Implementing Machine Learning Models to Predict Cardiovascular Target Engagement in Rats Treated with Vagus Nerve Stimulation

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RATIONALE

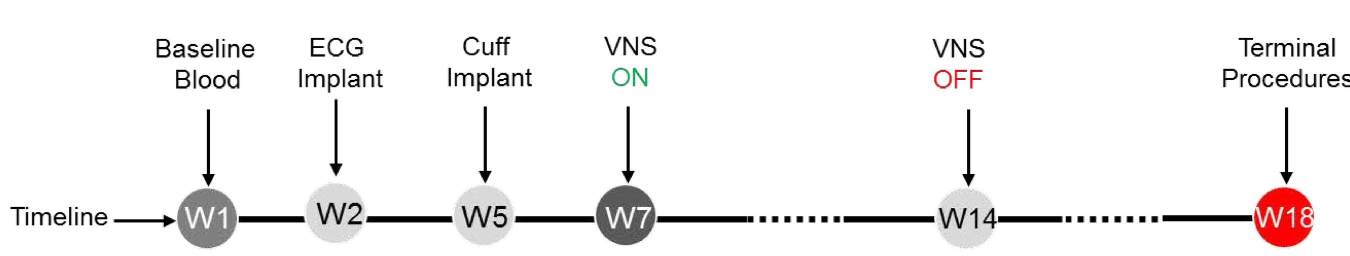
Vagus Nerve Stimulation (VNS) has been known as a safe and effective treatment for some clinical disorders such as epilepsy and severe depression. However, the long-term side effects of this approved neuromodulation therapy have not been thoroughly assessed. In order to study the cardiovascular side effects of VNS, we conducted chronic animal experiments using rats implanted with wireless physiological monitoring and neurostimulator devices.

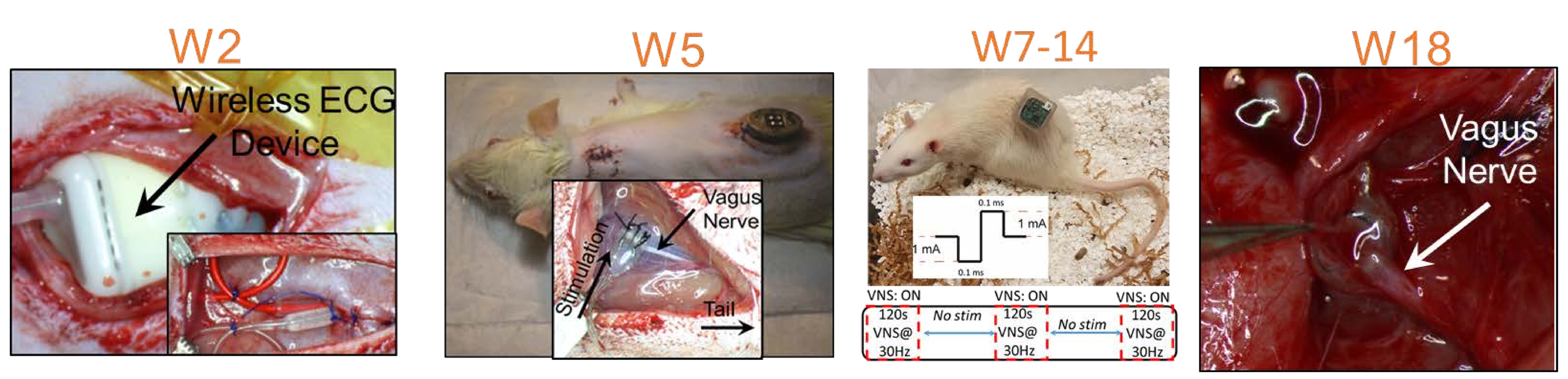
AIMS

- Identifying cardiovascular target engagement by VNS using ECG and heart rate variability (HRV) analyses.
- Implementing predictive algorithms based on deep neural networks to forecast cardiovascular variable trends following VNS.
- Quantify prediction error for predictive models using independent out-of-sample data.

