# VNS-induced dose-dependent pupillary dilation response (PDR) in Refractory Epilepsy

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## Introduction and objectives

- Vagus Nerve Stimulation (VNS) as a treatment for Refractory Epilepsy is only effective in **1/3 of patients** (**> 50%** seizure frequency reduction)[1]
- A complete understanding of the **mechanisms of action** is **still lacking**, preventing:
  - Identification **of Non-responders** (NR)
  - **Titration** strategies
- Vagal afferent fibers project to the **Locus Coeruleus** (LC), the main source of norephinephrine in the brain, and VNS is associated with the modulation of LC activity[2]
- Variations in **pupil size** are indicators of LC activity[3]

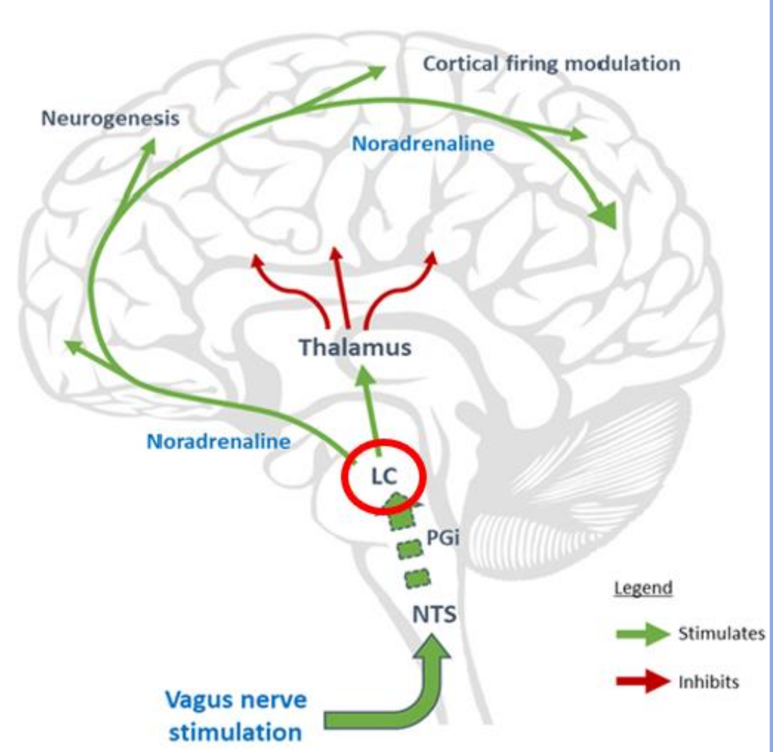


***Fig.1*** *VNS-induced activation of the norepinephrine system*

**This study aimed to :**

- **Assess the effects of VNS dosage on pupil dilation**
- **Compare VNS-induced pupil dilation responses (PDR) between responders (R) and non-responders (NR) to VNS therapy**
- **Analyze personalized titration strategies**

## Methods

- 13 VNS-implanted patients were recruited :
  - 9 R (5 F, 4 M)
  - 4 NR (2 F, 2 M)
- VNS intensities were varied from 0.25mA up to 2.25mA or until intolerability
- VNS onset was monitored using two electrodes placed in the laryngeal prominence region.
- Eyelink 1000 system was used to track pupil size changed.
- At the end of each stimulation block, the patient was asked to assess their subjective perception in a scale from 1 to 10.
- Mean PDR was analyzed in 1-second intervals after VNS onset
- Individual fitting curves were used to examine titration strategies.
- Mixed-effect models were used to study interactions and trends

