Research Article

Investigating the Subacute Effects of Two Vestibular Stimulation Methods and Their Combination on Spatial Memory in a Rat Model of Alzheimer's Disease

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Highlights

- Rotatory vestibular stimulation (RVS) improved the spatial memory
- The effects of noisy Galvanic Vestibular Stimulation (nGVS) was not stable
- The RVS alone or in combination with nGVS can improve spatial memory of rat with AD

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ABSTRACT

Background and Aim: Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline and spatial memory deficits. Recent studies have suggested a potential link between the vestibular system and cognitive function. Despite advancements in understanding the role of vestibular stimulation in neurological disorders, there is a paucity of research on this subject. In this regard, this study aims to assess the subacute effects two vestibular stimulation methods and their combination on spatial memory in a rat model of AD.

Methods: Thirty Wistar rats were divided into five groups of AD (without intervention), Rotational Vestibular Stimulation (RVS), noisy Galvanic Vestibular Stimulation (nGVS), nGVS+RVS, and healthy control. The intervention groups received stimulation for 14 days. After AD induction and its confirmation, to examine the sub-acute effects of the stimulation, their performance was assessed using the Morris Water Maze (MVM) test one month later.

Results: Statistically significant improvements were observed in the MVM test parameters in the RVS and nGVS+RVS groups compared to the AD group, in the training days and in the probe day, especially in the time to reach the platform and the time spent in the target quarter. Time spent in goal quarter improved in the RVS group compared to the nGVS+RVS group, but the difference was not statistically significant.

Conclusion: The RVS alone or in combination with nGVS can improve spatial memory of rats with AD.

Keywords: Alzheimer's disease; vestibular stimualtion; spatial memory; rat; rotational vestibular stimulation; noisy galvanic vestibular stimulation

Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by a syndrome that causes a cognitive decline and gradually affects daily functions [1, 2]. It has been estimated that, by 2050, the number of people with AD in the United States will reach approximately 14 million people. The prevalence of AD in people aged 67–87 years in Iran is estimated at 2.3% [3]. The etiology of AD involves the deposition of beta-amyloid plaques, tau pathology, and neurofibrillary tangles in vulnerable areas of the brain [4, 5]. The symptoms include a progressive memory decline, impaired executive functions, low visual orientation, motor system dysfunction [6], language disorders, and cognitive impairment. Both entorhinal cortex and hippocampus play major roles in encoding, consolidation, and retrieval of information and episodic memory. Patients with AD usually show severe injuries to the hippocampus, para-hippocampus, and medial temporal lobe [1]. Research indicates a high impairment in vestibular system function, especially the otolith and saccule compared to the semicircular canals, in people with AD compared to age-matched controls [7]. One hypothesis linking vestibular and cognitive disorders to each other, attributes the reduction of cholinergic inputs from the peripheral vestibular system to the medial temporal lobe and hippocampus [8].

A study investigated the effects of drug treatment and Rotational Vestibular Stimulation (RVS) on memory improvement of healthy rats. The finding revealed a notable increase in learning and memory among rats exposed to RVS [9]. Given the high risk of falling, pelvic fractures, and the associated care burdens and health costs, there is a need to prioritize fall prevention and balance enhancement in AD patient. Therefore, it is not enough to rely solely on RVS for treating these patients. Another study reported the effectiveness of noise Galvanic Vestibular Stimulation (nGVS) on improving spatial memory and increasing c-Fos protein levels in the hippocampus of rats with AD [10]. The release of acetylcholine and cholinergic pathway are important for encoding, consolidating, storing, and retrieving information in memory [11]. Therefore, AD patients often use acetylcholinesterase inhibitors such as Donepezil, Rivastigmine, and Galantamine to mitigate the disease progression [12, 13]. The c-Fos protein acts as a reliable neural marker, providing guidance for vestibular interventions [10]. Considering a connection between the vestibular system and the hippocampus, as evidenced by positive outcomes of Ngvs [14, 15] and RVS [9, 16] in improving behavioral outcomes and by molecular studies at the hippocampal tissue level, this study aimed to explore that the RVS alone or in combination with nGVS can improve spatial memory of rats with AD.

Methods

The steps of research are shown in Figure 1.

Animals

Animals were 30 male Wistar rats, aged 5 months and weighing 220–270 grams. They were randomly assigned to five groups: heathy (control), AD, RVS, nGVS, and nGVS+RVS. The rats were procured from the Animal Research Center of Zahedan University of Medical Sciences in Iran. Rats were housed in standard conditions with a 12:12 light-dark cycle. They had free access to food and water throughout the study.

