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Original Article



The Effect of Vagus Nerve Stimulation on Cognitive Performance

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Abstract

Objectives: This study aims to investigate the effect of transcutaneous auricular vagus nerve stimulation (taVNS) on working memory (WM) performance. The primary goal of the study is to comprehend the interindividual variations in taVNS responses and examine the factors underlying these differences. The fundamental hypothesis of the thesis is that taVNS enhances WM performance (WMP). The research anticipates that this effect will be particularly observed in the group receiving actual taVNS.

Methods: An equal number of female (n=15) and male (n=15) participants were selected from a cognitively healthy group aged between 18 and 45 years. Participants underwent a WM test (n-back) initially, followed by the sham taVNS. After receiving sham session participants completed the same WM task again. Followed by the real taVNS session and the WM task is given for the last time. Participants also filled out scales for the Big Five personality traits (BFS), Experiences in Close Relationships Scale-Revised, and the Symptom Checklist-90-Revised during the same period.

Results: The findings demonstrated a notable increase in WMP in the actual taVNS group. In addition, the results suggest that individuals exhibiting avoidant attachment, displaying phobic anxiety symptoms, and having high interpersonal sensitivity tend to benefit more from taVNS.

Conclusion: These outcomes imply that taVNS has the potential to enhance WMP and reflects the influence of individual factors. **Keywords:** Autonomic nervous system, behavior, memory, neuropsychological tests, object attachment, personality, vagus nerve stimulation.

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Why we can not learn, improve, remember, or recover at the same pace? Why do we have different systems that allow or prevent us from succeeding equally, why do some of us try harder to remember the same phone number, whereas others memorize it immediately, why all individuals do not benefit from cognitive therapies equally? The primary aim of the research is to investigate the effect of transcutaneous auricular vagus nerve stimulation (taVNS) on working memory (WM) performance by comparing

participants who receive active taVNS with those who receive sham stimulation. The secondary aim is to examine how individual differences, including attachment styles, personality traits, and psychological symptoms, influence the relationship between taVNS and WM performance (WMP), and to identify the psychosocial factors that contribute to differential responsiveness to taVNS. The existing literature suggests that acute psychological stress can reduce activity in the dorsolateral prefrontal cortex, a brain region crucial

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for WM functioning.[1] Neurobiological evidence supports this notion, showing reduced theta activity in the frontal area under acute stress, which is associated with WM.[2] In addition, stress-induced cold pressor tasks hinder executive functions required for WMP.[3,4] indicating an inhibiting effect of acute stress on WM. In contrast, individual differences in WM capacity (WMC) have been attributed to both inherent traits and current states that affect information management and the contents of WM.[5] Successful self-regulation and self-regulatory lapses are linked to WMC, highlighting the importance of assessing the big five personality traits and psychological symptoms that could influence WMC. [5] Furthermore, the development of self-regulation is influenced by early parent-child relationships, and innate temperament differences passed down through generations, as suggested by attachment theory. [6] Attachment styles have been found to impact WM by influencing one's selfregulation capabilities.^[7] Therefore, this study explores the effect of attachment styles, trait personalities, and psychological symptoms on the relationship between stress and WM. Various methods to facilitate WM, such as training or deep-brain stimulation, have limitations, such as high costs or lack of immediate effects.[8-10] Hence, the investigation of novel methods, such as taVNS, to enhance WMP is crucial for expanding the existing literature on WM facilitation.[11]

