Recovery of Autonomous Balance as Indicator of Normalizing Effects of Non-invasive Vagus Stimulation

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***Abstract*—Clinical studies have shown the effectiveness of electrical stimulation for mental and stress-related disorders. We analysed the effects of novel transcutaneous vagus nerve stimulation (tVNS) for boosting mental and physical health and performance in work conditions. 62 healthy volunteers 18-49 years old were recruited for the study. The tVNS (BrainPatch platform for non-invasive stimulation) was arranged as a 4-day course of 6-minute stimulation sessions with monitoring of heart rate variability (HRV). Psychological testing (State Anxiety, STAI; psychological stress level, PSM-25; emotional burnout level MBI; identification of depression, IDS) was carried out on the first and last day of the study. We detected beneficial changes in the psychoemotional state of the respondents: improvement of mood, reduction of work stress (PSM-25), beneficial effects on emotional exhaustion and professional reduction (MBI), as well as on depression symptoms (IDS). HRV effects of VNS were observable and significant in short-term and reflected the activation of the parasympathetic nervous system (the increase of vagally mediated parameter RMSSD and decrease of LF/HF ratio). An increase in the spectrum of high-frequency band indicates a high degree of recovery and readiness for stress. Our data suggests that the novel tVNS protocol attenuated the work related stress impacts. A normalizing effect of the tVNS on the psychoemotional state manifested in the form of shifting "sympatho-vagal balance" to the functional optimum.**

***Keywords*—Heart Rate Variability, Stress, Galvanic vestibular stimulation, Vagus Nerve Stimulation**

I. Introduction

In the modern world, a person is constantly exposed to various stress factors that negatively affect both the psychoemotional and physical state. The most common consequences of everyday stress are increased anxiety, burnout, and depressive disorders, which reduce productivity and impair quality of life [1, 2]. The intensity value of tension in the regulatory systems of the organism, its functional reserves affect various heart rate variability indicators (HRV) [3, 4]. Heart rate variability is considered as the most promising indicator of a psychological stress, wherechronic stress leads to the hyperactivation of the sympathetic nervous system [4].

HRV is an indicator of capacity to adapt and recover from stress [5] and a reduced HRV is a marker of vulnerability to stress and disease [6]. Heart rate (HR) and its variability (HRV) may reflect vagal activity [7]. The vagus nerve plays critical role in balancing the body's physiological functions [7].

The mechanisms involved in positive outcomes of non-invasive vagus nerve stimulation are not fully understood [8]. Heart rate variability is modulated by transcutaneous auricular vagus nerve stimulation (tVNS) in a charge-dependent way [9]. Improvement of spontaneous cardiac baroreflex sensitivity in healthy men is specific to stimulation of auricular branch of the vagus nerve [8]. In a systematic study of various tVNS locations the stimulation had varying side-dependent effects [10]. Active tVNS through the auricular branch of the vagus nerve significantly shifted the cardiac autonomic function toward parasympathetic predominance [11]. This shift is desirable in conditions characterized by enhanced sympathetic nerve activity.

Electrical stimulation of the auricular vagus nerve (aVNS) affects a set of chronic pain diseases, neurodegenerative and metabolic ailments, inflammatory and cardiovascular diseases [12]. The tVNS was also shown to affect nociception, however the directionality of the effects on nociception varied greatly between individuals [13]. While tVNS was shown to affect HRV, it appears to have no effect on heart rate, nor blood pressure [13]. While heightened vagal tone may have an effect on HRV, it does not always affect HR [7].

The current evidence from the aforementioned up-to-date state in heart rate variability and current stimulation application allows making several conclusions:

- HRV is a promising strong indicator of capacity to adapt and recover from stress,

- all studies demonstrate a strong impact of vagus stimulation on the state of patients with a range of disorders,

- tVNS was mostly shown to have normalizing effects on the sympathetic nerve activity,

- there exist contradictions in the studies of vagus nerve stimulation effects.

Considering all of the above, we aimed to explore the influence of a novel tVNS stimulation protocol on HRV time, frequency and non-linear metrics as well as psychological well-being in employees at workplace environment and university students and its dependence on baseline sympathetic and parasympathetic tone.

