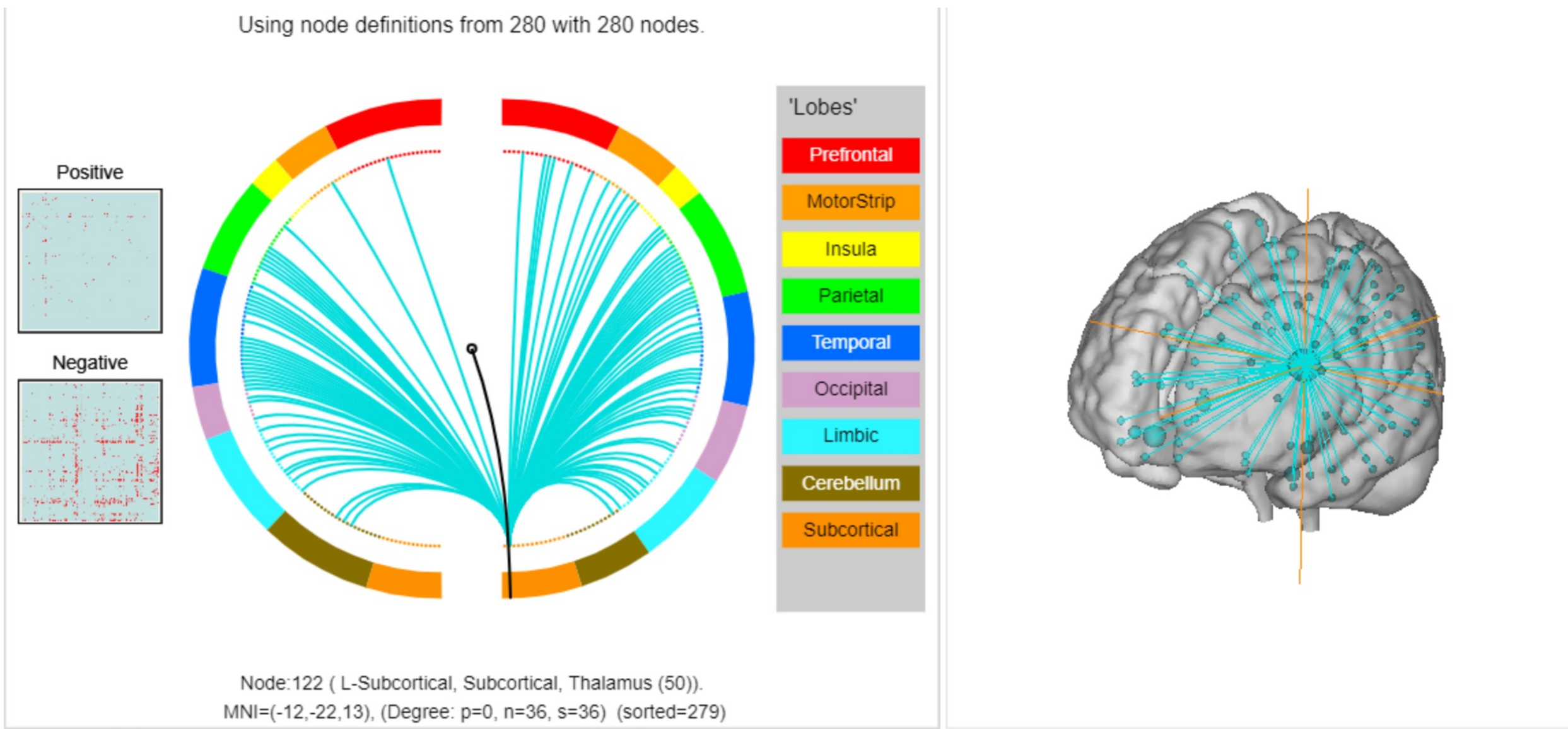

Fig. 2. Highest degree node: left dorso-lateral thalamus

Conclusion

This retrospective rs-fMRI study on 19 drug resistant VNS patients shows a trend toward lower connectivity between left nucleus accumbens, amygdala and thalamus – key structures of the vagal afferent network (6) - and the right hemisphere in patients with higher therapeutic effects compared to non-responders. These findings are in line with existing literature suggesting the involvement of thalamo-cortical circuitry in the therapeutic effect of VNS (7,8).

Further longitudinal studies, with higher number of patients are needed to confirm these findings and specify whether the observed connectivity profile reflects the neuromodulatory effect of VNS, or a prior connectivity profile predictive for future VNS response.

(1) Englot et al., 2016
(2) Workewych et al., 2020
(3) Fan et al., 2016
(4) Diedrichsen, 2015
(5) Shen et al., 2017
(6) Hachem, 2018
(7) Bartolomei et al., 2016
(8) Goebel et al., 2006