Existing literature indicates that taVNS can potentially enhance WMP.[12,13] However, it remains unclear why some individuals benefit more from taVNS while others show less improvement after receiving taVNS. To address this gap, the current research integrates measures of psychological symptoms (Symptom Checklist-90 [SCL-90]), adult attachment styles (Experiences in Close Relationships Scale-Revised), and personality traits (Big Five Scale) to explore the underlying factors contributing to differential responses to taVNS. The primary hypothesis of this study is that WMP scores will increase after receiving taVNS, and there will not be a significant difference between the baseline and sham sessions. Secondly, securely attached individuals will benefit more from taVNS, showing a more significant increase in WMP after stimulation. Participants with a lower general symptom index on the SCL-90, indicative of lower psychological distress, are also expected to exhibit more significant improvements in WM following taVNS. Moreover, individuals scoring high on neuroticism and openness but low on conscientiousness and extraversion are anticipated to show more significant benefits from taVNS due to their potential for increased neuroplasticity,[14,15] and more robust information retrieval mechanisms in the prefrontal cortex.[16] Furthermore, it is hypothesized that participants who undergo actual taVNS sessions will demonstrate a significant increase in WMP compared to those who undergo sham sessions, indicating the specific efficacy of taVNS in enhancing WM. The contribution of this research to science lies in its novelty as it aims to be the pioneering investigation exploring the individual differences behind the varying effects of taVNS on WMP, providing valuable insights into individualized cognitive enhancement techniques.

Vagus Nerve Stimulation (VNS)

VNS originated as a treatment method for refractory epilepsy. [17] However, its application expanded beyond epilepsy when researchers discovered that VNS ameliorates seizure activity and enhances cognitive performance in epileptic patients, making it a promising tool for various clinical demands. [18] The vagus nerve, the 10th cranial nerve, is pivotal in the parasympathetic nervous system (PNS). While the precise neurophysiological impact of VNS is not fully elucidated, current understanding suggests that VNS stimulates the tractus solitarius, which subsequently activates the locus coeruleus (LC). This chain of events ultimately leads to the secretion of norepinephrine, a neurotransmitter known to enhance cognitive performance.[18,19] The nucleus tractus solitarius in the medulla emerges as a critical player in this process, as it sends information to several vital brain regions, including the hypothalamus, LC, dorsal raphe nucleus, and parabrachial nucleus.[20,21] Due to its multiple impacts on different brain regions, VNS can potentially manipulate diverse neural signals for various therapeutic purposes. As a result, VNS finds applications in treating conditions such as fibromyalgia, migraine, depression, epilepsy, and posttraumatic stress disorder.[22] Moreover, solid theoretical evidence supports the enhancing effect of VNS on cognitive abilities. The activation of the nucleus of the solitary tract through VNS is particularly critical, as it houses several junctions of afferent vagal nerve fibers. Consequently, VNS is thought to induce metabolic changes in specific brain regions, impacting cognitive functioning.[23]

Attachment Style and taVNS

Attachment theory, proposed by Bowlby and Ainsworth, posits that attachment is an innate and biologically driven behavioral system that develops in early childhood and continues to influence individuals throughout their lives. [24,25] This theory suggests that the quality of early attachments to primary caregivers forms an internal working model that shapes individuals' perceptions, emotions, behaviors, and social interactions. Attachment styles are classified into three categories: secure, insecure-avoidant, and insecure-anxious/ambivalent. Securely attached individuals tend

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to have positive views of themselves and others, feel comfortable with intimacy, and exhibit effective emotion regulation. In contrast, insecure-avoidant individuals are more self-reliant, suppress their emotions, and avoid intimacy, while insecure anxious/ambivalent individuals are preoccupied with relationships, fear abandonment, and have difficulty regulating their emotions.^[26]

Materials and Methods

The Place Where the Study Takes Place

The study took place on the North Campus of Bahçeşehir University.

Duration of the Study

The data collection for the study lasted for 3 months but took place 8 months, including preparing the manuscript and receiving ethics approval.

Ethics Approval

The ethics approval was received from Istanbul Medipol University Non-interventional Clinical Research Ethics Committee Presidency on April 25, 2023 with the number of E-10840098-772.02-2574. The study was conducted in accordance with the Declaration of Helsinki.

Participant

According to the G power analysis, we aimed to make the study with 30 participants. T-tests and mean differences between two independent variables were set for the statistical test. The type of power analysis was set to compute the required sample size, given alpha, power, and effect size. With a 0.5 effect size and 0.05 error probability, output parameters indicated that 27 participants must have a 0.81 actual power with 26 degrees of freedom. In demographics questions, participants are asked to report if they have any chronic illness, whether they are on any psychiatric drug or alcohol, any caffeine intake frequency, marital status, and romantic relationship status. The informed consent forms were handed to the participants beforehand in the experiment.