Alzheimer's disease induction

After administering anesthesia by injecting ketamine (100 mg/kg) and xylazine (5 mg/kg), the rat's head

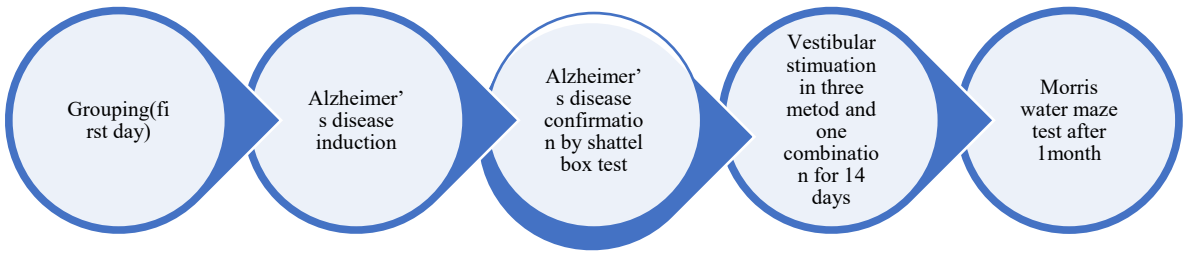

Figure 1. Flowchart of the study

was shaved and positioned in a stereotaxic machine. An incision was made in the scalp and the bregma and lambda areas were identified based on the Paxinos Brain Atlas. Following the atlas coordinates of AP=–0.5, ML=±1.5, and DV=–4, a hole was drilled to access the cerebral ventricles, after bilateral injection.

The acetate form of beta-amyloid and ibotenic acid (purity>98% by high-performance liquid chromatography) was purchased from Sigma-Aldrich Company (St. Louis, MO, USA). A 1-mg vial of beta-amyloid was dissolved in 200 µL of a 10% dimethyl sulfoxide solvent. Subsequently, the solution was aliquoted into microtubes containing a volume of 10 µL. To induce the formation of neurotoxic amyloid-beta fibrils, the solution underwent incubation at 37°C for 5–7 days. Finally, the surgical site was disinfected with penicillin and the incision was sutured.

Alzheimer's disease model confirmation

Seven days after inducing AD, the presence of the disease in the experimental rats was confirmed using the shuttle box task [17]. The used shuttle box apparatus (Iranian Omid Tajhizgostar company, Iran) has two compartments, one dark and the other light, with stainless steel rods spaced 1 cm apart on the chamber floor. Initially, each rat underwent a 10-minute acclimation period in the light compartment without exposure to electric shocks. On the second day, the rats were placed in the light compartment for 10 seconds, after which they naturally moved to the dark section. The time taken to enter the dark compartment was recorded as Initial Latency (IL) time. On the third day, the door between compartments was closed and a 3-second electric shock (50 Hz, 1 mA) was administered. After a five-minute interval, the rats were removed from the apparatus. Subsequently, 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) time.

Noisy galvanic vestibular stimulation

Electrodes, made from copper wire, were implanted at a distance of 1 cm from the earlobe and parallel to it using angiocath. This electrode implantation method was according to Shaabani et al.'s study [18]. Subsequently, a noise stimulus within the frequency range of 1–16 Hz was provided at an intensity below the threshold level (<0.2 mA) for 30 minutes and a span of 14 days. The stimulation was delivered using an electric device (Banafan Electric, Iran) set at a sub-threshold level.

Rotatory vestibular stimulation

The RVS was performed using a rotating chair designed for the animal model. This chair had a wooden surface with 46 cm in length, 18 cm in width, and 10 cm in height. The positioning place on this surface was a transparent octagonal cylindrical space, with 19 cm in length and height. Rats were put inside this glass space and the movement speed was controlled using keys installed on the box, maintaining a constant rotation speed of 50 rpm. This rotational stimulation was applied consistently for 30 minutes daily for 14 days.

Combined method

Taking into account the enhanced effectiveness of interventions when galvanic stimulation precedes motor stimulation [19], rats underwent nGVS first, immediately followed by RVS. Each intervention was administered for 30 minutes daily for 14 days. The mean threshold level for rats in nGVS group was 0.083 and for nGVS+RVS group it was 0.038.

