Research Article

Effect of Noisy Galvanic Vestibular Stimulation on Spatial Learning and Memory of Rats

Bahareh Soufinia[1,2], Younes Lotfi[1,2*], Mohammad Ali Mirshekar[3], Moslem Shaabani[2], Enayatollah Bakhshi[4]

[1.] *Psychosis Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran*
[2.] *Department of Audiology, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran*
[3.] *Clinical Immunology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran*
[4.] *Department of Biostatistics, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran*

Use your device to scan and read the article online

Citation: Soufinia B, Lotfi Y, Mirshekar MA, Shaabani M, Bakhshi E. Effect of Noisy Galvanic Vestibular Stimulation on Spatial Learning and Memory of Rats. Aud Vestib Res. 2024;33(3):263-72.

https://doi.org/10.18502/avr.v33i3.15508

Highlights

- GVS activates the multisensory network in the cortical and hippocampal areas
- The improvement of spatial memory in the Morris water maze test
- The spontaneous neuronal firing pattern are increased after nGVS induction

Article info:
Received: 14 Nov 2023
Revised: 24 Dec 2023
Accepted: 14 Jan 2024

* **Corresponding Author:**
Department of Audiology, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.
yo.lotfi@uswr.ac.ir

ABSTRACT

Background and Aim: Previous studies have shown promising findings on effectiveness of noisy Galvanic Vestibular Stimulation (nGVS) in various cognitive disorders. The connections of the vestibular system with the hippocampus has been proven. Here we investigated the effect of vestibular galvanic stimulation on the improvement of spatial learning and memory of rats.

Methods: Twelve Wistar rats were randomly divided into control and nGVS groups. The nGVS group underwent 30-minute sessions of stimulation at sub-threshold levels for a duration of fourteen days. Following the intervention, both groups underwent assessments of cognitive indices through the Morris water maze task, hippocampal neuronal spike rate by Single-Unit Recording (SUR) and the concentrations of c-fos protein in the hippocampus were measured using ELISA device.

Results: The nGVS group exhibited a significant difference compared to the control group in both the time taken to reach the target platform and the percentage of time spent in the goal quarter during the Morris water maze test. The nGVS treatment significantly enhanced spike rate of hippocampal dentate gyrus ($p<0.01$) compared to the control group. Additionally, c-fos protein concentrations were increased in the nGVS (5.833) than the control group (4.126), ($p<0.001$).

Conclusion: According to the obtained results, nGVS plays a role in improving spatial memory, and a longer duration of intervention is suggested to achieve more obvious improvement results.

Keywords: Galvanic vestibular stimulation; spatial cognition; single-unit recording; hippocampus; rat

Introduction

Noisy Galvanic Vestibular Stimulation (nGVS), encompassing techniques like transcranial Alternating Current Stimulation (tACS), as well as Direct Current (DC) stimulation, constitutes non-invasive and comparatively safe methods that have found application in various research endeavors. The type of stimulation noise exerts an influence on the system, modulating its performance favorably contingent upon the presence of irregular vestibular neurons and the level of stimulation [1]. It has been reported that this stimulation prompts alterations in synaptic plasticity through the release of excitatory neurotransmitters, with glutamate playing a significant role [2].

There are direct connections between the hippocampus and vestibular nerves [3]. Noteworthy, defects in the vestibular system have been linked to balance disorders, posture irregularities, and may further extend to atrophic and functional issues within the hippocampus [4, 5]. Individuals with vestibular denervation in these conditions exhibit difficulties in spatial orientation, and this is correlated with a reduction in hippocampal volume [6, 7].

Under rotational conditions and vestibular stimulation, Long-Term Potentiation (LTP) within the basal dendrites of CA1 (The first region in the hippocampal circuit) of the hippocampus surpasses that observed in resting states. Furthermore, rotation induces adjustments in the activity of spatial cells, consequently leading to improvements in spatial tasks, memory, and learning [8]. Studies have additionally illuminated the stimulation of cortical pathways, including parietal, hippocampal, and striatal regions, during galvanic stimulation, underscoring their significance in spatial abilities modulation [9, 10]. Investigations have emphasized the pivotal role of the c-fos protein in evaluating the effectiveness of GVS on the hippocampus and spatial memory in rats [11]. Moreover, its levels are correlated with Acetylcholine (ACh) release in the hippocampus, which indicates the beginning of the strengthening mechanism in the hippocampus [12]. The application of GVS activates a multisensory network within cortical and hippocampal areas, with implications for ACh release in the hippocampus [3].

Augmented ACh levels correlate with an increase in c-fos expression in the hippocampus, underscoring the protein's involvement in long-term and spatial memory formation [13]. Leveraging the in vivo extracellular Single-Unit Recording (SUR) technique, a prior investigation demonstrated alterations in the spontaneous activity of hippocampal neurons, encompassing changes in spontaneous firing rate and neuronal excitability following stimulation. These observed electrophysiological changes were intricately linked to the mechanisms underlying memory consolidation [14].

To the best of our knowledge, there is no published scientific report on the effects of nGVS on learning and memory in healthy rats. Therefore, the present study intended to examine the preventive effects of nGVS on avoidance memory, spatial learning, memory and hippocampal SUR determined whether these neuroprotective effects were modulated through of c-fos protein concentrations in the brain, behavioral tests and molecular assessment. In this type of stimulation, the noisy stimulus is presented through the implanted extra-cranial electrodes.