EXPRIMENTAL DESIGN

The experimental design included 8 weeks of VNS on a daily basis. VNS was conducted once a day with a duration of 10 minutes. For each simulation, continuous electrocardiogram (ECG) signals were analyzed for each rat, before and after the stimulation.

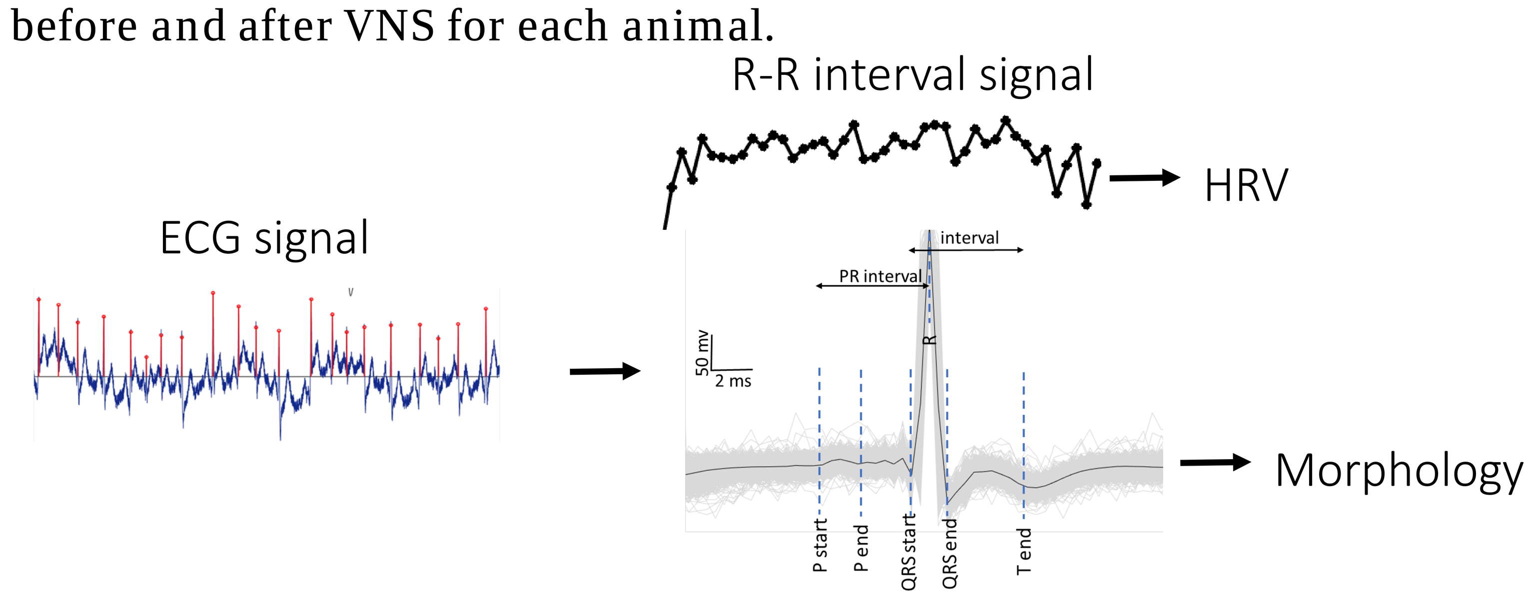




The timeline for our chronic animal study is show above. 16 rats (8 treatment and 8 sham) underwent surgical implantation of wireless ECG implant and then after 3 weeks of recovery, vagus nerve cuff electrodes connected to an implantable pulse generator for VNS delivery. Treatment group have received daily VNS with shown parameters while ECG signals have been recorded continuously.

