COST EMF - MED (Action BM1309):
European network for innovative uses of EMFs in biomedical applications

STSM Report:

Safety limits: Experimental data analysis and modeling of therapeutical non-invasive electrical stimulation of the vagus nerve

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Introduction

Possible neuroprotective effects of invasive stimulation of the vagus nerve had been previously reported in the scientific literature [1-3]. However, Prof Kaniusas has focused his research on the effects of the non-invasive auricular vagus nerve stimulation (VNS) on the blood perfusion and heart rate and we already set up a rat model for the stroke case [4-7]. This is the third year of a well established collaboration between Vienna and Madrid during which we have set-up an animal experimental model of non-invasive vagus nerve stimulation to prepare preclinical human studies and to establish the safety limits of such stimulation.

[01] Cunningham JT, Mifflin SW, Gould GG, Frazer A. Induction of c-fos and deltafosb immunoreactivity in rat brain by vagal nerve stimulation Neuropsychopharmacology 2008; 33:1884-95.

[02] Ay I, Napadow V, Ay H. Electrical stimulation of the vagus nerve dermatome in the external ear is protective in ratcerebral ischemia. Brain Stimul. 2015 Jan-Feb;8(1):7-12. doi: 10.1016/j.brs.2014.09.009.

[03] I. Ay, J. Lu, H. Ay, A. Gregory Sorensen. Vagus nerve stimulation reduces infarct size in rat focal cerebral ischemia. Neurosci Lett, 459 (2009), 147–151

[04] S. Kampusch, E. Kaniusas and J.C. Széles. New approaches in multi-punctual percutaneous stimulation of the auricular vagus nerve. Proc 6th Int IEEE EMBS Conf. Neur Eng, 263-66, 2013

[05] J.C. Széles, S. Kampusch, E. and Kaniusas. Peripheral blood perfusion controlled by auricular vagus nerve stimulation. Proc 17th Int Conf Biomedical Engineering, 73-77, 2013

[06] E.Kaniusas, S.Kampusch, J.C.Szeles: Depth profiles of the peripheral blood oxygenation in diabetics and healthy subjects in response to auricular electrical stimulation: Auricular vagus nerve stimulation as a potential treatment for chronic wounds. Proceedings of IEEE Sensors Applications Symposium, 1-6 (2015).

[07] S.Kampusch, F.Thürk, E.Kaniusas, J.C.Szeles: Autonomous nervous system modulation by percutaneous auricular vagus nerve stimulation: Multiparametric assessment and implications for clinical use in diabetic foot ulcerations. Proceedings of IEEE Sensors Applications Symposium, 1-6 (2015).

A. Purpose of the STSM

The scientific objectives of the present proposal were

1. Analyze the experimental data of the experiments performed in rats in terms of safety limits.
2. Develop a model of the dynamic system composed by the auricular branches/jugular ganglia of the vagi nerves, the nodose ganglia, the nuclei of the solitary tract and the heart, considering safety limits.
3. Compare animal data and model with human data obtained by the Vienna group in the last years and develop a more generic model of the dynamics of the vagus nerve system,
4. Design further experiments for the testing of the model in both animals and humans.

B. Work Description

In Vienna, during this STSM we worked on the safety limits of the electrical stimulation of the auricular branch of the vagus nerve to neuroprotect the stroke-damaged brain areas.

During 2016 we performed electrophysiology experiments in which we could determine significant physiological differences in the action of the left and right vagus nerve after stimulation of the auricle. Physiological differences were observed in both, heart rate and the variability of the heart rate. Furthermore we determined that such bilateral differences were also dependent on the stimulation parameters, like train duration, stimuli intensity and phase difference between onset of the stimulus and heart beating.

Here we studied relevant papers, we developed a methodology for data analysis and we applied the methodology to analyzed the data.

C. Results

Data analysis development of this methodology. Variables used for our study are the four first interbeat intervals (RRi)and the time intervals from the delivery of the stimulus and the heart beat (Fig.1).

