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Tragus based Vagus Nerve Stimulation for Stress Reduction

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Abstract: Non-invasive vagus nerve stimulation is fast becoming a popular alternative treatment method for various health disorders. The authors investigated the effects of auricular vagus nerve stimulation at tragus for activating the parasympathetic nervous system to reduce stress, in light of mixed results from other studies. Stimulation frequency of 25 Hz with a pulse-width of 200 μ s was administered at tragus with ECG data recorded during pre- and post-stimulation trials to investigate changes in the low-frequency (LF) and high-frequency (HF) parameters of heart rate variability (HRV). The results from five subjects demonstrate an increase in the HF component and a decrease in LF when comparing pre- and post-stimulation values, denoting that VNS stimulated more of the parasympathetic activity. The LF/HF ratio was reduced for all participants after stimulation, with an average reduction of 64.5% observed. Overall, this study has indicated the feasibility of using tragus as a stimulation site to stimulate the vagus nerve; tragus being easier to administrate than many alternative sites while still being effective for stress reduction.


1 INTRODUCTION


Constant demands in routine daily life are a catalyst for increased stress and anxiety issues leading to various mental disorders (Hidaka, 2012; Bandelow and Michaelis, 2015; Kessler et al., 2009). Stress is the leading contributory factor and major cause to the development of diseases such as cardiovascular, chronic skin conditions, chronic cluster headaches and various other psychiatric illnesses (Blixen et al., 2016). For clinicians, treating patients with stress-related illness through drug administered approaches is not a good solution as the average efficacy rate of most drugs does not exceed 50%, and moreover can cause intolerable adverse side effects (Ambrosini and Coppola, 2020). To address these issues and to minimise the adverse side effects of drugs, alternate treatments

have been sought in recent years, notably methods based on nerve stimulation are being explored widely. Such methods are sometimes referred as neuromodulation, due to their ability to modulate the nervous system. Amongst various neuromodulation techniques, vagus nerve stimulation (VNS) has been widely investigated since 1990 using implanted or invasive VNS devices (Akerman and Romero-Reyes, 2020).

The vagus nerve is the tenth cranial nerve that consists of approximately 80% afferent fibres projecting into the brain and 20% efferent fibres that project to the rest of the body. It is considered to be the major parasympathetic innervation of the autonomic nervous system (Akerman and Romero-Reyes, 2020; Johnson and Wilson, 2018; Kaniusas et al., 2019b; McClintock et al., 2009). Since the first human implant of VNS devices in 1989, over 50,000 patients have been treated with VNS worldwide and the vagus nerve is often considered protective, defensive and relaxing (Vonck et al., 2009). VNS has been recently approved by the FDA in the US for therapeutic use in

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patients aged over 12, as well as those presenting with drug resistant epilepsy and depression (Johnson and Wilson, 2018). However, there have been confounding results in the literature where one study (Borges et al., 2019) has indicated no difference between sham stimulation and VNS. Hence, in this study, we have investigated the effects of VNS at the tragus site, and investigated its stress reduction effect. For this analysis, we used Heart Rate Variability (HRV), as a promising marker (Malik et al., 1996) of stress. HRV is the fluctuation in the time intervals between adjacent heartbeats (Shaffer and Ginsberg, 2017). It is sensitive to changes in sympathetic and parasympathetic nervous systems from which stress levels can be inferred. Various studies report that when stress is induced, the HRV variable HF decreases, and LF increases, to lower the parasympathetic activity (Thayer et al., 2012; Kim et al., 2018).

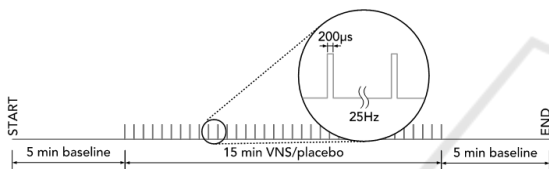


Figure 1: Stimulation protocol.

More recent studies have focused on non-invasive methods of VNS, which can circumvent complex implantation procedures and reduce associated risks such as infection. To address this, electrical stimulation of the auricular vagus nerve has been appropriately investigated using bioelectronics with the main focus being on the therapeutic effects (Kaniusas et al., 2019a). Stimulating the auricular branch of the vagus nerve (ABVN) also known as Alderman's nerve or Arnold's nerve has proven to be effective in the treatment of depression (Hein et al., 2013; Bermejo et al., 2017; Trevizol et al., 2015; Fang et al., 2016; Rong et al., 2016).

To apply electrical stimulation on the auricular branch, the location could either be the cymba conchae or tragus as these have most of the vagus fibres. Even though the conchae consists of 100% vagus fibres, the tragus is easier to apply electrical stimulation to both walls of the ear with a suitable stimulation clip (Badran et al., 2018) despite having fewer vagus fibres. Electrical stimulation frequency and pulse width are crucial parameters that need to be chosen carefully to activate any parasympathetic response. The stimulation pattern determines the activation of parasympathetic and sympathetic responses. Higher stimulation frequencies of 20–25 Hz are required to stimulate the parasympathetic system, while lower frequencies 0.5–10 Hz usually stimulate the sympathetic response

(Dietrich et al., 2008). One complicating factor is the frequency selectivity of the skin barrier between electrodes and nerve cells.

