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Original Article

The effects of transcutaneous auricular vagus nerve stimulation on visual memory performance and fatigue

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ABSTRACT

Objectives: This study aims to investigate the effects of transcutaneous auricular vagus nerve stimulation (taVNS) on visual memory performance and fatigue in healthy individuals.

Patients and methods: Between April 10, 2022 and May 25, 2022, a total of 60 physical therapy and rehabilitation students (27 males, 33 females; mean age: 20.6±1.6 years; range, 18 to 24 years) were included in the study. The individuals were divided into two groups as the experimental group (n=30) and the control group (n=30). The experimental group received taVNS, mobile device supported games, and low-medium intensity aerobic exercises, while the control group received mobile device supported games and aerobic exercises. The personal information form was applied to all participants. The level of fatigue was measured using a computer-based evaluation and Fatigue Severity Scale (FSS) to analyze the visual memory performance.

Results: All parameters used to evaluate visual memory performance showed a significant difference, while the FSS scores showed no significant difference ($p>0.05$). Only one sub-parameter in the control group was significantly different, while none of the other sub-parameters or FSS scores were significantly different ($p>0.05$). There was a significant difference between the two groups in terms of two of the visual memory sub-parameters, although no significant difference was found for the results of one parameter and the FSS ($p>0.05$).

Conclusion: Our study results show that taVNS can produce positive effects on visual memory performance, although it does not apparently affect fatigue.

Keywords: Fatigue, transcutaneous auricular vagus nerve stimulation, visual memory.

The development of technology has brought innovations in the field of neuroscience as in every field. New treatment options that can replace existing treatments have begun to emerge. One of these techniques is neuromodulation treatment.[1] Transcutaneous auricular vagus nerve stimulation (taVNS) is among the neuromodulation treatment methods. Compared to the invasive vagus nerve stimulation (iVNS), which was used earlier, it is a more suitable treatment method in terms of ease of operation, accessibility to the device and fewer side effects.[2,3] The taVNS is the stimulation of the vagal afferent branches of the outer ear at cymba concha where they extend with the help of an electrode. Due to its user-friendly design, it is possible to utilize it for various cases.[3] In addition, a consistent stimulability can be achieved in the brain region as a result of ear stimulation with cranial imaging techniques.[4] Afferent branches of the vagus extend to the nucleus of solitary tract (NTS) and locus coeruleus (LC) in

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the brainstem.[5] There are branches extending to areas of the brain such as the midbrain, amygdala and hippocampus from the NTS.[6,7] These regions are areas where cognitive functions such as re-evaluation of emotions are made.[8-10]

The taVNS is a promising method for conditions such as high-order cognitive functions and mood regulation.[11] Several studies have shown the efficacy of taVNS in cognitive control processes.[12-14] In two studies investigating the effectiveness of taVNS in the associative memory and response selection, favorable results were achieved.[15,16] In another study, there is consistent support for the role of taVNS in emotion regulation and social functioning.[17]

In recent years, taVNS began to be used for therapeutical purposes in the presence of conditions such as pain, fatigue, anxiety and depression. The regulation systems of the body are activated with the stimulation of the vagus nerve. Creating a response by reducing the peripheral response to inflammatory stress in the body may be given as an example.[18,19] Vagus nerve stimulation may also cause analgesic effect, since it interacts with the regions of the brain that perceive pain.[20] As a result of this situation and similar situations, vagus nerve stimulation has been suggested to be used in the treatment of musculoskeletal system diseases or other painful types of diseases.[21,22]

In the present study, we aimed to investigate the effects of taVNS on visual memory performance and fatigue in healthy individuals.

PATIENTS AND METHODS

This randomized-controlled study was conducted at Artvin Çoruh University, Department of Physical Therapy and Rehabilitation between April 10, 2022 and May 25, 2022. Inclusion criteria were age above 18 years and being volunteer to participate in the study and giving consent. A total of 60 students (27 males, 33 females; mean age: 20.6±1.6 years; range, 18 to 24 years) were included in the study. The individuals were divided into two groups as the experimental group (n=30) and the control group (n=30).

All participants filled in the personal information form and Fatigue Severity Scale (FSS), and a computer-based application was used to measure the visual memory performance. The program was introduced to the individuals before evaluation and the evaluation was started after a trial test was made. Red squares appear on the computer screen first in the game played for evaluation. With a hand that appears on the computer screen, these squares are marked in a mixed order and the participant is asked to follow this order correctly and mark accordingly. Markings start with easy ones and the game is made much more difficult by increasing the number of squares marked as the game continues. At the end of the test, the application gives sub-parameter results as "the longest correct marking duration, the number of correct markings and reaction time". The increase in these sub-parameter results enable us to comment on visual memory.