Morris water maze task

The Morris Water Maze (MWM) task was employed for spatial memory assessment using a Morris machine (Technic Azma company, Tabriz, Iran). Rats were put in a circular tank with 150 cm in diameter and 60 cm in height, filled with water at a temperature of 21°C. Their task was to locate a submerged platform positioned 1.5 cm beneath the water surface. The MWM room was equipped with extra-maze markers, including a door, a computer, and postcards affixed to the wall. A camera, mounted on the ceiling directly above the tank, monitored the rats' movements. Utilizing the software's tracking and recording capabilities, the animals' swimming paths, latency time, path length, speed, and the time spent in the target quadrant were calculated for each trial. The rats underwent a three-day training protocol. On the fourth day, the hidden platform was removed, initiating a probe test. During this test, the animal was placed in a specific area of the tank and allowed to swim for 60 seconds in the probe day and 120 seconds in the training days. After this period, the animal was removed from the tank [20, 21].

Statistical analysis

The analyses were conducted in Prism v. 8.4.3 software. One-way ANOVA was used to compare the IL and STL (as measures for confirming AD in rats) and the amount of time spent in the target quadrant in the probe day, followed by post-hoc test. Other parameters were calculated using repeated measures ANOVA in different groups. For each parameter, the normality of the data distribution was assessed using Shapiro-Wilk test. $p<0.05$ was considered statistically significant.

Results

Shuttle box test results

No significant difference was observed in the mean IL among the healthy control (8.83±5.71 seconds), AD (11.7±4.55 seconds), RVS (6.67±4.08 seconds), nGVS (10.8±4.67 seconds) and nGVS+RVS (8.50±5.89 seconds) groups, as shown in Figure 2. The STL for entering the dark compartment significantly decreased in the AD group compared to the control group ($p<0.001$). The means of STL in AD, RVS, nGVS, and nGVS+RVS groups were 15.7±1.52, 43.1±7.07, 22.5±2.59, and 47.4±21.4 seconds, respectively. These values were significantly different compared to the healthy control group (292±8.33 seconds) ($p<0.001$). Given this significant difference, AD induction was confirmed in the rats (Figure 3).

Morris water maze test results one month after intervention

Regarding the mean path length in the training days, the repeated measures ANOVA results for the latency to find the target platform showed the significant effects of stimulation ($F_{(1.89,47.3)}=28.9$; $p<0.001$) and time ($F_{(1.89,47.3)}=28.9$, $p<0.001$) in all training days. However, the interaction effect of stimulation and time was not significant ($p>0.05$). On the second day, a statistically significant difference was observed between the AD group and the control (1360±410 cm, $p<0.001$), RVS (649±400 cm), nGVS (591±391 cm, $p<0.05$) groups. On the third day, a statistically significant difference was observed between the AD group and the control (1163±231cm $p<0.01$), RVS (105±212 cm, $p<0.05$), nGVS (835±241cm, $p<0.05$) and nGVS+RVS (1103±208 cm, $p<0.05$) groups (Figure 4).

The results of repeated measures ANOVA for the speed to find the target platform demonstrated the significant effects of stimulation ($F_{(4,25)}=7.00$, $p<0.001$) and time ($F_{(1.86,46.4)}=16.2$, $p<0.001$) in all training days. However, the interaction effect of stimulation and time was not significant ($p>0.05$). On the first and second

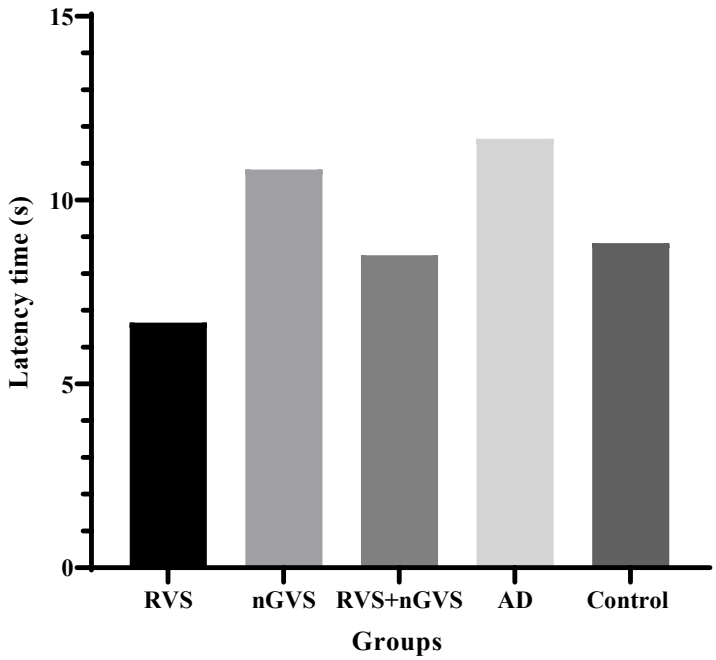

Figure 2. Mean initial latency in different groups. RVS; rotatory vestibular stimulation, nGVS; noisy galvanic vestibular stimulation, AD; Alzheimer disease

