Close NIT – Transauricular vagus nerve stimulation with closed-loop cardiac, respiratory and electroencephalography biofeedback: a pilot study in healthy volunteers

Background

Co-morbid depression is common in people with heart failure (HF) [1], difficult to treat [2] and leads to worse health outcomes [3]. **Autonomic nervous system** (ANS) dysregulation, with sympathetic hyperactivation and parasympathetic withdrawal as indexed by reduced heart rate variability (HRV), is seen in depression [4] and HF [5] independently. In HF, ANS dysregulation is associated with increased mortality [6] and negatively correlates with severity of co-morbid depression [7]. **This suggests** that ANS dysregulation is mechanistically involved in depression in HF patients, explaining the poor cardiac outcomes of depressed HF patients.

Implanted vagus nerve stimulation (VNS) directly targets the ANS. It is used clinically in depression [9]. In VNS trials in HF, open and closed-loop systems have been used [10]. Despite variable results regarding heart function, **VNS consistently improved QoL** in HF trials [10]. These QoL improvements replicate clinical findings from VNS in depression [11]. The mechanisms behind these QoL improvements with VNS across pathologies are not clear.

Transauricular VNS (taVNS) is a non-invasive alternative, which improves cardiac baroreflex sensitivity [12] and QoL [13] in pre-clinical samples, and mood [14] and fatigue [15] at least transiently in clinical samples. It holds promise but optimal stimulation parameters are not known [16]. **We have already delivered custom-built open-loop taVNS techniques to healthy volunteers**, developed scripts to process heart rate data and have identified parameter-specific effects of taVNS on the heart rate variability (HRV). Other groups have demonstrated that **respiratory-gated taVNS modulates cardiovascular ANS** [17]**,** that **electroencephalography (EEG) can be used a biomarker of taVNS** [18] and that **task performance reaction times are reduced by non-invasive VNS** [19]. These results need further replication and the development of local expertise to deliver it.

Aims

We aim to develop lab-based closed-loop taVNS techniques, to allow us to automate the delivery of non-invasive vagal nerve stimulation at specific target points of the respiratory cycle, while monitoring effects on HRV, blood pressure (BP), EEG and reaction times (RT) (Figure 1).

Objectives

1. Further develop the **concurrent analytics for various sensor streams** (ECG, BP, EEG, RT).
2. Develop algorithms for **closed-loop respiratory-gated taVNS** (e.g. based on respiration phase).
3. **Assess the effects of respiratory-gated taVNS on the HRV, BP, frontal midline theta EEG and reaction times** of healthy volunteers, by comparing non-respiratory-gated taVNS trials vs. two different phases of respiratory-gated taVNS (Figure 2). Modify algorithm in 2 iteratively if needed.