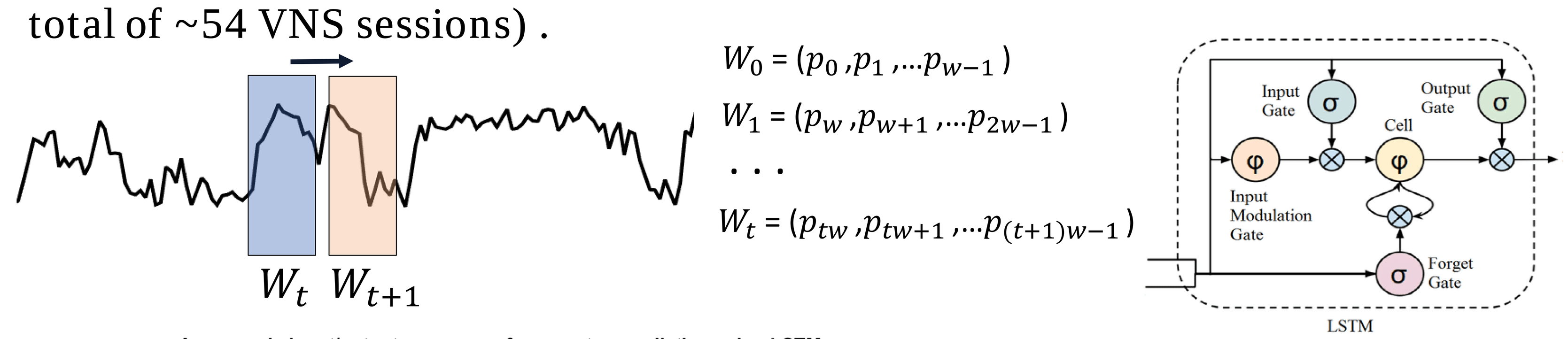
SIGNAL PROCESSING AND FEATURE EXTRACTION

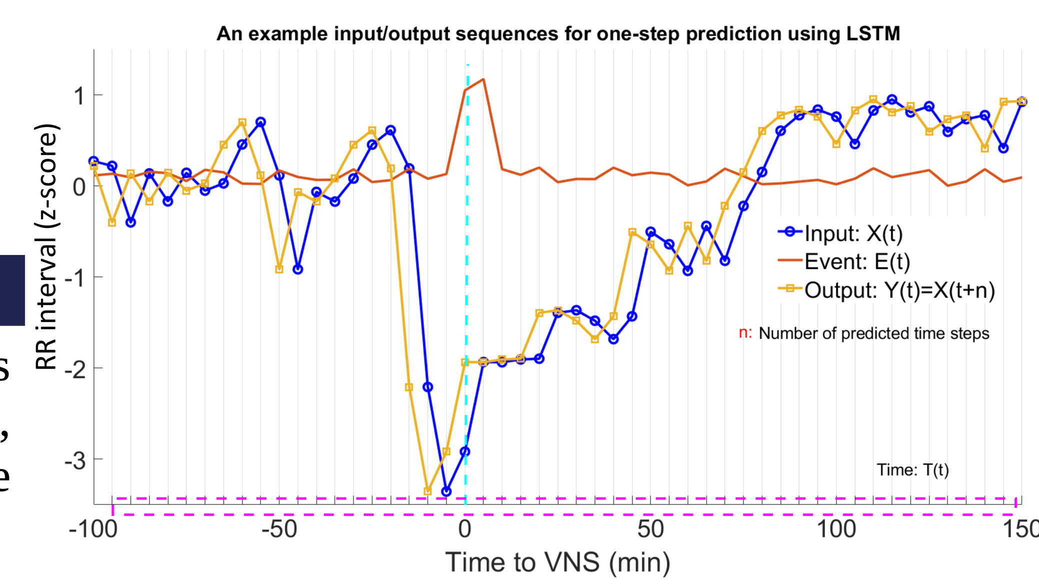
To study the cardiovascular effects of VNS, HRV analysis was performed using continuous ECG signals. ECGs were first preprocessed and analyzed for beat detection using LabChart Pro (ADInstrument) software. After R-wave detections, R-wave time-series were analyzed using MATLAB in 5-min segments for HRV/morphology analyses. Three groups of features using **time-domain**, **frequency-domain** and **nonlinear analyses** were extracted and compared before and after VNS for each animal.