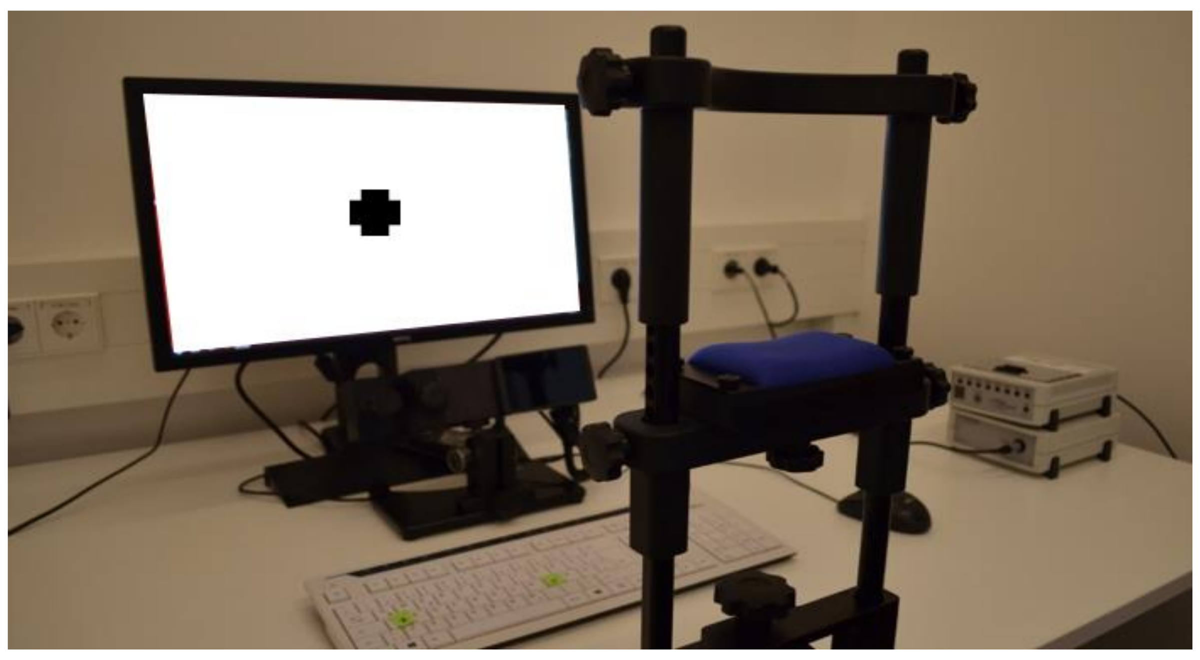

***Fig.2*** *Eyelink 1000 set-up*

## Conclusion

- ➢ Higher phasic LC activation at increasing VNS intensities in R compared to NR.
- ➢ Results independent of **perception**.
- ➢ Potential **inverted-U** pattern, specially in the 2s-3s interval, which would indicate the VNS intensity at which there is a peak of LC activation → potential titration strategy

## Results

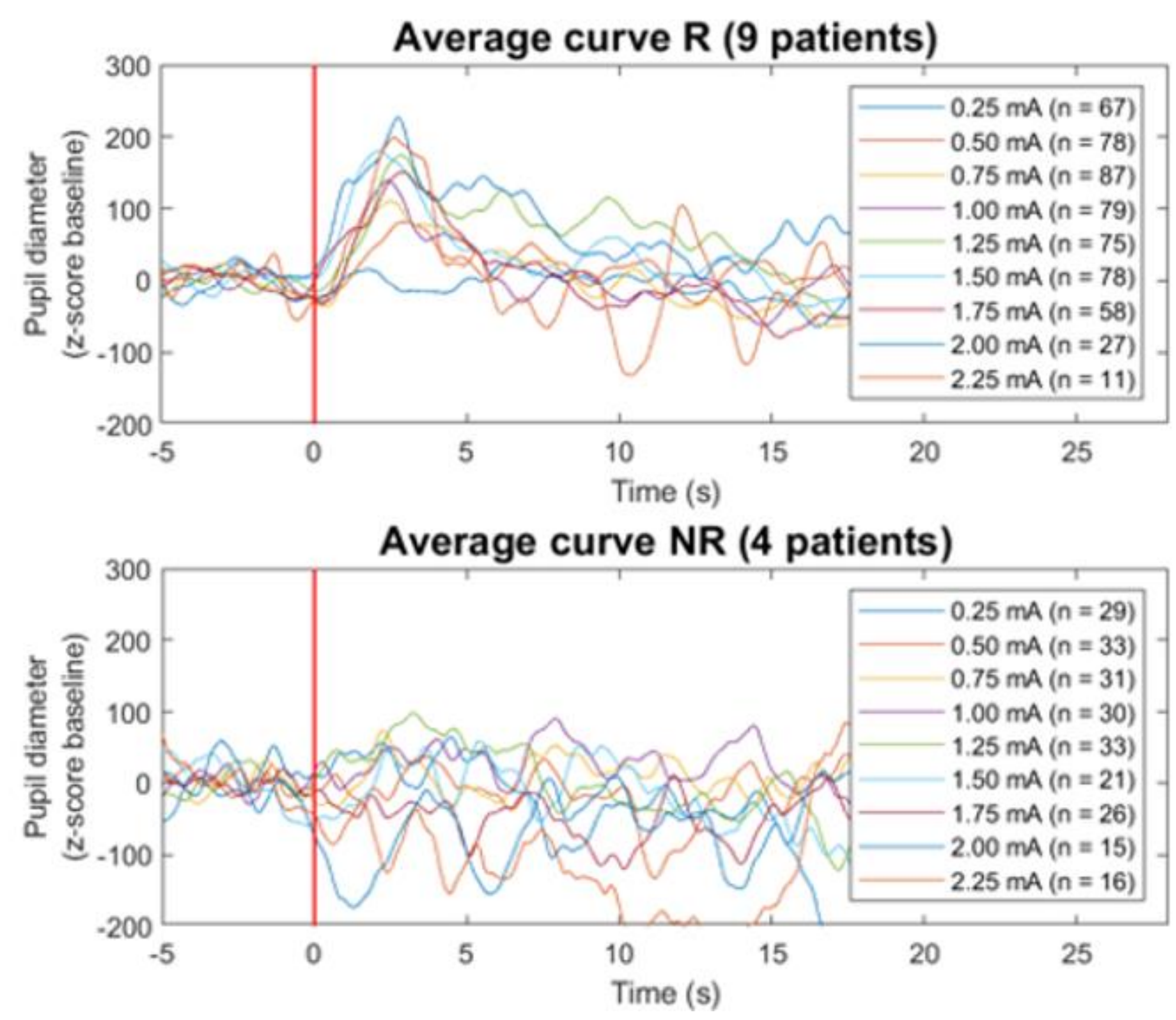


***Fig.3*** *Averaged PDR of the left pupil across VNS itnensities in Responders (9 patients) and non-responders (4 patients). In legends, « n » refers to the number of epochs averaged at each VNS intensity.*