Instruments

Big Five Personality Traits Scale

The Big Five Personality Traits Scale is a 5-point Likerttype scale comprising ten items that assess the five major dimensions of personality: extraversion, agreeableness, conscientiousness, neuroticism, and openness. The scale is handy for investigating the relationship between personality traits and various cognitive, emotional, and social outcomes.^[27] In the current research, the Turkish adaptation of the Big Five Personality Traits Scale, adapted by^[27] was utilized because the participants were Turkish-speaking. According to the linguistic equivalence study, the correlation coefficients between the Turkish and original English form scores were found to be 0.81 for the overall scale, 0.85 for extraversion, 0.87 for agreeableness, 0.85 for conscientiousness, 0.71 for neuroticism, and 0.86 for openness to experience dimensions. All correlations are significant at the 0.01 significance level.^[27] It took participants 10 minutes to complete the scale.

Experiences in Close Relationships-relationship Structures Ouestionnaire

The attachment style was assessed using the Turkish adaptation of the Experiences In Close Relationships–Relationship Structures Questionnaire. [28,29] The attachment scale measures two dimensions: anxiety and avoidance. Participants responded to items on an insert Likert scale ranging from 1="Strongly disagree" to 7="Strongly agree." The Cronbach's alpha was 0.86 for anxiety and 0.90 for avoidance, indicating strong internal consistency. Administration took approximately 7 minutes per participant.

The SCL-90-Revised (SCL-90-R)

The SCL-90-R is a self-report 5-point Likert scale questionnaire ranging from "not at all" to "extremely that assesses various psychological symptoms and distress." [30] It consists of 90 questions that measure nine symptom dimensions, including depression, anxiety, phobic anxiety, hostility, obsessive—compulsive tendencies, interpersonal sensitivity, somatization, paranoid ideation, and psychoticism. The Turkish version of the SCL-90-R was used in the current research, providing valuable insights into participants' mental health status. [29] The scale's reliability analysis in the Turkish adaptation yielded a high Cronbach's alpha coefficient of 0.97, indicating excellent internal consistency. [30]

The application of the scale took approximately 15 minutes per participant.

The Montreal Cognitive Assessment (MOCA)

The MOCA is a widely used cognitive screening tool designed to assess various cognitive domains, including attention, memory, language, and visuospatial abilities. ^[31] In the current research, the Turkish-validated version of the MOCA, known as the "Montreal Bilişsel Değerlendirme Ölçeği (MOBİD)," as developed by Selekler et al. ^[31] in 2010, was utilized. According to the results of the receiver operating characteristic analysis, a cutoff score of 21 points was determined for the total score of MOBİD.

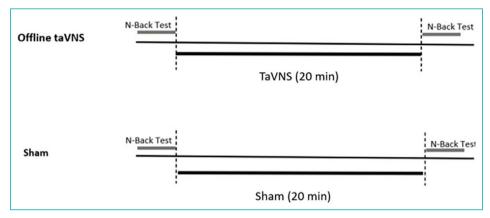


Figure 1. Research design.

taVNS: Transcutaneous auricular vagus nerve stimulation; min: Minute.

Therefore, participants who scored below 21 on MOBİD were planned to be excluded from the analysis in the study. The application of the scale took approximately 15 minutes per participant.

Working Memory Assessment

The n-back test presents participants with a sequence of stimuli one by one. In the current study, a 2-back task will be used, where participants must respond if the current letter matches the letter from two trials ago. The stimulus set will consist of 15 letters (A, B, C, D, E, H, I, K, L, M, O, P, R, S, and T), and each letter will be presented for 500 ms with a 2500-ms black period following. Participants will have 3 s to respond to each trial, and a new stimulus will be presented every 3000 ms. The n-back test will consist of three blocks, each containing 25 trials, and participants will receive detailed feedback on their responses. [33] The application of the scale took approximately 10 minutes per participant.