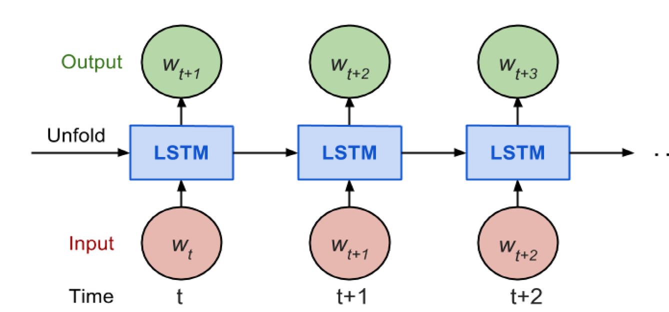


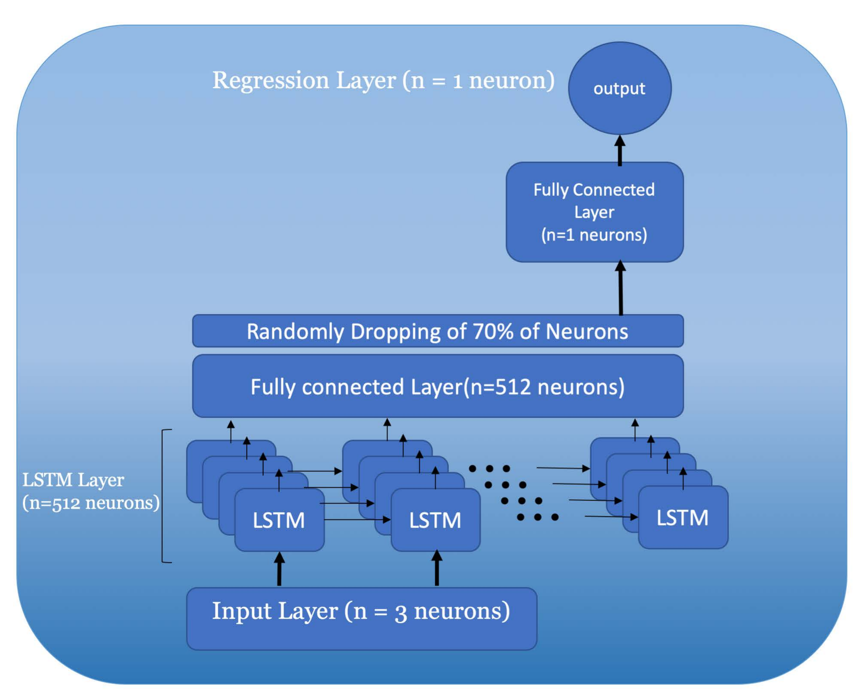
METHODOLOGY

To characterize the VNS target engagement, a time-series forecasting model using Recurrent Neural Networks (RNNs) was trained (using data from 6 rats and total of ~150 VNS sessions) and tested (using data from the remaining 2 rats with total of ~54 VNS sessions) .