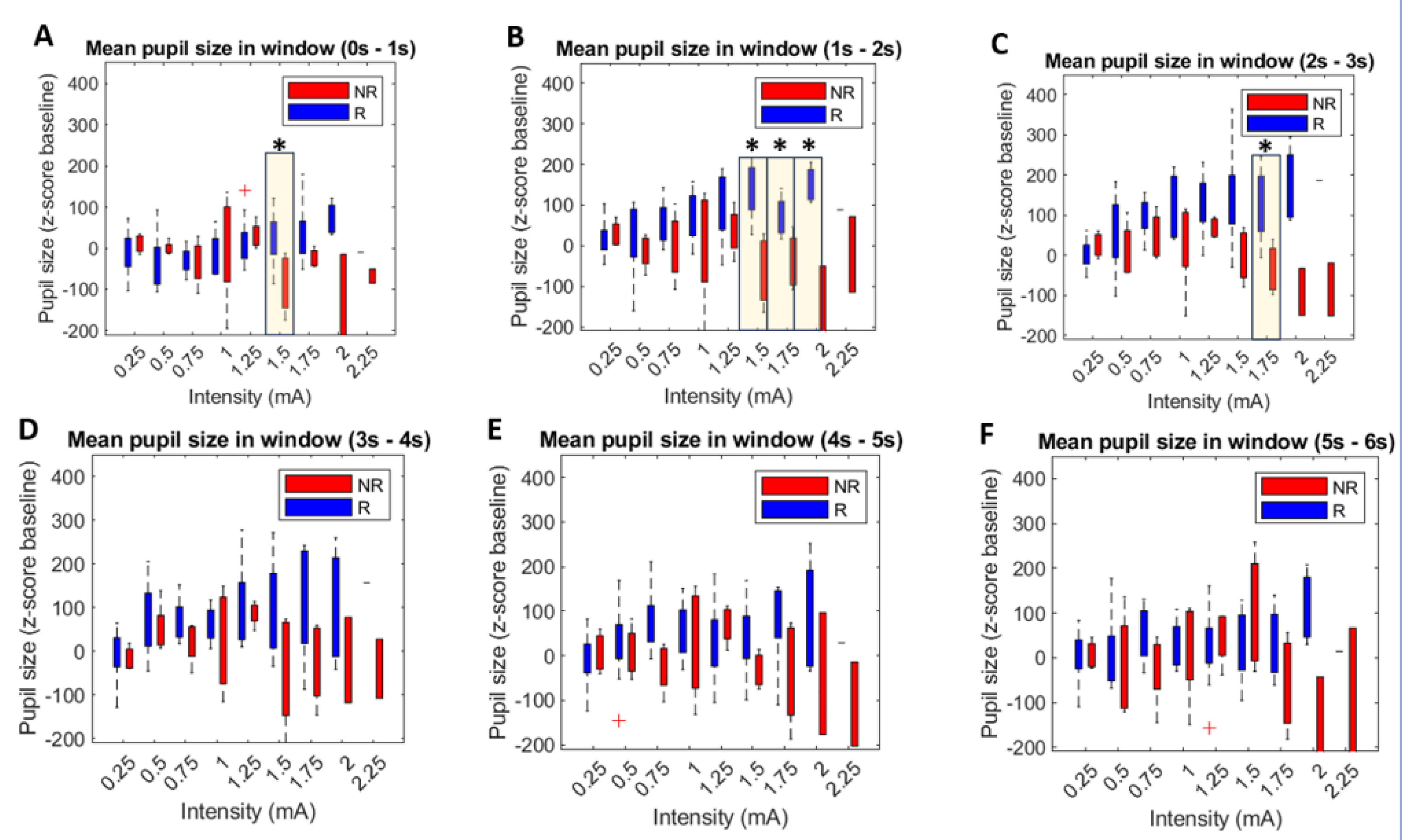


***Fig.4*** *Boxplots showing the evolution of the PDR at increasing VNS intensities within 1-second time intervals up to 6s after VNS onset.In yellow rectangles, the single VNS intensities at which there was a signficant difference (using a t+test) between R and NR were marked.*

**Main results:**

- **Higher VNS intensities induce higher PDR in Responders up to 3s after VNS onset**
- **The 2s-3s interval fitted a quadratic mixed-effect model**

## References

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