II. Materials and Methods

A. Sample

62 healthy volunteers 18-49 years old were recruited for study (26 - Stimulation group, M_{age} = 26.3, SD = 7.81 years, and 22 – Sham group, M_{age} = 26.1, SD = 6.47 years, 14 persons were excluded for different reasons). The remaining 48 participants (24 employees, telecom operators of the contact center of telecommunication company JSC Kazakhtelecom (6 male and 18 female), 24 students and employees of al-Farabi Kazakh National University (5 men and 19 women) were randomly divided into two equivalent study groups (Stimulation and Sham) in a double-blinded way. The study was approved by the al-Farabi Kazakh National University Local Ethics Committee (IRB00010790 al-Farabi Kazakh National University IRB#1, protocol No. IRB-A343b November 25, 2021) and conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants.

Participants were eligible to enrol in the study if they were over 18 years old and did not have clinical manifestations of mental disorders or cognitive impairment, neurological, cardiovascular diseases, problems related to the vestibular system and were not taking psychoactive medication, drugs, or alcohol. Additional exclusion criteria were skin diseases, wounds and cracks at the stimulation site, metal implants in the head or piercings under the stimulation site. We asked participants to abstain from alcohol for at least 12 hours before the stimulation session.

Termination criteria were participant violations of the study instructions, voluntary refusal to participate at any of its stages, non-conformance to the acceptance criteria.

B. Procedure

The study was carried out according to the protocol in 6 sessions spread over a period of approximately two weeks.

(1) Psychological testing was carried out on the first ("0") and last ("4+1") days of the study.

(2) The state of autonomic regulation of the cardiovascular system (heart rate variability) was measured continuously on each day of stimulation was administered as well as the first and the last days of the study.

(3) Stimulation was carried out on 4 days with at least a day between the stimulation sessions for 6 min, with the exact protocol delivered (tVNS or Sham) dependent on the randomisation group. Neither the participant, nor the present experimenter were aware of the protocol being delivered.

C. Stimulation Procedure

Stimulation/SHAM was arranged as a 4-day course of 6-minutes stimulation sessions using BrainPatch Headphone stimulators (https://www.brainpatch.ai/). BrainPatch headphone stimulators (fig. 1) are a combination of wireless headphones that broadcast music or relaxing high quality sounds, and wireless non-invasive current stimulators (micropolarizers) with safe parameters of the generated electric current. The current stimulator (electrodes built into the headphones) consists of an analog-to-digital converter and a circuit that allows the delivery of a weak current signal (current up to +/-1.5 mA and voltage up to ~+/-30 V) to the electrodes. Since the amplitude utilised in this study was limited by the "LOW" setting, the maximum delivered current was ~0.6 mA, that is, peak-to-peak wave amplitude was ~1.2 mA. For the safety of stimulation, in addition to the limitations included in the application, the electronics itself contain 2 mA hardware limits in both directions. A porous electrolyte carrier ("sponge") saturated with electrolyte (~150 mM NaCl) is used as an interface between the electronics and the skin, which reduces skin irritation. A publicly available BrainPatch application for iOS or Android operating systems used by the experimenter was controlled by a proprietary cloud-based system used by system administrator for randomisation and for delivery of assigned protocols to the BrainPatch device as well as for collection of data on the execution of the protocol. This study used a protocol that combines pleasant meditative sounds and slow bipolar wave (0.1 Hz) electrical stimulation, which causes a relaxing effect and, according to preliminary results, may increase cognitive abilities [14]. The sham stimulation consisted of 10s 0.1 Hz, stimulation at 0.6 mA, to provide a false sense of real stimulation, after which the maximum delivered placebo stimulation current was ~0.05 mA, thus peak-to-peak wave amplitude was ~0.03-0.06 mA.

The stimulation zone included the mastoid area where the auricular branch of the vagus nerve exits the cranium by passing through the tympanomastoid fissure between the mastoid process and the tympanic part of the temporal bone, and divides into two branches (first one joins the posterior auricular nerve, the other spreads to the skin of the auricle area of the ear and to the posterior part of the ear canal). Below the mastoid processes, the vestibular nerve directs from the inner ear to the vestibular nuclei of the brain stem, which, in turn, are interconnected with the relay nuclei of the thalamus (ventroposterolateral thalamic nucleus).