A stimulation frequency of 25 Hz is commonly used in experimental studies related to auricular VNS (Badran et al., 2018; Sclocco et al., 2017; Badran et al., 2019), and a pulse width of 200 μs is considered to be effective and safe for long periods of stimulation (Bikson et al., 2018).

2 METHODOLOGY

To administer VNS on the left tragus, a stimulation protocol as shown in Figure 1 was followed. The stimulation frequency was fixed at 25 Hz with a pulse width of 200 μs. Data collection was performed in three trials over two sessions, starting with a rest period of five minutes for the baseline recording, stimulation/placebo session for 15 minutes and a post stimulation session of five minutes. Custom hardware was developed for administering the stimulation as explained in the Hardware Design section.

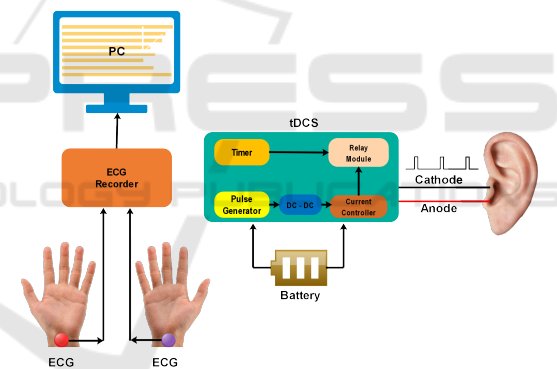


Figure 2: Functional block diagram of the equipment developed for the experiments.

2.1 Hardware Design

Functional blocks for the hardware are shown in Figure 2. To collect the ECG data, a Biosemi Active Two system with standalone battery pack was used with two electrodes attached using conductive gel to the left and right wrists of each participant. CMS and DRL electrodes were used as reference and ground. For stimulation, the pulse was generated using an ARM Cortex M4 microcontroller, which was programmed to generate PWM pulses for use in our protocol (Mouli and Palaniappan, 2017; Mouli and Palaniappan, 2020). Along with the hardware prototype, code was developed to generate pulses at a rate of 25 Hz with a pulse-width of 200 μs. This was fed

to a DC-DC controller to regulate the output current (which did not exceed 2 mA as a safety precaution (Bikson et al., 2018)), and provided pulse amplitudes of 2.2 volts. The output timing was controlled by using another ARM Cortex M4 microcontroller to set the stimulation time duration of 15 minutes as well as controlling a dual pole, dual throw relay module to switch the pulses ON/OFF when the stimulator was activated. The output of the relay module was connected to a small ear clip as shown in Figure 3 with two circular electrodes that can comfortably attach to both sides of the tragus wall.

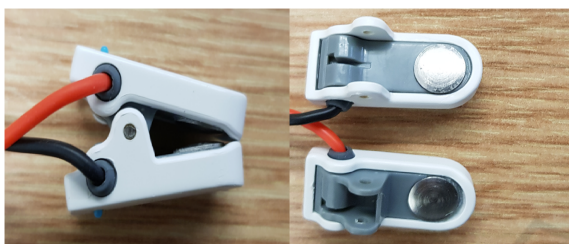


Figure 3: Tragus clip.

The chosen pulse width and rate are based on other VNS experimental studies (Kaniusas et al., 2019b; Badran et al., 2019), although in this case we stimulated the tragus site. The hardware prototype is a standalone unit with pre-programmed stimulation frequency and powered by 5 V DC battery pack, which makes it safer to use and avoids any external power surges and interferences.

2.2 Procedure

For this study, five healthy participants (three females, two males, with age 38.6 ± 12.5 years) took part in the data recording for two sessions, which comprised stimulation and placebo on different days. Each participant was seated comfortably with electrodes attached using gel to both wrists for ECG collection. The current stimulator ear clip was coated with conductive paste and was connected to the left tragus with the anode on the inner side of the tragus and the cathode on the outer side of the tragus. Each session involved taking three separate ECG recordings beginning with a five-minute baseline (pre-stimulation) followed by a 15 min session without stimulation (placebo) and ending with a five-minute post 'stimulation' session, as shown diagrammatically in Figure 1. The recordings were repeated for the same participant on a different day, once with placebo and once with active current stimulation. The precise order of stimulation/placebo was randomised between participants who were not informed which session was placebo and which involved active VNS. Ethics ap-

proval for the experiment was obtained from the Sciences Research Ethics committee at the University of Kent. The collected data were anonymised and analysed to study the effects of current stimulation.