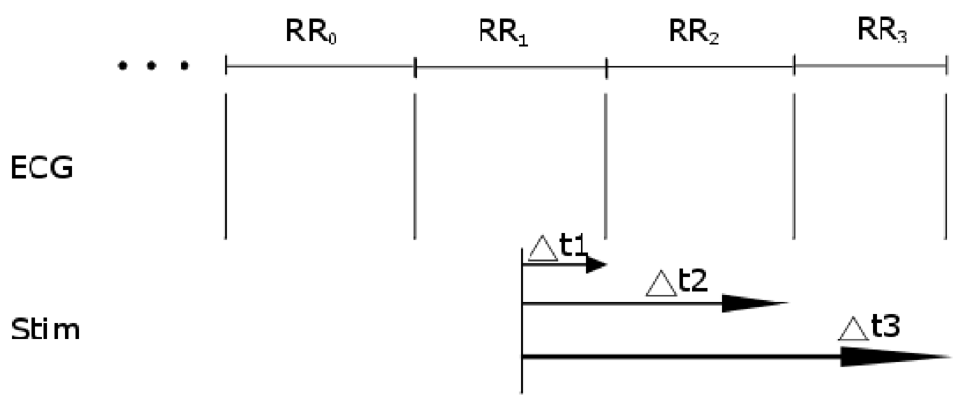


Figure 1. Variables used for our calculi. ex2

<u>ΔRR</u>

Relative error is calculated as:

$$\Delta RR_i = \frac{RR_i \quad RRB}{RRB}$$

with RRB = mean (RR_0, RR_{-1}, RR_{-2}, RR_{-3}, RR_{-4})

<u>Δt</u>

Two methods are defined for calculation of relative Δt:

<u>Method 1</u>

$$\Delta t_i = \frac{\Delta t_i}{RRB}$$

<u>Method 2</u>

$$\Delta t_i = \frac{\Delta t_i}{RR_1}$$

The <u>Δt and ΔRR Plots</u> are arranged in sequences, each sequence belongs to a stimuli stage. A plot from a typical recording is shown in Figure 2.

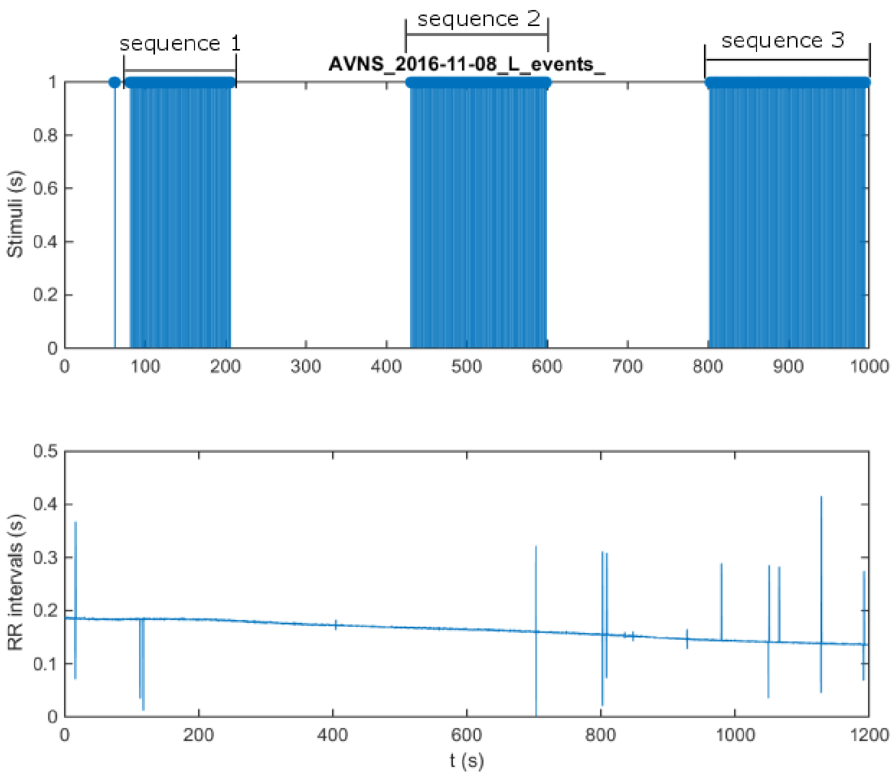
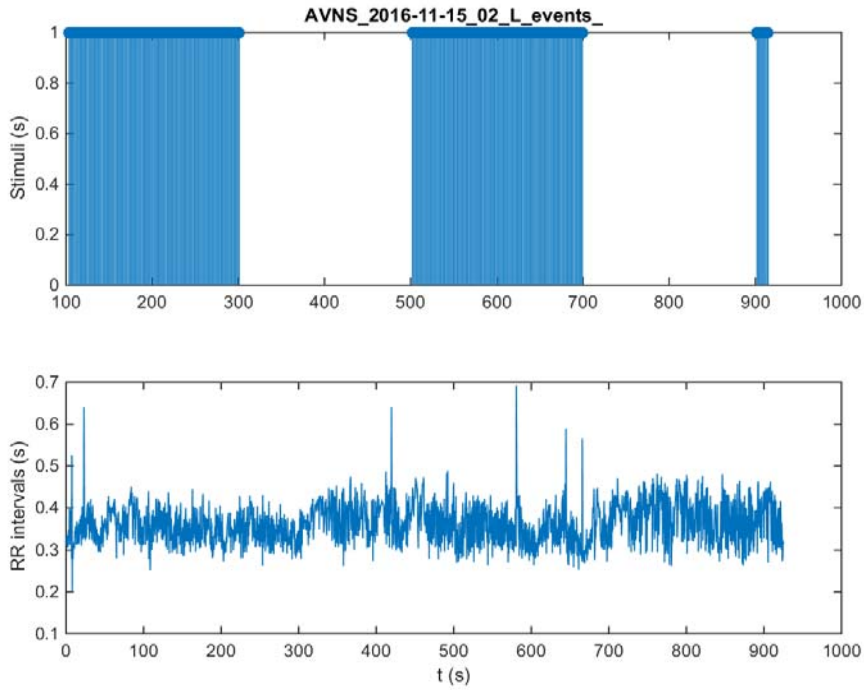