Vagustim

2×AA batteries power the device. With the help of Vagustim, we non-invasively stimulated both sides of the Vagus nerve through the auricular canal transcutaneously. The conductive gel was used on both ears, followed by the placement of electrodes. Participants were asked about their satisfaction with the electrodes and if they felt any discomfort. The stimulation threshold intensity was measured separately for each participant. We used the modulation mode and set the width to 300 ms, rate to 10 Hz, and the duration to 20 minutes.

Research Protocol

Design

After an eligibility screening, participants are invited to the Medipol University. First, participants are asked to complete

a WM test called the n-back test. This first session of the n-back test is named "Baseline." Later, participants received 20 minutes of sham taVNS and were asked to sit still and avoid walking or standing up to prevent any sympathetic nervous system activation. They were told that there would be no feelings or irritation in their ear since the currency is set to a minimum for attenuation. After 20 minutes of the sham taVNS session, named "Sham," participants were asked to complete the n-back test again. The n-back test is represented online and randomly differs each time it is presented. Participants complete the n-back test before and after the Sham session to compare each session's score and investigate if there is any significant difference between the two. There should not be any significant difference since there is no actual taVNS administration on the participants. After participants complete the second round of the n-back test, the actual taVNS administration is given for 20 minutes. This time, participants are asked to raise their hands whenever they feel a slight titillating sensation in their ears to set an individual threshold for them. Hence, each participant received a different mV of currency according to their level in starting to feel the stimulation. This session is called taVNS. After receiving taVNS for 20 minutes, participants were asked to complete the n-back task for the last time. Therefore, we collected three WM data from each participant: Baseline, Sham, taVNS. We used these three data sets to compare each participant's increase rate from baseline to taVNS. The research design and protocol are illustrated in Figures 1 and 2 below.

Statistical Analysis

Descriptive statistics were calculated, and then the assumption of normality for the n-back test scores was assessed using the Shapiro–Wilk test, which indicated a non-normal distribution. Therefore, the Wilcoxon signed-rank

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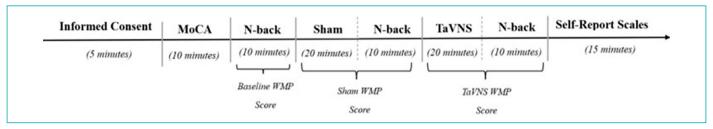


Figure 2. Research protocol.

MoCA: Montreal cognitive assessment, taVNS: Transcutaneous auricular vagus nerve stimulation, WMP: Working memory performance.

test was employed to assess the difference in n-back scores before and after the taVNS administration (Md=64, n=30), z=-4,789, p<0.05 compared to baseline (Md=57, n=30), z=-4,602, p<0.05 and sham (Md=57, n=30), z=-0.48, p<0.05. According to Wilcoxon signed-rank test, there is a significant difference between taVNS and baseline (z=-4,789, p<0.001); taVNS and sham (z=-4,602, p<0.001). Therefore, results indicate that participants' WMP is higher in taVNS sessions compared to baseline and sham sessions. However, there is no significant difference between baseline and sham (z=-0.048, p>0.001). Therefore, this supports that there is no placebo effect of taVNS; hence, its effect on WMP is accurate. Test statistics of Wilcoxon signed-rank test as shown in Table 1.

Results

Descriptive Analysis

Thirty participants, 50% were female, 50% were male. 67% were in the 18–24 year range, 63% were in the 24–34 year range, and 30% were in 35–45 year range. Most of the participants, 40% were postgraduates, 13.3% had high school degrees, 33.3% had an undergraduate degree, and 13.3% were Ph.D. students. 3.3% of the participants reported low socioeconomic status (SES), 60.9% reported medium SES and 36.7% of them reported low SES. 63.3% of the participants to use up to 20 mg of alcohol weekly whereas 36.7% of them use 20–40 alcohol weekly. 80% of the participants drink up to 2 cups of coffee daily, whereas 20% of them drink 3–5 cups daily.