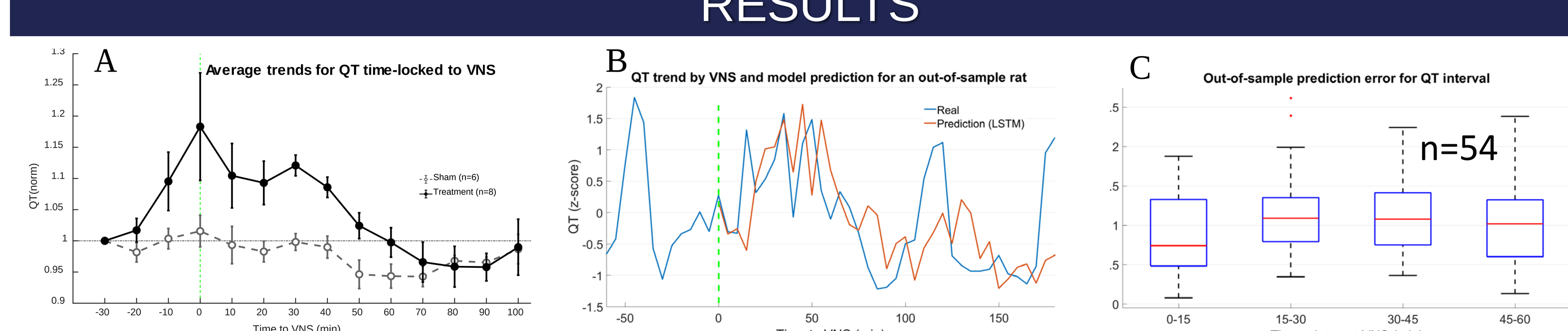




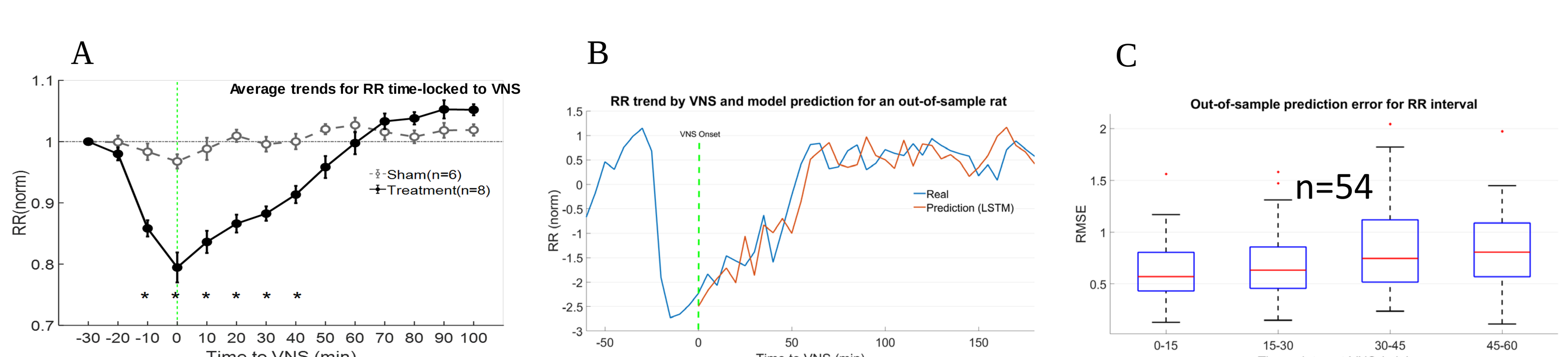


The network architecture including a Long Short-Term Memory (LSTM) layer is shown. Hyperparameters were empirically optimized as: '*adam*' solver, reducing learning rate (0.01 to 0.000001 by 0.1 factor after 150 epochs). The RRN model consist of input Sequence Layer, LSTM Layer, Fully Connected Layer, Drop Out layer, Fully Connected Layer and Regression Layer as Output.