Methods

Animals: a cohort of twelve male Wistar rats, aged 5 months and weighing between 220–270 grams. The rats were placed under standard conditions, with a 12:12 light-dark cycle and free access to food and water. These rats were purchased from the animal laboratory of Zahedan University of Medical Sciences and the research was also conducted in this laboratory.

The rats were subsequently randomized into two groups, with distinctive markings employed for group differentiation. One group underwent daily vestibular noisy galvanic intervention for 30 minutes over the course of two weeks. In addition, before the intervention, the rats were examined using the landing reflex test and the absence of balance disorders was confirmed in them [15]. Following intervention completion, spatial memory was assessed via the Morris Water Maze (MWM) test. Subsequently, rats were euthanized, and their hippocampi extracted for c-fos protein level examination. The chart of research steps is shown in Figure 1.

Figure 1. The flowchart of the research steps. nGVS; noisy galvanic vestibular stimulation, MWM; Morris water maze

Noisy galvanic vestibular stimulation

The intervention involved the insertion of cathodic and anodic copper wire electrodes, positioned 1 cm posterior to the earlobe, aided by an angiocath. This method involves connecting an electrode, composed of a copper wire measuring 51 mm in length and 1 mm in diameter, is connected to the tip of a gray angiocath needle, which has dimensions of approximately 1.7 in length and 45 mm in diameter. The electrode is then implemented under the skin of the mastoid area, akin to pricking with a needle, such that it rests parallel to and approximately 1 cm away from the earlobe. In order to mitigate the risk of skin infections resulting from electrode implantation, topical application of 3% tetracycline ointment was administered twice daily for a period of three days. The stimulation was delivered via Banafan Electric device, set at a sub-threshold level.

A two-day resting period ensued for wound healing, with tetracycline and vitamin A administered for recovery support. Stimulation commenced at 0 mA and progressed incrementally, with the threshold determined based on observable head movement and unusual behavior in the rats. Stimulation was subsequently administered at a level below this threshold within the 0–16 Hz frequency range, reflecting a weak noise current. In accordance with prior studies showcasing its efficacy, this stimulation regimen persisted for 14 days, with daily sessions lasting 30 minutes [15, 16].

Shuttle box for passive avoidance test

The shuttle box test was performed to confirm the absence of memory impairment. The shuttle box setup had two compartments, one dark and one light. The chamber floor has stainless steel rods spaced 1 cm apart. Initially, each rat spent 10 minutes in the light compartment without electric shocks to acclimate. On the second day, rats were placed in the light compartment for 10 seconds. Naturally, they moved to the dark section. The time taken to enter the dark compartment was noted as Initial Latency (IL). On the third day, the door between compartments closed, and a 3-second electric shock (50 Hz, 1 mA) was given. After five minutes, rats were removed. On the fourth day, the door opened after 10 seconds, and the time taken to enter the dark area was recorded as Step-Through Latency (STL) [17].

Morris water maze task for spatial cognition

Employed to assess spatial memory, the MWM test featured rats navigating a tank filled with water to locate a target platform. The tank, measuring 150 cm in diameter and 60 cm in height, was coated internally with a black finish. The platform was approximately 1.5 cm below the water. The rats were trained according to a three-day training protocol. During the initial three days, the hidden platform was situated in the southwest quadrant of the tank, submerged approximately 1.5 cm below the water surface. The position of the platform remained unchanged throughout this three-day period. Each learning block consisted of four trials. In each trial, the animal was released into the water from one of four starting zones (north, south, east, and west), facing the wall of the tank. The animal was then allowed to swim and find the hidden platform. In each trial, the animal was given 120 seconds to locate the hidden platform. Once the platform was found, the rat was allowed to remain on it for 20 seconds before the onset of the next trial. After the end of the learning phase, the animal was dried with a towel and returned to its cage. On the fourth day, the hidden platform was removed, and a probe test was conducted. In this test, there was no platform in the tank. The animal was placed in one of the areas of the tank in the water and was allowed to swim in the tank for 60 seconds. After this time elapsed, the animal was removed from the tank [17]. In this test, the following values are checked: the time it takes for the animal to find the platform during each trial; the distance traveled by the animal to find the platform during each trial; the speed of the animal in finding the platform during

each trial; the amount of time the animal spends in each quadrant (the two latter criteria were used in the recall or probe test).

Electrophysiological investigation

This study involved in vivo single-unit recording from hippocampal pyramidal neurons conducted in anesthetized rats. Extracellular recordings of spontaneously active pyramidal neurons in the dentate gyrus region of the hippocampus were carried out over a period of approximately 20 minutes. The steps of recording single cells using the extracellular method have already been explained. Briefly, a tungsten microelectrode coated with parylene, featuring an exceptionally fine tip and a 1 megaohm impedance, was precisely inserted into the Hippocampal Dentate Gyrus (HDG) on the left side of the brain using stereotactic coordinates (AP=3.8 mm, ML=3.2 mm, DV=2.7 mm). Subsequently, a manual microdrive was employed to guide the electrode within the HDG until optimal spike activity was identified, ensuring a signal-to-noise ratio exceeding 2 by isolating it from background noise [14].