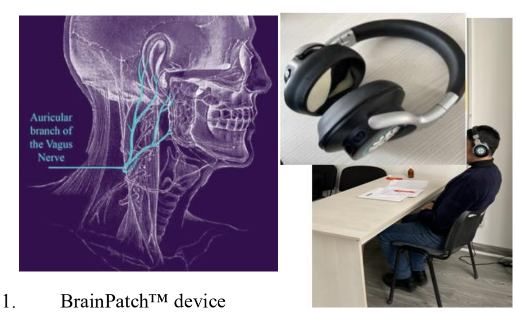

Fig. 1. BrainPatch™ device

At each stimulation session the presence of side effects of Stimulation/SHAM was monitored.

D. ECG recording (HRV) and preprocessing

Heart Rate monitoring was carried out throughout the entire day of the study by Polar H10 Heart Rate Monitor Chest Strap (Polar Electro, USA). Physiological indicators were processed using the Kubios HRV Software (Kubios Oy, Finland). Each heart rate record was pre-processed for artefact removal, divided into "time-stamped" 6-minute Samples and loaded into the Kubios program. The 6-minute heart rate samples (pre-stimulation (baseline), stimulation, and post-stimulation condition) were processed with the calculation of 88 indicators (HRV time-domain, frequency-domain, and non-linear measures) [15].

HRV time-domain

The used HRV time-domain indicators are reflecting the balance of activity of sympathetic and parasympathetic divisions of the autonomic nervous system.

RMSSD (ms) is used to assess vagal-mediated changes reflected in HRV and parasympathetic activity and is calculated as root-means-square difference between successive RR intervals.

HRV frequency-domain

Frequency-domain measurements allow to decompose the rhythmogram using the Fourier transform into four frequency bands (ultra-low-frequency, very-low-frequency, low-frequency, and high-frequency bands) and to quantify the contribution of each of them.

The tone of the sympathetic nervous system reflects the low-frequency (LF) - power of the spectrum of RR intervals in the low frequency region (0.04 - 0.15 Hz), while high-frequency (HF) spectrum power of RR intervals (0.15 - 0.4 Hz) reflects the tone of the vagus nerve and can be considered as an indicator of the parasympathetic tone of the heart. The coefficient of vagosympathetic balance is considered to be the ratio of LF-to-HF power [15].

E. Psychological testing

Symptoms of Burnout

In order to measure the severity of emotional burnout in students, we used the 22-item Maslach Burnout Inventory (MBI). The MBI is designed for the diagnosis of occupational burnout and comprises of three components: emotional exhaustion (EE, the 9-item scale), depersonalization (DP, the 5-item scale) and reduction of personal achievements (PA, the 8-item scale) [1, 16].

Personality and mental health variables

Lemur-Tessier-Fillion Psychological Stress Measure (PSM-25) was used to assess current levels of occupational stress on an 8-point Likert scale ranging from 25 to 200 points [17].

The 30-item Inventory of Depressive Symptomatology (IDS) [18] measures the severity of depressive symptoms and differentiates endogenous from nonendogenous depressions.

The 7-item Generalized Anxiety Disorder-7 (GAD-7) self-rating scale is used to measure the generalized anxiety disorder (5 levels of anxiety ranging from mild to severe) as a persistent and pervasive disorder characterized by unfocused worry and anxiety across various settings without connection with recent stressful events [19].

The State-Trait Anxiety Inventory (STAI adapted by Yu. Hanin) detects the level of anxiety on the basis of 4- point Likert self-assessment scale (high, medium, low anxiety). State Anxiety is defined as a reaction to socio-psychological stressful situations. Trait Anxiety provides insight into individual stress tolerance based on personality traits. [17].

The Big Five Inventory (BFI) is designed to assess personality factors by 44 items (simple sentences) that are rated in the 5-point Likert scale. Big Five personality traits (FFM, the five-factor model of personality) identified the following five factors and ten values: openness to experience (inventive/curious vs. consistent/cautious), conscientiousness (efficient/organized vs. extravagant/careless), extraversion (outgoing/energetic vs. solitary/reserved), agreeableness (friendly/compassionate vs. critical/judgmental), neuroticism (sensitive/nervous vs. resilient/confident) [20, 21].

To measure Emotional Intelligence the Trait Meta-Mood Scale (TMMS) was used. A 30-item (three subscales), 3-factor self-report assess three components of emotional intelligence (Attention - attention to feelings, Clarity - emotional clarity, and Repair - mood repair) [22].