The individuals in the experimental group of our study received 10 sessions of taVNS and they ran for 1 h a day as low-to-moderate physical activity. The application was carried out, for 10 min, using a modulation waveform with a pulse duration less than 100 μsec and a frequency of 10 Hertz. Amplitude was adjusted according to the sensory threshold level. In addition, they played mobile games to make visual memory stronger.

The individuals in the control group played mobile games to improve visual memory for 10 sessions and they participated in running as the physical activity (Figure 1).

Data Collection Tools

Personal information form

A personal information form consisting of 11 questions regarding age, sex, educational status, marital status, monthly income, and place of residence was prepared by the researchers through the literature review.

The FSS, consisting of nine questions, is based on a scoring between 1 and 7 for each question. Scale responses range between 1-Totally disagree and 7-Totally agree. Higher scores indicate a greater severity of fatigue. The cut-off score for severe fatigue was set at an FSS score of ≥4, as previously described.[23]

Statistical analysis

Study power and sample size calculation were performed using the G*Power version 3.1 software (Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany). With a 0.80 power and 0.80 effect size, 42 individuals were needed to be recruited. Statistical analysis was performed using the IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). Normality distribution of the variables was checked using the Kolmogorov-Smirnov test. Descriptive data

Figure 1. Transcutaneous auricular vagus nerve stimulation and the device insertion.

were expressed in mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables and in number and frequency for categorical variables. The independent sample t-test was used to compare normally distributed variables between the two independent groups, while the Mann-Whitney U test was used to compare non-normally distributed data. The Wilcoxon signed-rank test was used to analyze non-normally distributed variables between two dependent groups. Two-way analysis of variance (ANOVA) was used for multiple comparisons of normally distributed variables. A *p* value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows sociodemographic characteristics of the participants. Accordingly, age and sex statistically differed between the groups (p<0.05). However, there was no significant difference in the BMI (p>0.05).

Both the pre-test and post-test comparisons for the group and the comparison between the groups were made for the longest correct answer, number of correct answers, reaction time and fatigue variables (Table 2). Accordingly, there was a statistically significant difference for the longest correct answer, number of correct answers and reaction time variables in the pre-test and post-test comparison of the experimental group (p<0.05). No significant difference was found in terms of fatigue variable (p>0.05). In the comparison of the pre-test and post-test of the control group, there was a statistically significant difference for the reaction time variable (p<0.05); no statistically significant difference was found for the longest correct answer, number of correct answers and fatigue variables (p>0.05). In the comparison of the experimental and control groups, there was a significant difference for the longest correct answer and the number of correct answers (p<0.05); no significant difference was found for reaction time and fatigue variables (p>0.05).

TABLE 1
Demographic data of the participants

	Experimental group (n=30)			Control group (n=30)			Between group
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			20.07±1.39			21.23±1.57	0.003*
Sex							<0.001**
Male	3	5		24	40		
Female	27	45		6	10		
Body mass index (kg/m²)			21.17±2.61			22.23±2.61	0.139

SD: Standard deviation; * Wilcoxon signed rank test; significance with p<0.05; ** Mann-Whitney U test; significance with p<0.05.

TABLE 2
Data analysis

Variables	Experimental group (n=30) Median	IQR	*p*	Control group (n=30) Median	IQR	*p*	Between group *p*
Longest correct marking			<0.001*			0.475	<0.001**
Pre test	5.00	2.25		6.00	2		
Post test	6.00	1.00		6.00	1.44		
Number of correct markings			<0.001*			0.431	<0.001**
Pre test	6.00	4.25		7.50	3.00		
Post test	8.00	3.00		7.00	4.00		
Reaction time			0.001*			0.019*	0.525
Pre test	692.00	288.25		833.00	538.90		
Post test	622.00	159.00		707.10	283.33		
Fatigue			0.096			0.259	0.151
Pre test	39.50	29.50		34.00	14.00		
Post test	42.00	27.50		30.50	17.75		

IQR: Interquartile range; *Wilcoxon signed-rank test; significant at p<0.05; ** Mann-Whitney U test; significant at p<0.05.

TABLE 3
Sex-related attentional variables

	No fatigue group (FSS≤4) Female (n=15) Mean±SD	Male (n=15) Mean±SD		Severe fatigue group (FSS≥4) Female (n=18) Mean±SD	Male (n=12) Mean±SD
Longest correct marking	5.13±0.81	5.33±0.72		4.92±1.42	5.13±1.09
Number of correct markings	6.20±1.77	7.40±1.60		7.19±2.81	6.20±2.23
Reaction time	809.94±233.99	812.31±184.25		687.79±154.71	929.88±362.61
	Sum of Squares	df	F	Partial Eta Squared (Effect size)	*p*
Longest correct marking					
Sex	0.61	1	2401	1.00	0.01*
Fatigue	0.66	1	2601	1.00	0.01*
Sex-Fatigue	0.00	1	0	0.00	0.99
Number of correct markings					
Sex	0.17	1	0.10	0.01	0.94
Fatigue	0.14	1	0.01	0.01	0.94
Sex-Fatigue	17.55	1	3.66	0.61	0.61
Reaction time					
Sex	219524.58	1	1.04	0.51	0.49
Fatigue	77.03	1	0.00	0.00	0.98
Sex-Fatigue	211094.00	1	3.82	0.64	0.06

FSS: Fatigue Severity Scale; SD: Standard deviation; * Two-way ANOVA test; significant at p<0.05.