Determination of c-fos protein concentrations

To investigate the molecular implications of the intervention, we examined the levels of c-fos protein in the hippocampus. The animals were sacrificed and their entire skulls were removed. The hippocampus tissue was then frozen in liquid nitrogen and maintained at a temperature of 80 degrees Celsius. We homogenized the tissue in a 17-molar phosphate solution at a speed of 8000 minutes. After removing the tissue supernatant, it was frozen at a temperature of 37 degrees Celsius. Subsequently, we measured the supernatant solution at a wavelength of 523 nm, using a volume of 1 ml.

In this study, we measured the level of c-fos protein using the Zell Bio GnbH c-fos pro kit and ELISA device.

Statistical analysis

Prism statistical software version 8.4.3 was employed for data analysis. The Shapiro-Wilk test was employed to verify data normality. Considering the normality of the data, the t-test was used to check the goal quadrant percentages on the probe day, the level of c-fos protein and neuronal firing between two groups.

Results

Shuttle box task results

Results of initial latency parameter in the shuttle box test

Due to the normality of the data based on the Shapiro-Wilk test, unpaired t-test was administered. The mean of the control group was 18.33 and the mean of the nGVS group 14.17. No significant difference was observed in the average IL between the control and nGVS (4.167±2.267, p=0.095) as shown in Figure 2.

Results of step-through latency analysis in the shuttle box test

On the fourth day, the mean of STL was in the control group (258.3) and in the nGVS group (250), no significant difference was observed in the average STL between the control and nGVS, (8.333±23.86, p=0.734) as shown in Figure 3.

Morris water maze results

Mean path length on training days

Repeated measurement two-way ANOVA of the path lenght to find the escape platform demonstrated a significant effect in time ($F_{(2,20)}$=17.4; p<0.001) across all training trial days. However, no significant significant effects of stimulation ($F_{(1,10)}$=0.135; p>0.05) and

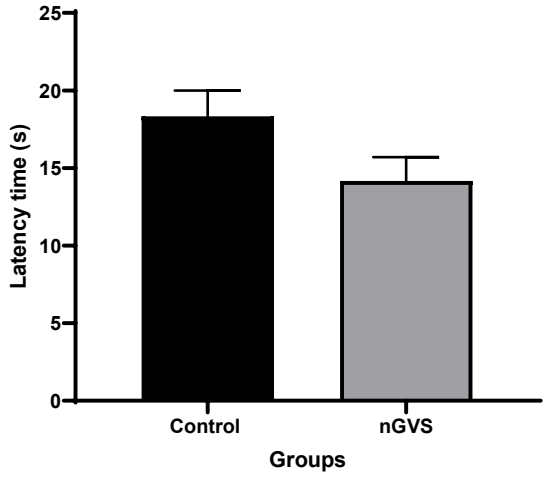

Figure 2. The average of initial latency incontrol and noisy galvanic vestibular stimulation rats in the training days. nGVS; noisy galvanic vestibular stimulation

treatment×time interaction effect was detected during the training trial days ($F_{(2,20)}$=0.158; p=0.720).

The difference in the mean of the path length was observed between the two groups on the first (4.27±286), second (192±286) and third day (4.03±286). There was no significant statistical difference between the two groups in the mean distance traveled to reach the target platform on training days (Figure 4).

Mean velocity on training days

Repeated measurment two-way ANOVA of the speed to find the escape platform demonstrated a significant effect in time ($F_{(1.83,18.3}$=21.8; p<0.001) across all training trial days. However, no significant significant effects of stimulation ($F_{(1,10)}$=0.2.54; p>0.05) and treatment×time interaction effect was detected during the training trial days ($F_{(2,20)}$=0.158; p=0.3386).

The difference in the mean of the velocity was observed between the two groups on the first (0.648±4.51) second (1.83±4.05) and third day (9.44±4.66). There was no statistically significant difference between the two groups in the mean speed traveled to reach the target platform (Figure 5).

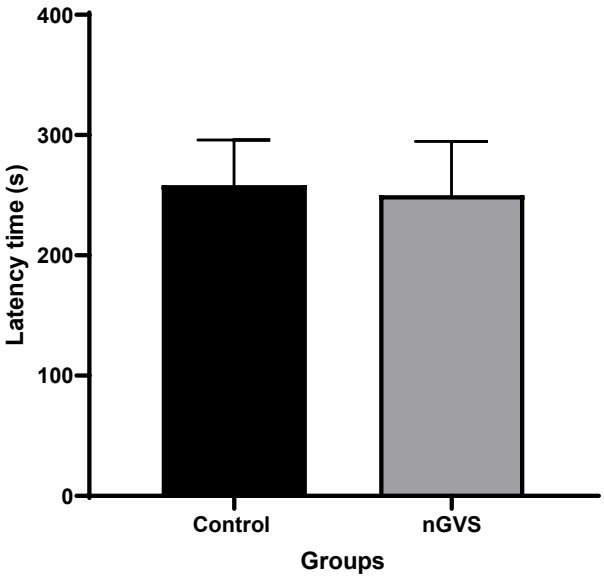

Figure 3. The average step-thought latency in control and noisy galvanic vestibular stimulation rats in training days. nGVS; noisy galvanic vestibular stimulation