The 20-items Positive and Negative Affect Schedule (PANAS) was used to assess levels of positive and negative effect, experienced emotions during a specified timespan [23].

Visual analogue scales (VAS's) were used for subjective ratings of emotion and their intensity. The state is assessed according to 10 components of the emotional profile - surprise, joy, happiness, bliss, delight, fear, anxiety, disgust, sadness, anger. [24].

F. Statistical data analysis

Statistical analysis was performed using SPSS (version 15.0). To compare group characteristics, the independent student's t-tests (for normally distributed parameters), Mann–Whitney U tests for abnormally distributed numeric parameters, and the χ^2 tests (for frequency distribution of nominal parameters) were applied.

To detect the effects of stimulation and sham in the whole sample as well as in each group a two-way repeated measures we used ANOVA and one-way repeated measures ANOVA (a within-subjects ANOVA) for each of the following factors: condition (pre-stimulation, stimulation/sham, post-stimulation), study day (1-4 stimulation days, pre-stimulation 0, or post-stimulation 4+1). The Greenhouse–Geisser correction $\ddot{\varepsilon}$ was applied for the data that did not meet sphericity in repeated measures ANOVA. Bonferroni correction was used for post hoc pairwise comparison after the detection of significant main effects and interactions. The Paired Samples t-test was applied for the same reasons as well in each group separately.

The value of the shift of HRV parameters was expressed in percentage from the pre-stimulation point and its direction in plus or minus sign.

III. RESULTS

Sensations and side effects.

Non-invasive stimulation was rated by the participants as a positive experience. Some subjects felt various effects on their skin during the stimulation procedure, which they were quickly accustomed to. Analysis of the items of the issued questionnaire about side effects (7 points) after the stimulation session indicate sensations, which are normal and expected for this type of stimulation when it is working correctly. Among the most frequently observed sensations in the area of the electrode contact, subjects indicated: mild heat-like sensation, skin irritation/itching, feeling of warmth. No severe side effects were reported.

The presence of vertigo/dizziness (from 22% to 29% of all reported sensations depending on the day of stimulation), suggests that one of the effects is galvanic stimulation, involvement of the vestibular system. It was previously shown that possible mechanisms of the effects of nVNS most likely include connections between the trigeminal, vestibular, and vagal systems in the brainstem [25]. The first major relay station for vagal afferents (nucleus tractus solitarius, NTS) receives afferents from the ipsilateral medial vestibular nucleus, the ipsilateral nucleus prepositus hypoglossi and bilateral inferior vestibular nuclei [26]. There are vestibulo-autonomic pathways to the dorsal motor nucleus of the vagus nerve from the caudal portion of the medial vestibular nucleus and the inferior vestibular nucleus [27].

However, the same vestibular side effects in the control group (15 participants) raise doubts about the vestibular mechanism being the sole contributor to the observations.

Psychoemotional state

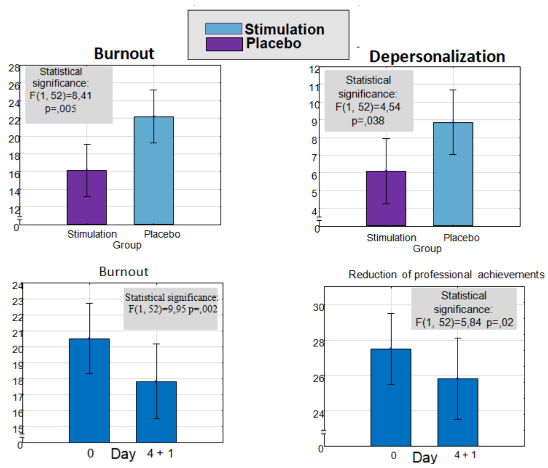

Fig. 2. Course dynamics of occupational burnout (Maslach Burnout Inventory MBI).

Beneficial changes in the psychoemotional state of the respondents were revealed after the stimulation course. The Positive and Negative Affect Assessment (PANAS) indicates a positive effect of stimulation on improving mood ($p=0.027$; $F=2.588$). There are detected significant reductions in the severity of anxiety (GAD-7, $p=0.028$; $F=5.551$) and indicators of occupational stress (PSM-25, $p=0.007$; $F=8.677$). Unexpectedly, depression scores also revealed an improvement (IDS, $p = 0.014$; $F = 6.471$). A set of stimulation significantly improved the job burnout (MBI, reduction of personal achievements, $p<0.001$; $F=20.893$) (Fig 2). In combination, the data appears to corroborate that the stimulation attenuates negative impact of job-related stress and improves emotional state associated with professional activities.