Pre taVNS and Post taVNS Evaluation Scores of the Participants

The difference in n-back scores across conditions that refers to H1 was assessed using the Wilcoxon signed-rank test. Participants completed the n-back task at 3 time points: baseline, after sham stimulation, and after taVNS administration.

H1: There is a significant effect of taVNS on WM.

The results indicated a statistically significant increase in WMP following taVNS (Md=64, n=30), as compared

to both baseline (Md=57, z=-4.789, p<0.001) and sham stimulation (Md=57, z=-4.602, p<0.001). However, no significant difference was found between baseline and sham conditions (z=-0.048, p=0.962).

These results support the hypothesis that taVNS has a significant effect on WM, and the absence of a significant difference between sham and baseline further suggests that the observed effects are not due to placebo, but rather to the neuromodulatory influence of taVNS. Wilcoxon signed-rank test statistics are presented in Table 1.

Backward Multiple Linear Regression Analysis

By using the backward linear regression, it is aimed to see the relationship between sociodemographic and psychological factors with the taVNS effect. SES (Low, Mid, High), gender (female and male), age (18–24; 25–34; 35–45), SCL-90 (GSI and sub-dimensions: hostility, anxiety, phobic anxiety, paranoid ideation, interpersonal sensitivity, depression. somatization, psychoticism, obsessivecompulsive and other), attachment (avoidant and anxious), big five personalities (extraversion, openness, agreeableness, conscientiousness, and neuroticism) are included into the model. SPSS generated 14 models, among which Model 14 was selected for the evaluation of our hypothesis. The results derived from this model are presented in detail in Table 2.

In the 14th model, the dependent variable (taVNS effect) was regressed on predicting variables of attachment psychological symptoms (interpersonal sensitivity, anxiety,

Table 1. Pairwise comparison between taVNS, sham, and baseline conditions

	taVNS-baseline	taVNS-sham	Sham-baseline
Z	-4.789 ^b	-4.602 ^b	-0.048 ^c
р	0.000*	0.000*	0.962

*p<0.001: Wilcoxon Signed Ranks, taVNS: Transcutaneous Auricular Vagus Nerve Stimulation, Sham: The taVNS session in which the participant had received a sham treatment. Baseline: Before taVNS implementation, b: Based on negative ranks, c: Based on positive ranks.

Table 2. Backward multiple linear regression analysis predicting working memory performance (Model 14)

	Unstandardized Coefficients		Standardized Coefficients		
	В	SE	Beta	t	р
(Constant)	12.681	1.059	_	11.979	<0.001
Avoidant attachment	-1.273	0.290	-0.801	-4.393	0.00*
Anxious attachment	0.880	0.334	0.461	2.636	0.015*
Interpersonal sensitivity	0.820	0.275	0.403	2.979	0.007*
Hostility	-1.353	0.513	-0.349	-2.634	0.015*
Phobic anxiety	-1.109	0.392	-0.444	-2.831	0.010*

^{*:} p<0.001: Backward multiple linear regression analysis, B: Unstandardized regression coefficient, SE: Standard error of the coefficient, Beta: Standardized regression coefficient, t: t-value.

Table 3. ANOVA table for Model 14: Predicting the effect of taVNS

	SS	df	MS	F	р
Regression	251.781	7	35.969	11.465	<0.001*
Residual	69.019	22	3.137		
Total	320.800	29			

^{*:} p<0.05: ANOVA. ANOVA: Analysis of variance, Model 14: Final step of the backward linear regression analysis, taVNS: Transcutaneous auricular vagus nerve stimulation, SS: Sum of squares, df: Degrees of freedom, MS: Mean square (SS/df),F: F-ratio (ANOVA test statistics).

hostility, and phobic anxiety). As shown in Table 3, the independent variables apart from anxiety and depression significantly predict the taVNS effect, F (7,22) = 11,464, p<0.001 in the 14th model. R²=0.785 depicts that the model explains 78.5% of the variance in the taVNS effect.