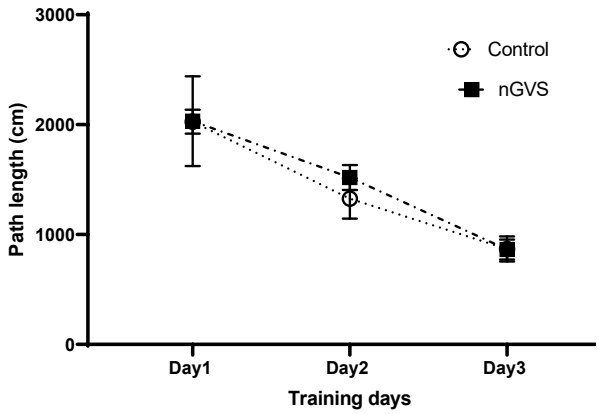

Figure 4. The average of path length in control and noisy galvanic vestibular stimulation rats in the training days. nGVS; noisy galvanic vestibular stimulation

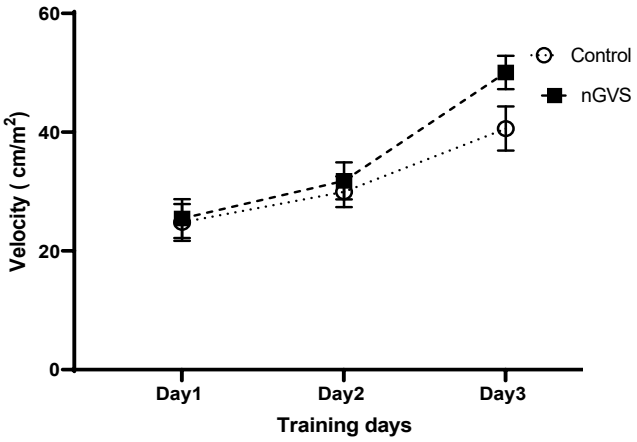

Figure 5. The average of velocity in control and noisy galvanic vestibular stimulation rats in the training days. nGVS; noisy galvanic vestibular stimulation

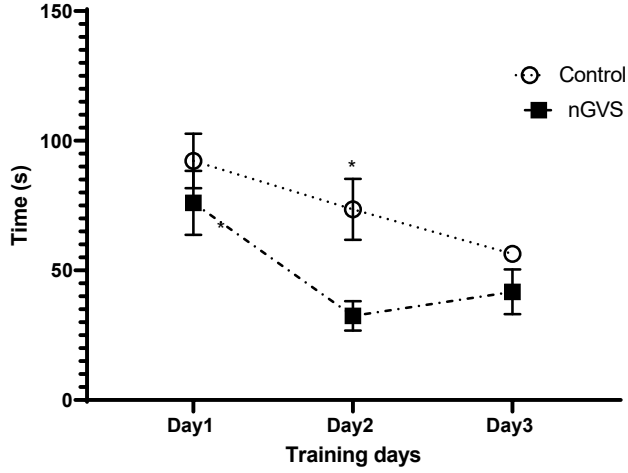

Figure 6. The average of latency to reach the target platform in control and noisy galvanic vestibular stimulation rats in the training days. nGVS; noisy galvanic vestibular stimulation

Mean scape latency reaches to target platform on training days

Repeated measurement two-way ANOVA of the scape latency to reach the platform demonstrated significant effects of stimulation ($F_{(1,10)}$=10.6; p<0.01) and time ($F_{(1.87,18.7)}$=8.46; p<0.01) across all training trial days. However, no significant treatment×time interaction effect was detected during the training trial days ($F_{(2,20)}$=1.27; p=0.3035).

The difference in the mean of the scape latency was observed between the two groups on the first (16.2±16.2) second (41.1±13) and third day (14.6±8.87). a statistically significant difference was observed between the galvanic and control groups (41.1±13, p=0.045) in the meantime to reach the target platform only on the second day (Figure 6).

Mean time spent in goal quarter on training days

Repeated measurement two-way ANOVA of the scape latency to reach the platform demonstrated significant effects of stimulation ($F_{(1,10)}$=21.1; p<0.001) and time ($F_{(1.97,19.7)}$=12.4; p<0.001) across all training trial days. However, no significant treatment×time interaction effect was detected during the training trial days ($F_{(2,20)}$=2.09; p=0.150).

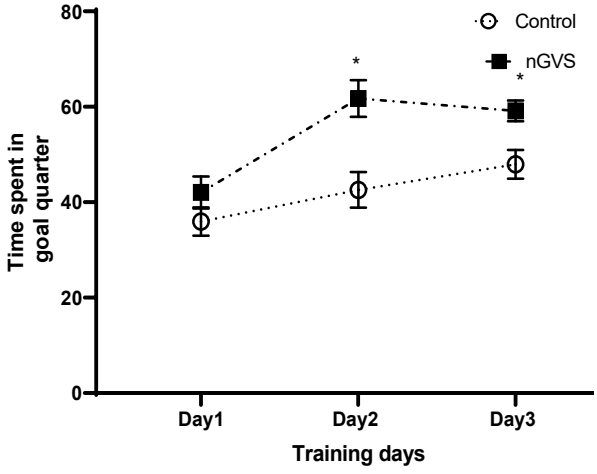

Figure 7. The percentage of the time spent in goal quarter between control and noisy galvanic vestibular stimulation rats in the training days. nGVS; noisy galvanic vestibular stimulation
* Comparing the control and nGVS rats on the second and the third day, p<0.05.

A statistically significant difference was observed in the mean time spent in the goal quarter on the second (19.2±5.35, p<0.05)and third day (11.2±3.71, p<0.05), and GVS group spent significantly more time in the goal quarter (Figure 7).