Dynamics of heart rate variability (HRV)

A significant increase in RMSSD ($F(2, 64)=5.76$ $p=.011$) at the time of stimulation compared to the control group indicates an activating effect on the parasympathetic division of the autonomic nervous system (Fig. 3). In contrast, no significant differences were found in the SHAM group. The effect of stimulation turned out to be short-term, which was manifested in a drop in the value of the RMSSD parameter immediately after the end of stimulation.

An increase in the vagus nerve tone was reflected in the changes in the spectral power of high-frequency (HF) - there was an increase in the absolute power of HF bands (HF, $F(2, 64)=4.28$, $p=.032$) and the relative value of the power of HF bands (HF%, $F(2 , 64)=5.30$, $p=.021$), relative value of HF band power, expressed in normalized units (HF in n.u., $F(2, 64)=5.35$, $p=.019$). (Fig. 4).

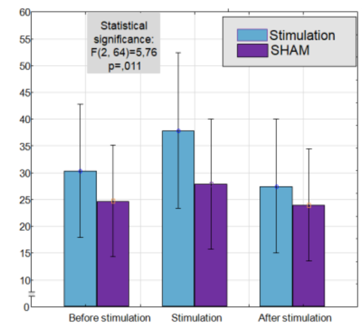

Fig. 3. Dynamics of HRV indicators in the time domain. RMSSD: square root of the sum of the differences of successive R–R intervals, 4th day.

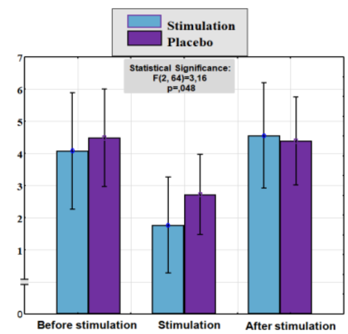

Fig. 4. Dynamics of HRV indicators in the frequency domain. LF/HF: The ratio of the power of low frequency band to the power of high frequency band, 4th day.

The vagosympathetic balance coefficient showed a statistically significant decrease in the stimulation group at the time of stimulation (Fig. 4): LF/HF indicator ($F(2, 64)=3.16$, $p=.048$), LF/HF_AR indicator ($F(2, 64)=3, 91$, $p=.03$). This reflects a shift towards parasympathetic nervous system dominance.

The obtained data indicates that positive effects of used stimulation technique are realized by vagus nerve through central mechanisms. High-frequency fluctuations could be the result of the activity of the parasympathetic cardioinhibitory center of the medulla oblongata [28]. A key role in the relationship between stress and depressive symptoms belongs to the nucleus accumbens [29]. Visceral and cardiovascular afferent inputs (from ventrolateral medulla) influence the activity of neurons in the shell region of the nucleus accumbens [30]. Brain mechanism underlying tVNS treatment of major depressive disorder includes the modulation of low frequency functional connectivity (FC) of the nucleus accumbens and surrounding areas (the putamen, caudate, and distinct areas of the medial prefrontal cortex (MPFC) and the anterior cingulate cortex) that are involved in reward and motivation processing [31]. Cortical areas involved in the stressful situations assessment (including the ventromedial prefrontal cortex) may be linked with HRV [32]. Pilot study showed that the beneficial effects of tVNS on the emotional state was accompanied by increased activity of the left frontal and right dorsolateral prefrontal cortex, left occipital cortex [14].

IV. CONCLUSION

Obtained data detected the activation of the parasympathetic nervous system in response to the novel tVNS stimulation protocol, which is characteristic of the resting state [33]. An increase in the parasympathetic nervous system activation indicates a high degree of recovery and the system's capacity for handling stress. The observed positive dynamics of improvement in indicators of stress, anxiety, depression, professional burnout and mood is of particular importance as it indicates the high effectiveness of the method used to stimulate the vagus nerve. Taken together with the protocol's reasonable safety profile and the fact that this study was performed in office and academic environments, the results of this study suggest that the novel tVNS protocol has the potential to become an effective tool for mental wellbeing for work and for education environments.

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