RESULTS

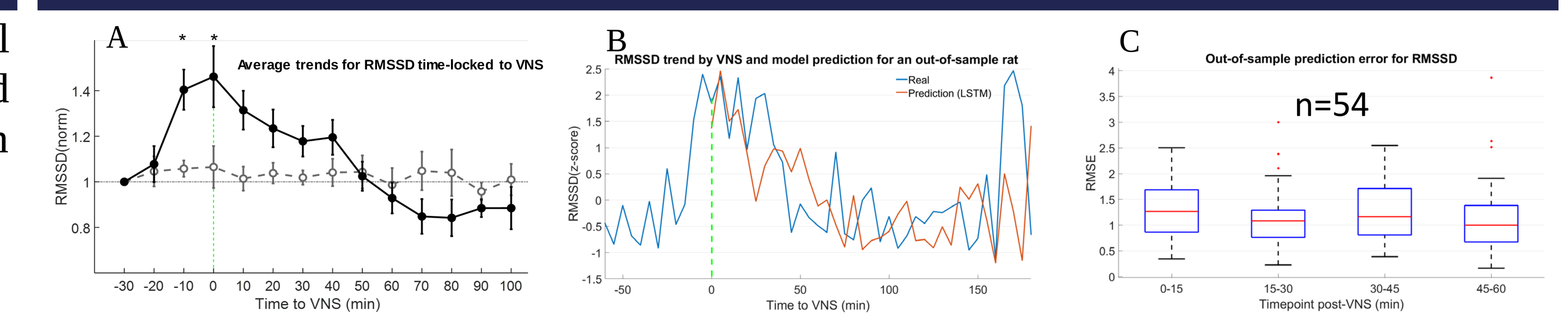


QT interval:
A) Reflects ventricular activity time→ elevated by VNS in treatment group with ~1hrs recovery time.
B) A trend (blue) pre- and post-VNS along with model prediction (red) from an out-of-sample recording.
C) The root mean squared error (RMSE) of prediction: minimum for the first 15min window post-VNS.

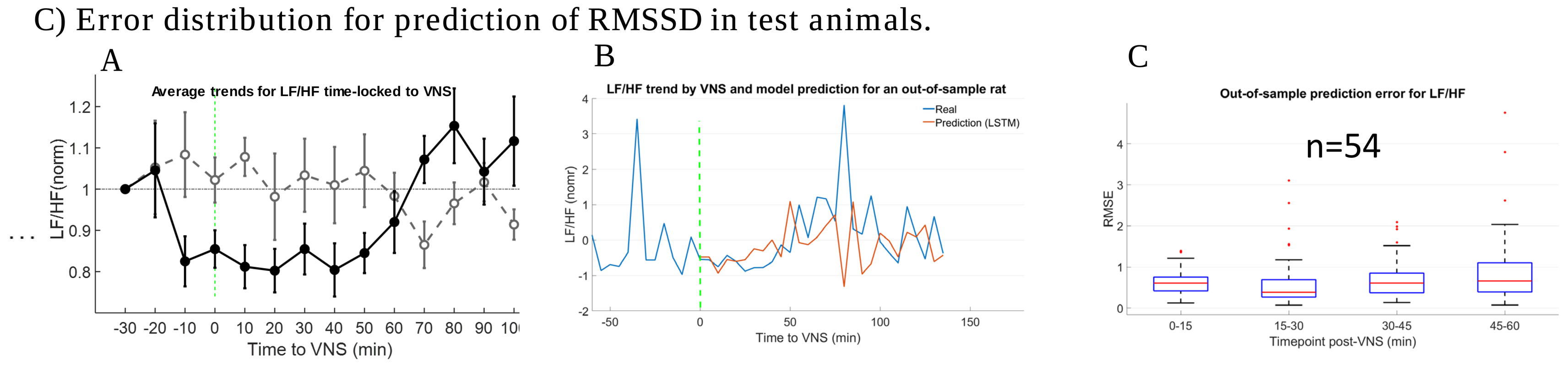


RR interval
A) Inverted heart rate→ significant tachycardia (elevated HR) post-VNS
B) Out-of-sample prediction for RR trend pre- and post-VNS.
C) Distribution of prediction error (RMSE) for test set (n=54) at different time point post-VNS.