Mean time spent in goal quarter on probe day

The mean of time spent in the goal quarter on the probe day showed a significant difference between the two groups (16.29±5.38, p<0.05) (Figure 8).

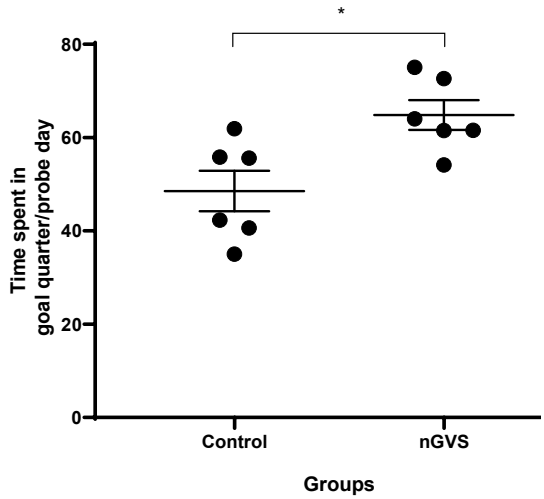

Figure 8. The percentage of the time spent in goal quarter for each rat in control and noisy galvanic vestibular stimulation rats in the probe day. nGVS; noisy galvanic vestibular stimulation
* Comparing the control and nGVS rats, p<0.05.

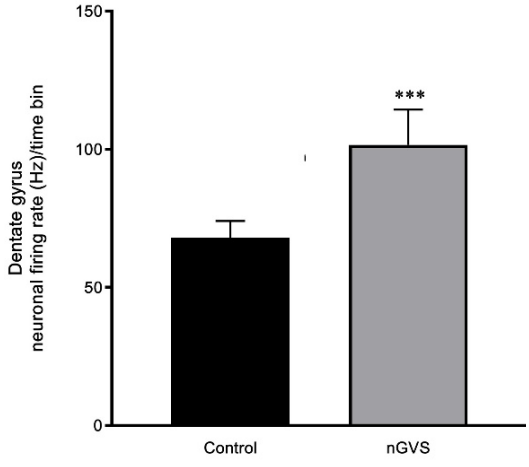

Figure 9. Average number of spikes/bin in the control and noisy galvanic vestibular stimulation rats. Data is presented as mean±SEM. nGVS; noisy galvanic vestibular stimulation
*** Comparing the control and nGVS rats, p<0.001

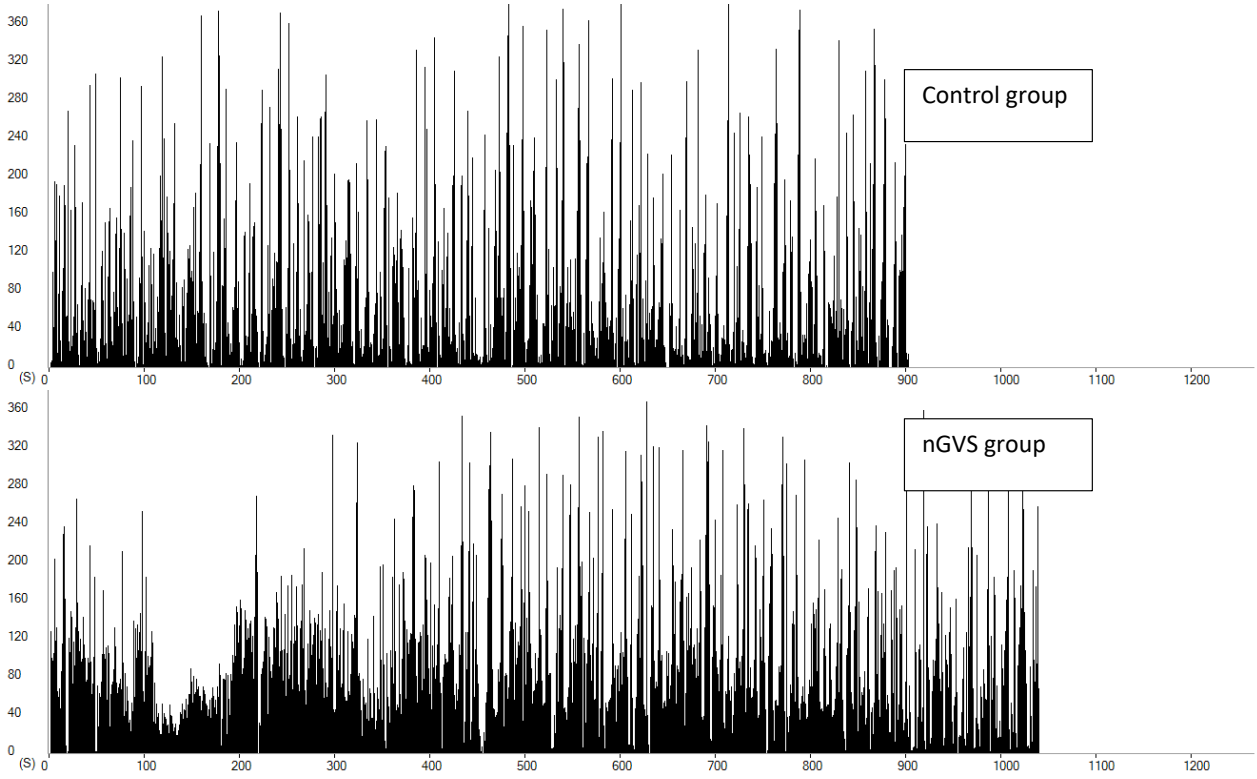

Figure 10. Representative tracings of spontaneous firing pattern of dentate gyrus neurons. Above image: control group. Bottom image: noisy galvanic vestibular stimulation