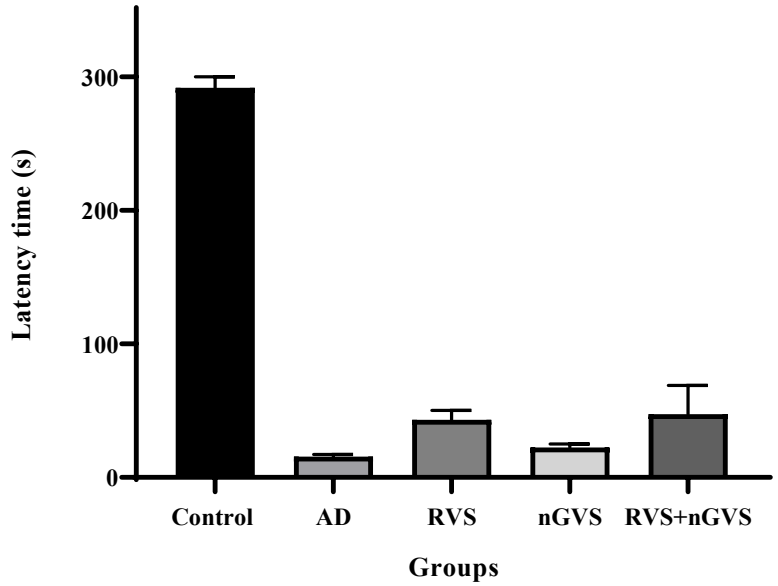

Figure 3. Mean of the Step-Through Latency between groups. AD; Alzheimer disease, RVS; rotatory vestibular stimulation, nGVS; noisy galvanic vestibular stimulation

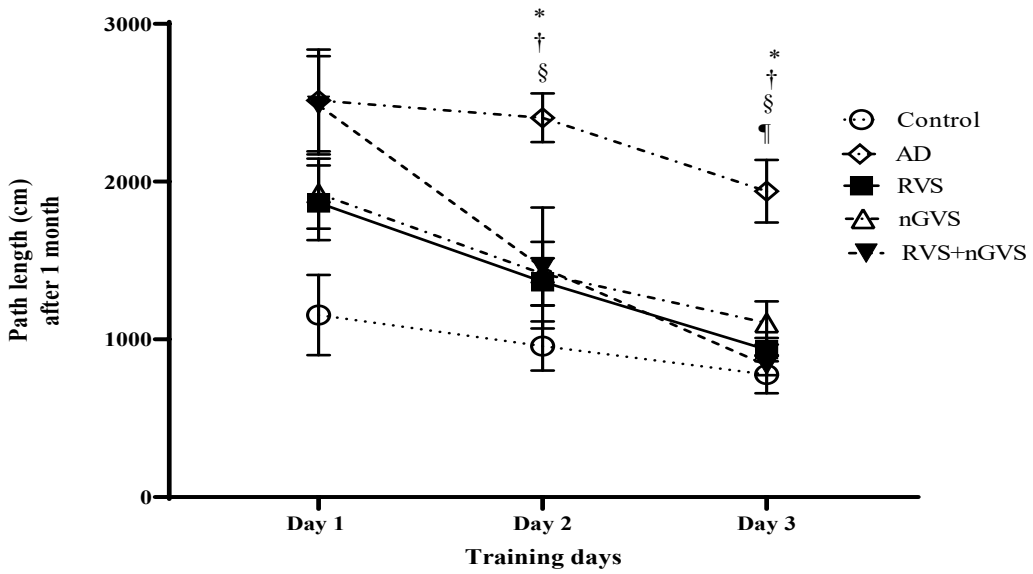

Figure 4. The mean of path length between groups in the training days. AD; Alzheimer disease, RVS; rotatory vestibular stimulation, nGVS; noisy galvanic vestibular stimulation
* Comparing between AD and control group, † comparing between AD and RVS, § comparing between AD and nGVS groups, ¶ comparing between AD and RVS+nGVS groups

days, a significant difference was observed between AD and control groups (9.78±2.66 cm/m^2 and 8.31±2.33 cm/m^2, respectively; $p<0.05$). On the third day, a significant difference was observed between AD and the control (10.1±2.53 cm/m^2, $p<0.05$) and nGVS+RVS (11.5±2.96 cm/m^2, $p<0.05$) groups (Figure 5).