In Table 3, there was a difference in the longest correction level according to sex and fatigue (p<0.05). However, there was no statistically significant difference in the longest correct marking level of the sex and fatigue interaction (p>0.05).

DISCUSSION

Review of the literature reveals a large number of studies to examine the effects of taVNS on the brain. In one of these studies, Kaniusas et al.[24] sought to explain

the current aspects of auricular vagus nerve stimulation (aVNS). As a result of their study, the release of neurotransmitters and endorphins started with taVNS stimulation and this was effective in providing long-term brain plasticity and sympathovagal balance. The authors also explained that taVNS made it possible to modulate the effect of the mind on the body through vagus nerve. In another study, Yakunina et al.[25] reported that, for taVNS, stimulation of cymba conchae in the auricle was more effective than stimulation in the inner tragus. They attributed the stimulus to the strongest activation in the vagal pathways in the brainstem. In addition, Zhang et al.[26] showed that taVNS caused a signal reduction in LC and that resting state increased functional connectivity in the regions of the brain such as temporoparietal junction, amygdala, and hippocampus. The authors reported that, in patients with migraine, taVNS modulated vagus nerve pathway and pain meditation networks. Kaniusas et al.[24] attempted to explain the current pathways of aVNS. As a result of this study, they explained that electroceuticals for aVNS were effective in modulating the brain and its environment emphasizing the difficulty in utilizing appropriate stimulation protocols for aVNS.

In addition to its effects on the brain, there are also studies in the literature examining the effects of taVNS on cognitive functions. In a study, Sellaro et al.[27] showed increased post-error deceleration with no clear effect on basic performance criteria. In a study, Jacobs et al.[15] reported the positive effects of taVNS on memory performance in elderly individuals. The authors concluded that taVNS could have a positive effect on both learning and delayed recall performance of an episodic memory task. In another study, Mertens et al.[28] reported that taVNS did not have a significant effect on verbal memory performance in young, elderly, and healthy participants. Furthermore, Giraudier et al.[29] found that taVNS did not have any effect on word processing, while it had subtle effects on reminder-based memory. Hansen[30] concluded that taVNS was safe, well-tolerated, inexpensive, and useful in modulating fear and declarative memory function in adults. In a study, De Smet et al.[31] investigated the effects of taVNS on cognitive mood regulation. They showed as a result of applications on healthy individuals that taVNS had modulating effects on psychological markers of cognitive re-evaluation. In another study, Thakkar et al.[32] examined the effects of taVNS on learning new letters and sounds. The authors concluded that taVNS was effective in improving learning letters-sounds. In a recent study, Zaehle et al.[33] reported that taVNS could efficiently modulate LC-NE (LC-norepinephrine) system in both healthy and clinical populations and, therefore, it could be considered for the treatment of attention problems in patients with Parkinson's disease. In the present study, we examined the effects of taVNS on visual memory performance, which is a cognitive function. In our study, taVNS caused improvements in sub-parameters of the visual memory performance. In the light of these findings, we found that taVNS caused a significant improvement on visual memory performance, consistent with previous findings in the literature.

In their study, Aranow et al.[34] examined the effectiveness of taVNS in patients with systemic lupus erythematosus and showed that taVNS caused a significant decrease in pain and fatigue and joint scores. In another recent study, Jiao et al.[35] examined the effects of taVNS on sleep and they concluded that taVNS significantly alleviated insomnia. The authors also showed that taVNS improved conditions such as fatigue, depression, and anxiety. Of note, there are few studies in the literature examining the effects of taVNS on fatigue. In our study, we were unable to find a significant effect of taVNS on fatigue. We, therefore, recommend further studies to draw more reliable conclusions on this subject.

The main limitations to this study include that only students from a single center were recruited and taVNS was applied for only 10 sessions.

In conclusion, our study results show that taVNS can produce positive effects on visual memory performance, although it does not apparently affect fatigue. However, further studies investigating the effects of taVNS on cognitive functions and fatigue using different number of sessions, duration and type of application are needed to confirm these findings.

Ethics Committee Approval: The study protocol was approved by the Artvin Çoruh University Ethics Committee (date: 31.03.2022, no: E-18457941-050.99-45688). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from participant.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Literature review with ideas and design of the study: R.Y; Oversight, references and ideas; critical review: A.V.Ö.; Data collection function: B.C.D., O.S.N.; Analysis: Z.Y.K.; Article writing: R.Y., A.V.Ö.

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