The impact of noisy galvanic vestibular stimulation on the firing rate of neurons in the hippocampal dentate gyrus

SUR was employed to assess the frequency of neuronal firing in the dentate gyrus area. The spike count per bin was determined over a 1200-second duration for all experimental groups. Figure 9 displays representative tracings and a magnified view of a sample spike depicting the neuronal activity of granular cells. The nGVS group exhibited a statistically significant increase in the number of spikes per time compared to the control group ($p<0.001$). The crude pattern of SUR is shown in Figure 10.

The impact of noisy galvanic vestibular stimulation on the level of c-fos protein

A significant statistical difference was observed between the two groups. The c-fos protein concentrations in the nGVS group were significantly higher than the control group (1.707±0.5054, $p<0.001$), (Figure 11).

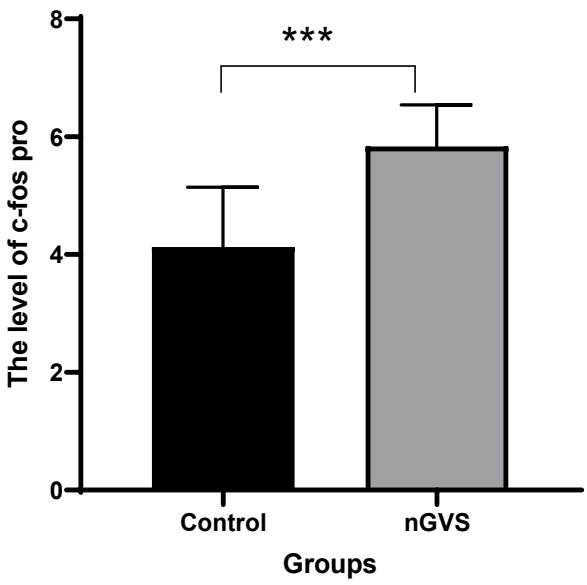

Figure 11. The difference of the level c-fos protein concentrations in control and noisy galvanic vestibula stimulation rats. nGVS; noisy galvanic vestibular stimulation

*** Comparing the control and nGVS rats, $p<0.001$

Discussion

The vestibular system plays a crucial role in maintaining and stabilizing posture, as evidenced by its influence on both the vestibule-spinal reflex and the vestibule-ocular reflex pathways. These pathways work together to contribute to the preservation of posture and gaze stability [18]. One pathway is the transmission of vestibular information related to the head direction of the vestibular nerves to the dorsal tegmental, lateral mammillary nucleus and anterior-posterior thalamic nucleus to the hippocampus, and the other pathway is the transmission of information from the vestibular nerves to the pontine reticular structure through the supra mammillary nucleus and the internal septum to the hippocampus [3].

The nGVS intervention, which involves the application of cathodic and anodic electrodes for current delivery, impacts both the peripheral vestibular organs (i.e. semicircular canals and otoliths) and the central vestibular system. Optimal results have been observed when applying noisy stimulation at a sub-threshold level within the system's preferred frequency range of 0–30 Hz, highlighting the efficacy of this approach [19, 20], According to the finding of this study, there were no significant differences observed in the path length and velocity criteria between the groups. In these two criteria, no significant difference was observed between the two groups on training days. However, in each group, between the first and third day, an increase in velocity and a decrease in the distance traveled to reach the target platform was observed. It has been mentioned in the study that speed and distance criteria do not have a specific relationship with cognition [21]. However, there was a statistically significant difference in the average time taken to reach the target platform on the second day, with the nGVS demonstrating a shorter mean time. Additionally, there was a significant disparity in the mean of time the rats spent by the rats in the goal quarter on the second and third day. With the nGVS group spending a higher percentage in this area. This difference remained significant during probe day as well. The results of the study demonstrate that the nGVS group exhibited a reduction in time to reach the platform and an increase in time spent in the goal quarter on training days, indicating improved spatial memory and ability to remember the location of the platform. On the probe day, the nGVS group spent a significantly higher percentage of time in the goal quarter compared to the control group, indicating the effect of nGVS on spatial memory. This finding is consistent with previous study that have highlighted the role of this measure in enhancing spatial memory in rats [11].

ACh serves as a modulator of cognitive functions such as arousal, attention, learning, and memory. Moreover, evidence suggests its role in sustaining synaptic transmission in the hippocampus [22]. Augmented ACh levels correlate with an increase in c-fos expression in the hippocampus. The Fos gene and the c-fos protein indirectly correlate with heightened neuronal activity in the hippocampus, with particular emphasis on its recurrence under learning conditions [23]. The study found that the level of c-fos protein in the group receiving nGVS was significantly higher than the control group.