Figure 2. Stimuli plot (top) and ΔRR vs time Plots (bottom) of a typical heart beat recording

Below we graphically represent our EKG signal analysis done in one unilateral stimulation-recording experiment (AVNS 2016-11-15_02 Left)



Fiure 3. ECG and stimuli plot

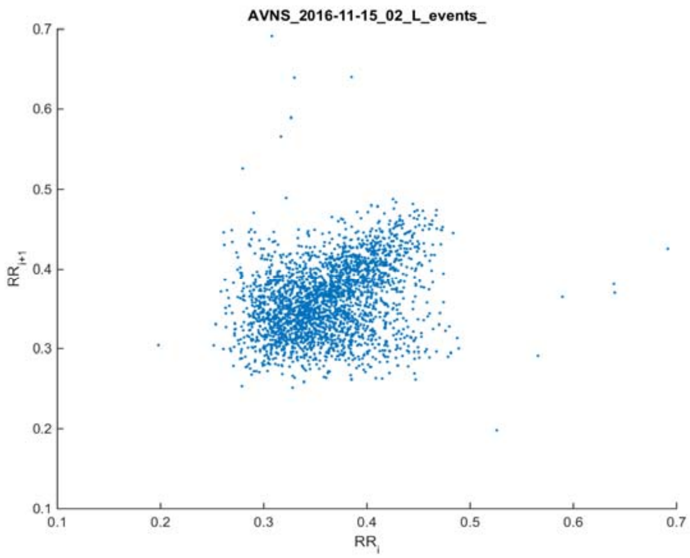


Figure 4. Poincaré Plot

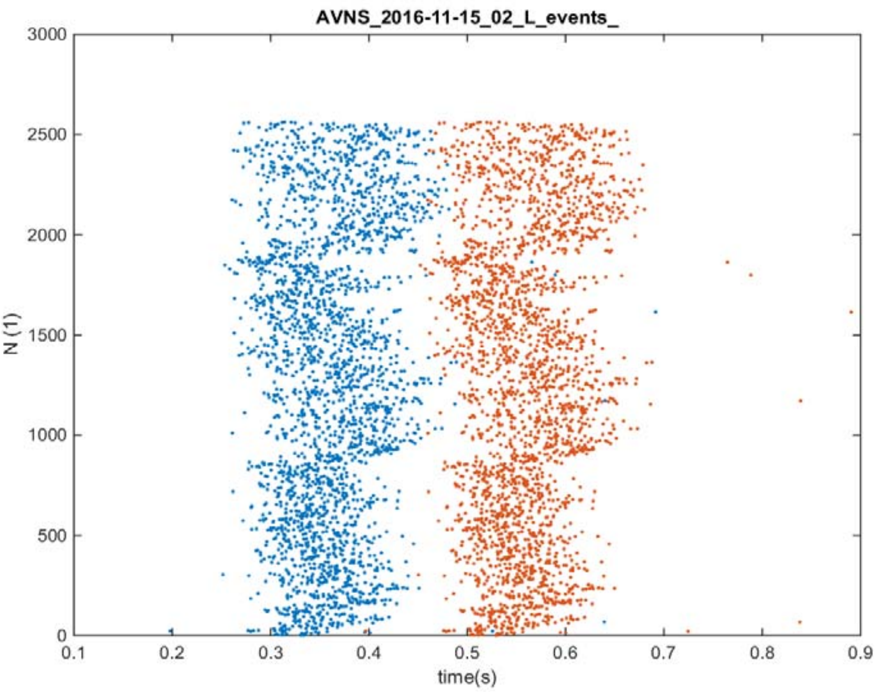


Figure 5. Scatter Plot

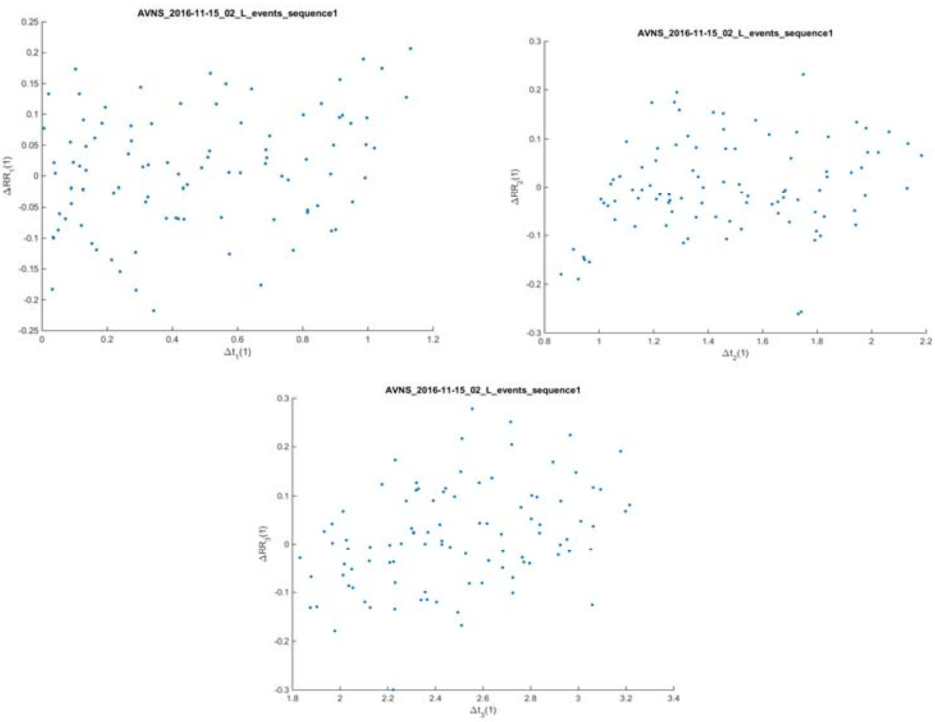


Figure 6. Δt and ΔRR Plots: Stimuli Sequence 1

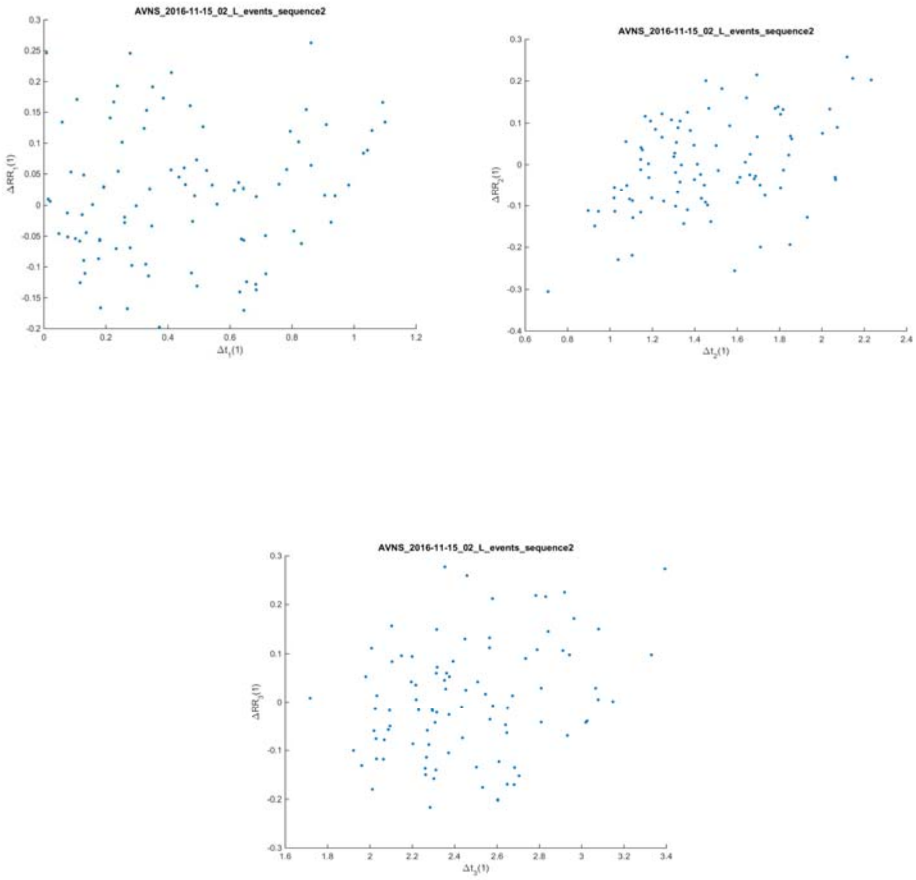


Figure 7. Δt and ΔRR Plots: Stimuli Sequence 2

The analysis of our data leaded us to design a new experimental protocol with modified stimulation parameters to highlight heart dynamics that are hidden in the actual recordings. We also decided to extend our work to the dynamics of the heart-respiration correlation.

D. Discussion