2.3 Data Processing

Two sets of data were analysed separately for placebo and VNS sessions in each participant. Data was converted from the 128 Hz sample rate of the 24-bit Biosemi Data Format (BDF) recordings to European Data Format (EDF) using the EEGLAB plug-in in MATLAB. Data was filtered from 1 to 35 Hz using an IIR Elliptic filter and the ECG was extracted from the channel corresponding to the left wrist with the right wrist used as a re-reference channel. R-R peaks were detected using a peak detection method in MATLAB that involved a pre-defined threshold that was verified manually for each experiment to ensure that artefact induced peaks were excluded. These R-R intervals were fed into Kubios HRV 3.3.1 analysis software (Tarvainen et al., 2014) to compute the values for LF (0.04-0.15 Hz), HF (0.15-0.4 Hz) and the ratio LF/HF.

3 RESULTS AND DISCUSSION

From HRV, the LF and HF components can be computed to evaluate the influence of VNS. Computed values from pre- and post- VNS sessions are shown in Table 1 for all the five participants. Based on these results, it is evident that LF values were reduced and HF values were increased with VNS, denoting a stronger activation of the parasympathetic system compared to the sympathetic system. The overall reduction in the LF/HF ratio from the pre-VNS and post-VNS sessions was also computed. Over all five participants, an average reduction of 64.5% was observed between pre- and post- VNS sessions. Meanwhile an average reduction of 6.8% was observed between pre- and post- placebo sessions. Figure 4 also shows the reduction in electrocardiogram derived respiration (EDR).

A small reduction is to be expected when someone is sitting down relaxed for short periods of time, however the increased reduction observed for the VNS sessions may indicate the effectiveness of the stimulation in reducing stress. Figure 4 shows an example of the HRV frequency analysis from one participant for both pre- and post- VNS sessions where the higher HF increase over LF increase in post-VNS can be seen showing an increase in the parasympathetic activity as compared to sympathetic. Changes in the HRV parameters as a result of VNS has also been reported

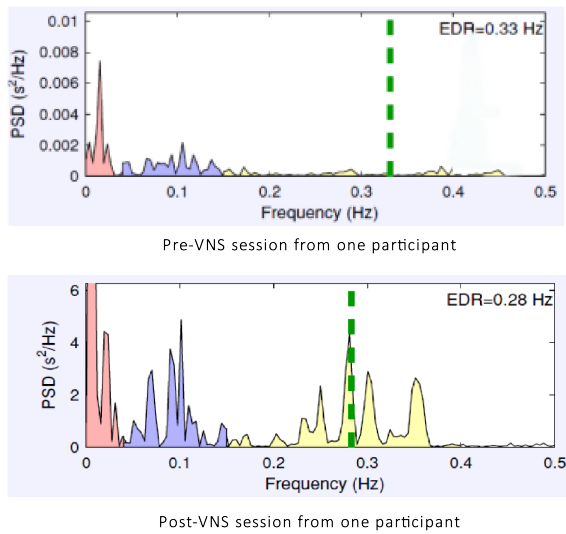


Figure 4: Pre - and Post - VNS session from one participant.

Table 1: Pre- and Post - VNS results from all participants.

Session	Participant	P1	P2	P3	P4	P5
Pre- VNS	LF (n.u.)	88.40	67.50	46.50	57.70	93.13
	HF (n.u.)	11.60	30.30	53.40	42.20	6.85
	LF/HF (%)	7.62	2.23	0.87	1.37	13.60
Post- VNS	LF (n.u.)	71.20	40.00	26.20	35.70	81.8
	HF (n.u.)	28.80	59.90	73.20	64.20	18.17
	LF/HF (%)	2.47	0.67	0.36	0.56	4.50
% Reduction		67.56	70.02	58.90	59.33	66.89

in various studies using similar frequency (Constantinescu et al., 2019; Kamath et al., 1992; De Couck et al., 2017).

4 CONCLUSION

The study reported here explored the possibilities of non-invasive auricle vagus nerve stimulation at the tragus. The experiments stimulated the left tragus for 15 minutes to activate a parasympathetic response, inducing a more relaxed (less stressful) state. A frequency of 25 Hz using a pulse width of 200 μ s was generated using portable standalone hardware and administered during stimulation. The vagus nerve was easily stimulated at the tragus using a generic ear clip for both anode and cathode, in contrast to the cymba conchae location, which would require custom-shaped attachments for each participant. A reduction in LF/HF ratio after VNS was observed for all participants even with a relatively stimulation short period of 15–minutes, with LF components decreasing and HF components increasing after the stimulation to indicate a higher parasympathetic vs sympathetic activation. For this study, the VNS period was limited to 15 minutes to explore the influence of non-invasive stimulation, but future studies could explore

longer periods of stimulation, or the effect of sessions at regular intervals involving clinical patients. Customised cymba conchae designs to stimulate the vagus nerve could also be explored, which may lead to improved results, given that the density of vagus nerve fibres is higher at the conchae compared to the tragus.

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