In addition, coefficients were further assessed to ascertain the influence of each factor on the criterion variable (taVNS effect). The following hypothesis was proposed: H2: There is a significant negative impact of psychological symptoms (somatization, hostility, interpersonal sensitivity, phobic anxiety, depression, anxiety, paranoid ideation, psychoticism, and obsessive–compulsive) on the effect of taVNS. H3: There is a significant impact of Big Five personality on the taVNS effect. H4: There is a significant negative impact of attachment styles on the taVNS effect.

H2 evaluates whether dimensions in SCL-90 that is used to assess the psychological symptoms, significantly and negatively influence the taVNS effect. The results revealed that people with high interpersonal sensitivity (B=0.820, t=2,979, p<0.05), lower hostility (B=1,353, t=-2,634, p<0.05), and lower levels of phobic anxiety (B=-1,109, t=-2,831, p<0.05) had a greater effect of taVNS. Hence, H1 is partially supported since two dimensions in SCL-90 negatively influence the taVNS effect. In addition, H3 evaluates whether

the big five personalities significantly influence the taVNS effect. According to the fourteenth model, personality has no significant effect on the taVNS effect. Finally, H4 evaluates whether avoidant and anxious attachment styles significantly influence the impact of taVNS. According to the results, people with lower levels of avoidant attachment (B=-1,273, t=-4,393, p<0.05) and higher levels of anxious attachment (B=0.880, t=2,636, p<0.05) had a greater effect of taVNS. H3 is partially supported since avoidant attachment negatively influences the taVNS effect.

Discussion

This study investigated the acute and offline effects of taVNS on WMP, along with the role of psychological symptoms, attachment styles, and personality traits. The results demonstrated that taVNS significantly improved WMP, while no significant difference was found between baseline and sham sessions. This suggests that a 20-minutes offline taVNS session can effectively activate the PNS and enhance cognitive performance. Moreover, individuals with avoidant attachment, higher hostility, and phobic anxiety, as well as lower anxious attachment and interpersonal sensitivity, benefited less from taVNS.

Our findings partially supported the hypothesis that psychological symptoms negatively influence the taVNS effect. Among the nine SCL-90-R dimensions, hostility and phobic anxiety showed significant negative associations. Previous research has linked hostility to reduced parasympathetic activity and autonomic imbalance due to chronic stress. This could explain the diminished responsiveness to taVNS in individuals with high hostility.

The study found contrasting effects of attachment styles on taVNS responsiveness. Anxious attachment was positively associated with taVNS effects, while avoidant attachment showed a negative association. These results align with 68 BAU Health and Innovation

psychobiological models indicating that anxiously attached individuals exhibit heightened emotional reactivity and interoceptive sensitivity, [36] potentially enhancing their responsiveness to vagal modulation. In contrast, avoidantly attached individuals tend to suppress emotional needs and display reduced vagal tone and interoceptive awareness making them less receptive to taVNS stimulation. [37,38]

Although we hypothesized that Big Five personality traits would influence taVNS effects, no significant associations were found. Prior studies suggest traits like conscientiousness and low neuroticism are linked to better health outcomes and ANS function. [37,38] However, uneven trait distribution among participants may have limited our ability to detect effects, as statistical power is sensitive to sample balance. [37,38]

Conclusion

This study highlights the intricate interplay between taVNS, WMP, and individual psychological factors. This research offers a comprehensive perspective by examining acute and offline taVNS effects while considering psychological symptoms, attachment styles, and personality traits.

The findings reveal taVNS's potential to enhance cognitive performance, especially in individuals with distinct psychological profiles, and contribute to a nuanced understanding of these effects. Despite complexities, the study's holistic approach and alignment with existing literature bolster its significance.

Disclosures

Ethics Committee Approval: The study was approved by the İstanbul Medipol University Non-interventional Clinical Research Ethics Committee (no: E-10840098-772.02-2574, date: 25/04/2023).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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