Furthermore, Hilliard et al. reported that nGVS enhances spatial learning and increases hippocampal sensitivity to spatial information in both men and women. The study also mentions that individuals with low memory capacity may benefit more from this intervention [24]. Besides, the potential role of this stimulation in cognitive disorders is discussed [25, 26]. In a study on rats with bilateral labyrinthectomy, stimulation with an amplitude of 0.1 mA for 30 minutes daily improved spatial memory in the MWM and Y maze tests [16]. Amelioration of dentate gyrus neurons function accompanied by variation in the electrical activity, including the spontaneous firing rate [27]. The magnitude of spikes, and the spontaneous neuronal firing pattern are increased after nGVS induction. Additionally, in a study on healthy rats, vestibular stimulation showed more specific results compared to memory-facilitating drugs. It caused activation of the hippocampus, parietal cortex, and retrosplenial cortex. The study also reported an increase in dendritic branches and synaptic connections in pyramidal neurons of the hippocampus [28]. Vestibular stimulation increases LTP in hippocampal synapses, which is necessary for spatial information processing. In rat models, it has been observed that LTP of basal dendrite in hippocampal increases with vestibular stimulation [8]. This suggests that GVS can be used to improve memory functions in the hippocampus, likely due to the connection between the vestibular system and the hippocampus [3, 29]. It cannot be presumed that enhancing the amplitude and duration of stimulation will necessarily result in improved effects. This phenomenon underscores the importance of

determining optimal stimulation parameters, including both duration and intensity, based on preclinical data.

Conclusion

Based on the conducted studies and the established correlation between the vestibular system and the hippocampus, as well as the outcomes derived from this research, it can be inferred that galvanic stimulation through vestibular demonstrates efficacy in enhancing spatial memory. Due to the improvement of spatial memory in the Morris water maze test and the confirmed increase the level of the c-fos pro in the hippocamp.

Ethical Considerations

Compliance with ethical guidelines

The experimental procedures were conducted in compliance with the guidelines established by the National Institutes of Health (NIH) for the care and use of laboratory animals and were approved by the University of Social Welfare and Rehabilitation Sciences, Tehran, IRAN (IR.USWR.REC.1401.183).

Funding

This study was the PhD. project supported by University of Social Welfare and Rehabilitation Sciences (Code: 1402/801/ت/3981).

Authors' contributions

BS: Study design, acquisition of data, interpretation of the results, statistical analysis, and drafting the manuscript; YL: Study design, interpretation of the results, and drafting the manuscript; MAM: Study design, acquisition of data, interpretation of the results, statistical analysis, and drafting the manuscript; MS: Study design, interpretation of the results; EB: Statistical analysis.

Conflict of interest

There are no competing financial interests.

Acknowledgments

We thank of all personnel of University of Zahedan and University of Medical Sciences of Zahedan especially Mr. Mohsen Rashidi Ravari and Miss Mahsa Rohani Anaraki who helped us in this research.

References

1. Goldberg JM. Afferent diversity and the organization of central vestibular pathways. Exp Brain Res. 2000;130(3):277-97. [DOI:10.1007/s002210050033]

2. Chan YS, Chen LW, Lai CH, Shum DK, Yung KK, Zhang FX. Receptors of glutamate and neurotrophin in vestibular neuronal functions. J Biomed Sci. 2003;10(6 Pt 1):577-87. [DOI:10.1159/000073522]

3. Previc FH. Vestibular loss as a contributor to Alzheimer's disease. Med Hypotheses. 2013;80(4):360-7. [DOI:10.1016/j.mehy.2012.12.023]

4. Lopez C, Blanke O, Mast FW. The human vestibular cortex revealed by coordinate-based activation likelihood estimation meta-analysis. Neuroscience. 2012;212:159-79. [DOI:10.1016/j.neuroscience.2012.03.028]

5. Bense S, Stephan T, Yousry TA, Brandt T, Dieterich M. Multisensory cortical signal increases and decreases during vestibular galvanic stimulation (fMRI). J Neurophysiol. 2001;85(2):886-99. [DOI:10.1152/jn.2001.85.2.886]

6. Holstein GR, Friedrich VL Jr, Martinelli GP, Ogorodnikov D, Yakushin SB, Cohen B. Fos expression in neurons of the rat vestibulo-autonomic pathway activated by sinusoidal galvanic vestibular stimulation. Front Neurol. 2012;3:4. [DOI:10.3389/fneur.2012.00004]

7. Zheng Y, Darlington CL, Smith PF. Bilateral labyrinthectomy causes long-term deficit in object recognition in rat. Neuroreport. 2004;15(12):1913-6. [DOI:10.1097/00001756-200408260-00016]

8. Tai SK, Leung LS. Vestibular stimulation enhances hippocampal long-term potentiation via activation of cholinergic septohippocampal cells. Behav Brain Res. 2012;232(1):174-82. [DOI:10.1016/j.bbr.2012.04.013]

9. Kim DJ, Yogendrakumar V, Chiang J, Ty E, Wang ZJ, McKeown MJ. Noisy galvanic vestibular stimulation modulates the amplitude of EEG synchrony patterns. PLoS One. 2013;8(7):e69055. [DOI:10.1371/journal.pone.0069055]

10. Lee JW, Lee GE, An JH, Yoon SW, Heo M, Kim HY. Effects of galvanic vestibular stimulation on visual memory recall and EEG. J Phys Ther Sci. 2014;26(9):1333-6. [DOI:10.1589/jpts.26.1333]

11. Adel Ghahraman M, Zahmatkesh M, Pourbakht A, Seifi B, Jalaie S, Adeli S, et al. Noisy galvanic vestibular stimulation enhances spatial memory in cognitive impairment-induced by intracerebroventricular-streptozotocin administration. Physiol Behav. 2016;157:217-24. [DOI:10.1016/j.physbeh.2016.02.021]