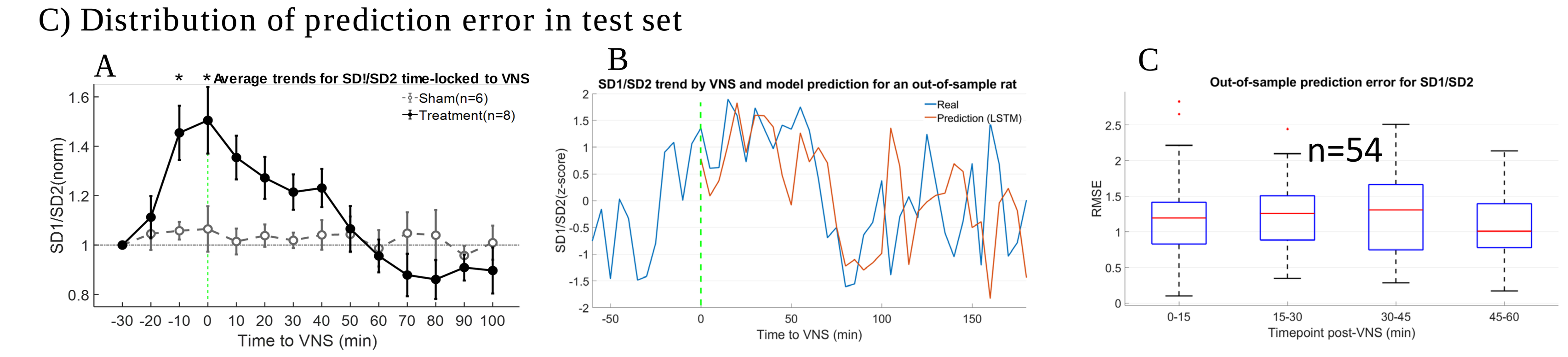
RESULTS-CONTINUED



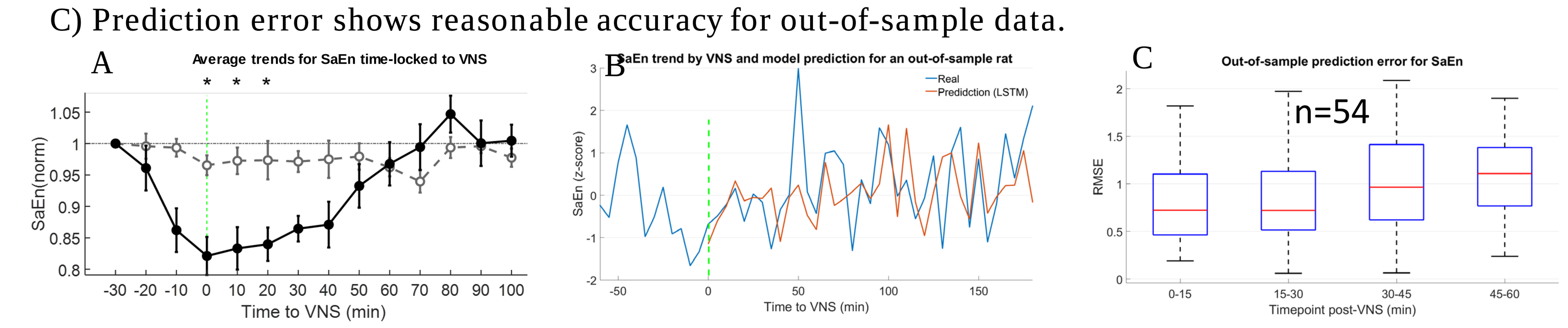
RMSSD :
A) RMSSD is Root mean square of successive RR interval differences→ elevated by VNS with ~50 min recovery time, and reflecting short-term variability in HR mediated vagally.
B) RMSSD trend pre- and post-VNS along with model prediction from an out-of-sample recording.
C) Error distribution for prediction of RMSSD in test animals.



LF/HF ratio:
A) LF/HF reflects sympatho-vagal balance→ parasympathetic modulation is evident by VNS
B) An out-of-sample LF/HF trend and pre- and post-VNS along with model prediction
C) Distribution of prediction error in test set



SD1/SD2 ratio:
A) Nonlinear analysis reflecting short-term over long-term HRV→ elevated by VNS in treatment group.
B) LSTM model predicts trends for SD1/SD2 in an out-of-sample recording.
C) Prediction error shows reasonable accuracy for out-of-sample data.



SaEn:
A) Reflecting the complexity of the heart rate→ heart rate is more predictable post-VNS
B) SaEn trend pre- and post-VNS along with model prediction from an out-of-sample recording.
C) Prediction error shows larger variability; forecasting the next step is difficult due to nonlinear nature of the SaEn variable.

CONCLUSION

Cardiovascular target engagement of VNS was studied using in-detail HRV analyses. A LSTM model to predict post-VNS trends (one-step) was successfully implemented and out-of-sample validation results have shown accurate forecasting. The proposed model can be applied in implementing closed-loop VNS and adaptive optimization of parameters for safety purposes. As part of a future plan is to implement hybrid deep neural networks (e.g. RNN-CNN-GAN) and multiple-step prediction.

ACKNOWLEDGMENTS

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