Auricular vagus nerve stimulation effectively acts on heart rhythm and autonomic homeostasis in mice. Our preliminary results indicate possible modulation of heart rate and heart rate's variability by auricular vagus nerve stimulation through the afferent projection of the auricular branch to the nucleus of the solitary tract.

Vagus nerve innervation of the viscera makes such nerve the ideal vehicle for minimally invasive neuromodulatory therapies for neurological, inflammatory and cardiovascular diseases as well as for pain relief. Percutaneous auricular vagus nerve stimulation could modulate heart rate as well as heart variability, both of them being estimators of autonomic homeostasis. It is known that heart rate changes due to efferent cervical vagus nerve stimulation can be modulated by considering the timing of stimulation in the cardiac cycle [1].

E. Future collaboration with host institution

Perform further experiments to complete the present work

Publish the results of the present study

Prepare a review paper on AVNS

Write a joint proposal for Horizon2020

Support the host institution in any future research, development or dissemination activities for which they could need help.

We have established a new collaboration between the host institution, Universidad Complutense de Madrid and Università della Campania (Prof. Papa) to study the anatomical substrate of AVNS effects.

F. Expected Publications

As mentioned in Section D. are expected two publications

The results of the present work

A review paper on AVNS

G. Other Comments

No other comments

[1] G. Brown and J. Eccles, "The action of a single vagal volley on the rhythm of the heart beat," J. Physiol., pp. 211–242, 1934.

Confirmation by the host institution of the successful execution of the STSM:

We confirm that Prof. Fivos Panetsos has performed the research work as described above.

Contact Person of Host Institution	Name of researcher
Prof. Eugenijus Kaniusas	Prof. Fivos Panetsos
Signature	Signature