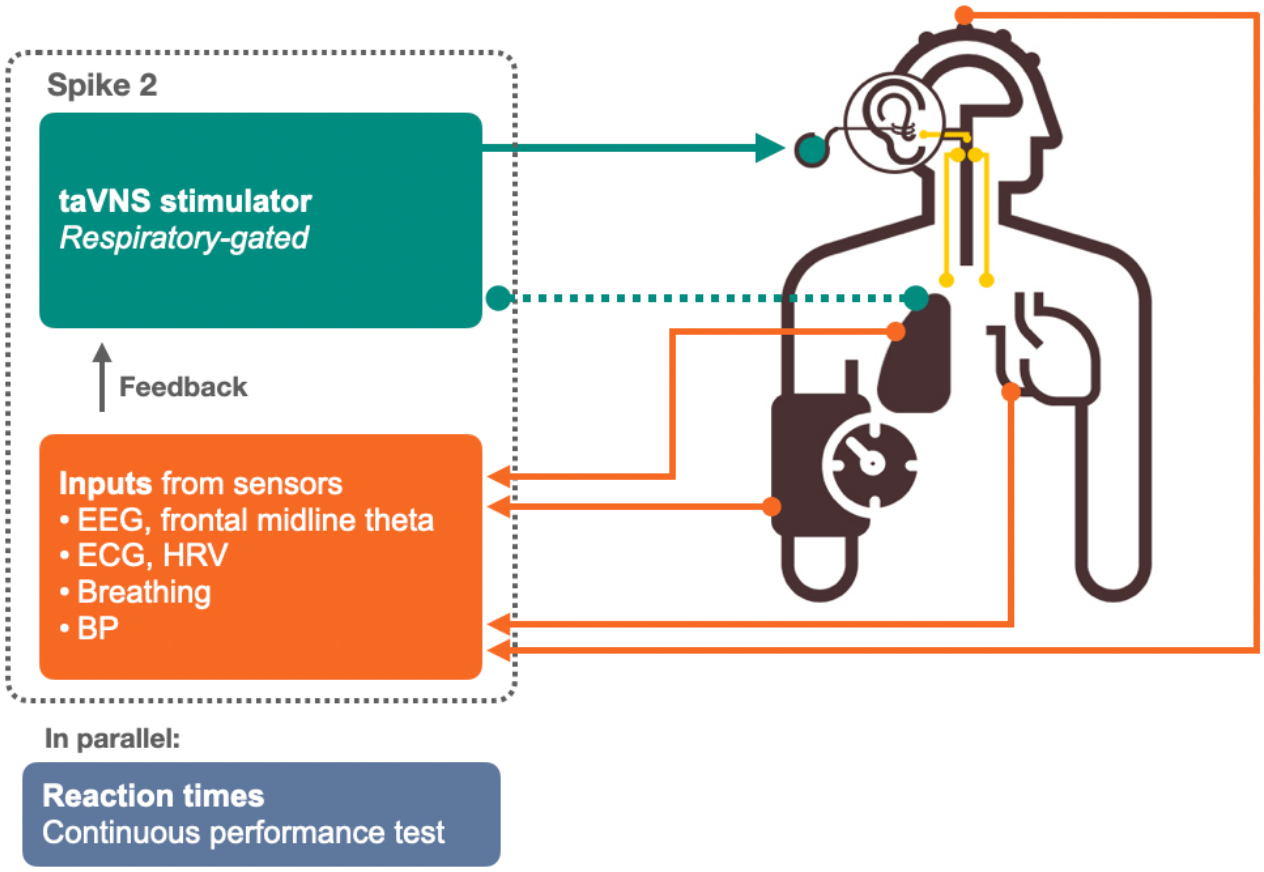
Project plan

Months	1	2	3	4	5	6	7	8	9	10	11	12
Experimental setup development												
Data acquisition												
Data analysis & dissemination												

References

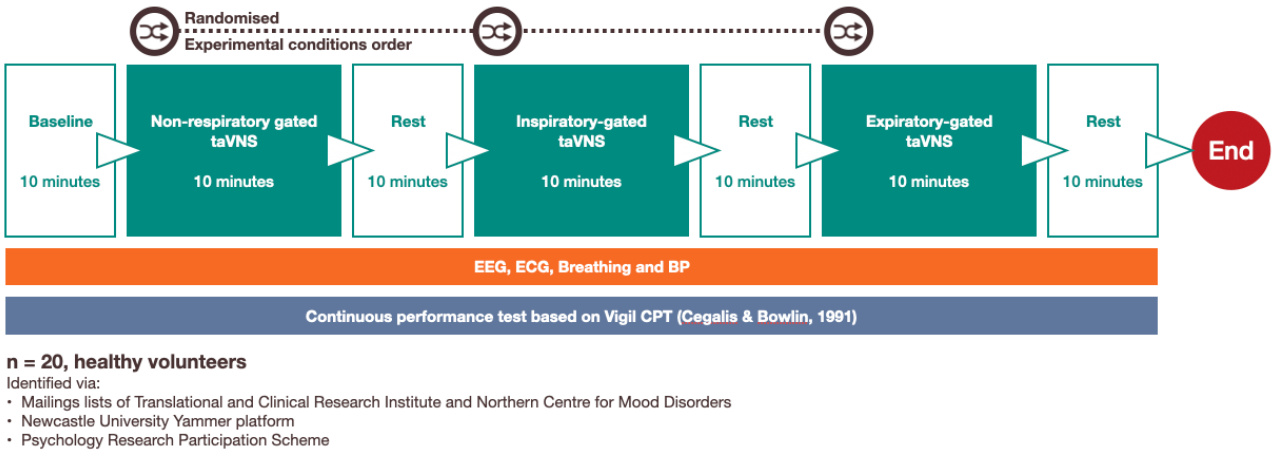
1. Rutledge et al. J Am Coll Cardiol, 2006. **2.** Zambrano et al. J Am Heart Assoc, 2020. **3.** Sullivan et al. Am J Cardiol, 2004. **4.** Kemp et al. Biological Psychiatry, 2010. **5.** Aronson et al. The American Journal of Cardiology, 2004. **6.** Triposkiadis et al. Journal of the American College of Cardiology, 2009. **7.** Walter et al. Annals of Behavioral Medicine, 2019. **8.** Tanaka et al. J Physiol Sci, 2015. **9.** Aaronson et al AJP, 2017. **10.** Byku & Mann, JACC, 2016. **11.** Conway et al. J. Clin. Psychiatry, 2018. **12.** Antonino et al., Brain Stimulation, 2017. **13.** Bretherton et al. Aging, 2019. **14.** Wu et al. Medicine, 2018. **15.** Badran et al., Bioelectron Med, 2022. **16.** Thompson et al. Front. Neurosci., 2021. **17.** Paleczny et al. Clin Auton Res, 2021. **18.** Gianlorenco et al. Biomedicines, 2022. **19.** Lerman et al. Brain Stimulation, 2022.

Diagrams annex



BP: blood pressure; ECG: electrocardiogram; EEG: electroencephalogram; HRV: heart rate variability; taVNS: transauricular vagus nerve stimulation.

Figure 1. Simplified scheme of experimental setup for closed-loop taVNS experiments



n = 20, healthy volunteers
Identified via:
- Mailings lists of Translational and Clinical Research Institute and Northern Centre for Mood Disorders
- Newcastle University Yammer platform
- Psychology Research Participation Scheme

Figure 2. Schematic illustration of experiment