12. Duelli R, Schröck H, Kuschinsky W, Hoyer S. Intracerebroventricular injection of streptozotocin induces discrete local changes in cerebral glucose utilization in rats. Int J Dev Neurosci. 1994;12(8):737-43. [DOI:10.1016/0736-5748(94)90053-1]

13. Jee YS, Ko IG, Sung YH, Lee JW, Kim YS, Kim SE, et al. Effects of treadmill exercise on memory and c-Fos expression in the hippocampus of the rats with intracerebroventricular injection of streptozotocin. Neurosci Lett. 2008;443(3):188-92. [DOI:10.1016/j.neulet.2008.07.078]

14. Arabmoazzen S, Mirshekar MA. Evaluation of the effects of metformin as adenosine monophosphate-activated protein kinase activator on spatial learning and memory in a rat model of multiple sclerosis disease. Biomed Pharmacother. 2021;141:111932. [DOI:10.1016/j.biopha.2021.111932]

15. Shaabani M, Lotfi Y, Karimian SM, Rahgozar M, Hooshmandi M. Short-term galvanic vestibular stimulation promotes functional recovery and neurogenesis in unilaterally labyrinthectomized rats. Brain Res. 2016;1648(Pt A):152-62. [DOI:10.1016/j.brainres.2016.07.029]

16. Nguyen TT, Nam GS, Han GC, Le C, Oh SY. The Effect of Galvanic Vestibular Stimulation on Visuospatial Cognition in an Incomplete Bilateral Vestibular Deafferentation Mouse Model. Front Neurol. 2022;13:857736. [DOI:10.3389/fneur.2022.857736]

17. Mirshekar MA, Miri S, Shahraki A. A Survey of the Effects of Diosmin on Learning and Memory Following the Use of Paraquat Herbicide Poisoning in a Model of Rats. Shiraz E-Med J. 2020;21(5):e94143.[DOI:10.5812/semj.94143]

18. Lopez C, Blanke O. The thalamocortical vestibular system in animals and humans. Brain Res Rev. 2011;67(1-2):119-46. [DOI:10.1016/j.brainresrev.2010.12.002]

19. Moss F, Ward LM, Sannita WG. Stochastic resonance and sensory information processing: a tutorial and review of application. Clin Neurophysiol. 2004;115(2):267-81. [DOI:10.1016/j.clinph.2003.09.014]

20. McDonnell MD, Abbott D. What is stochastic resonance? Definitions, misconceptions, debates, and its relevance to biology. PLoS Comput Biol. 2009;5(5):e1000348. [DOI:10.1371/journal.pcbi.1000348]

21. Ning H, Cao D, Wang H, Kang B, Xie S, Meng Y. Effects of haloperidol, olanzapine, ziprasidone, and PHA-543613 on spatial learning and memory in the Morris water maze test in naïve and MK-801-treated mice. Brain Behav. 2017;7(8):e00764. [DOI:10.1002/brb3.764]

22. Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol. 1973;232(2):331-56. [DOI:10.1113/jphysiol.1973.sp010273]

23. Vann SD, Brown MW, Erichsen JT, Aggleton JP. Fos imaging reveals differential patterns of hippocampal and parahippocampal subfield activation in rats in response to different spatial memory tests. J Neurosci. 2000;20(7):2711-8. [DOI:10.1523/JNEUROSCI.20-07-02711.2000]

24. Hilliard D, Passow S, Thurm F, Schuck NW, Garthe A, Kempermann G, et al. Noisy galvanic vestibular stimulation modulates spatial memory in young healthy adults. Sci Rep. 2019;9(1):9310. [DOI:10.1038/s41598-019-45757-0]

25. Wilkinson D, Nicholls S, Pattenden C, Kilduff P, Milberg W. Galvanic vestibular stimulation speeds visual memory recall. Exp Brain Res. 2008;189(2):243-8. [DOI:10.1007/s00221-008-1463-0]

26. Wilkinson D, Ko P, Kilduff P, McGlinchey R, Milberg W. Improvement of a face perception deficit via subsensory galvanic vestibular stimulation. J Int Neuropsychol Soc. 2005;11(7):925-9. [DOI:10.1017/s1355617705051076]

27. Naghizadeh M, Mirshekar MA, Montazerifar F, Saadat S, Shamsi Koushki A, Jafari Maskouni S, et al. Effects of quercetin on spatial memory, hippocampal antioxidant defense and BDNF concentration in a rat model of Parkinson's disease: An electrophysiological study. Avicenna J Phytomed. 2021;11(6):599-609. [DOI:10.22038/AJP.2021.18526]

28. Devi NP, Mukkadan JK. Impact of rotatory vestibular stimulation in memory boosting. MOJ Anat Physiol. 2017;4(4):337-42. [DOI:10.15406/mojap.2017.04.00143]

29. Klatt BN, Ries JD, Dunlap PM, Whitney SL, Agrawal Y. Vestibular Physical Therapy in Individuals With Cognitive Impairment: A Theoretical Framework. J Neurol Phys Ther. 2019;43 Suppl 2 (Suppl 2 Spec INTERNATIONAL CONFERENCE ON VESTIBULAR REHABILITATION):S14-S19.