The results of repeated measures ANOVA for the time to reach the platform demonstrated the significant effects of stimulation ($F_{(4,25)}=10.0$, $p<0.001$) and time ($F_{(1.97,49.2)}=24.5$, $p<0.001$) in all training days. However, the interaction effect of stimulation and time was not significant ($p>0.05$). In the third day, a significant difference was observed between the control group and the AD (73±6.03 s, $p<0.001$), RVS (18.3±4.8 s, $p<0.05$), nGVS (47.9±6.75 s, $p<0.01$) and nGVS+RVS (37.9±16.2 s, $p<0.001$) groups. Also, a significant difference was observed between the RVS and nGVS groups (29.6±7.68

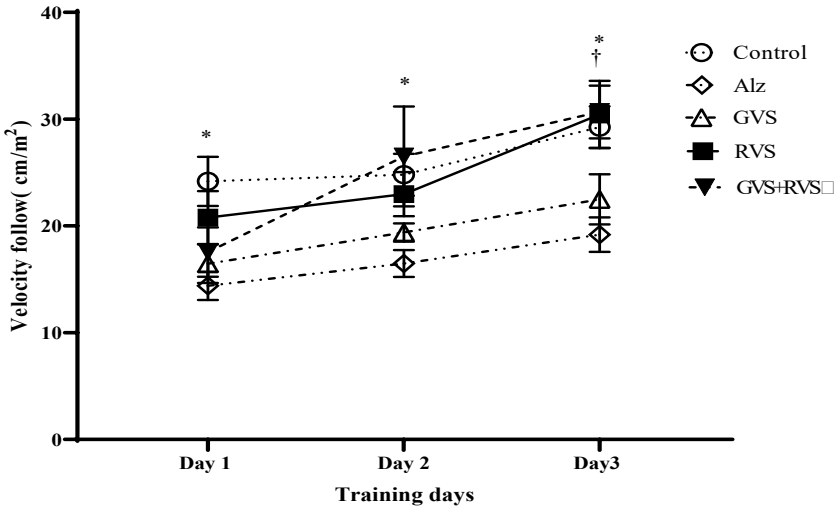

Figure 5. Mean of velocity between groups in the training days. AD; Alzheimer disease, nGVS; noisy galvanic vestibular stimulation, RVS; rotatory vestibular stimulation
* Comparing between AD and Control, † comparing between AD and RVS + nGVS groups

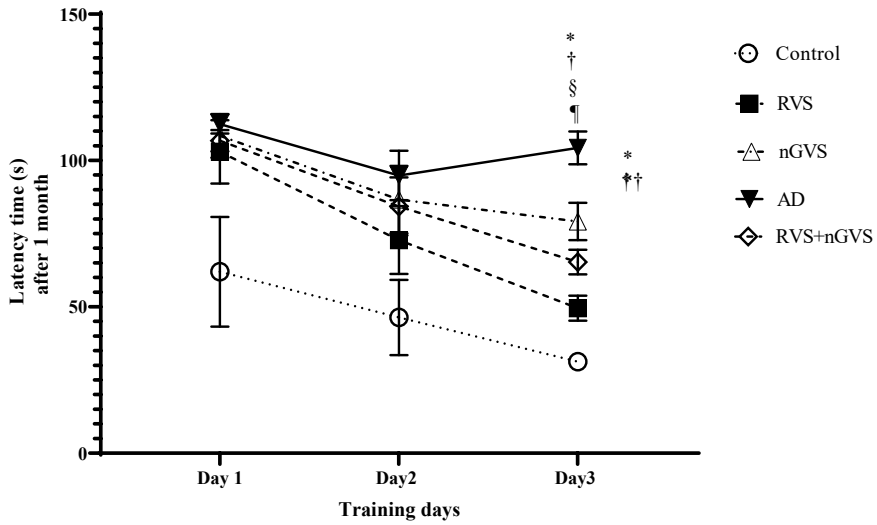

Figure 6. Mean of time to reach the target platform between groups in the training days. RVS; rotatory vestibular stimulation, nGVS; noisy galvanic vestibular stimulation, AD; Alzheimer disease
* comparing AD and Control, † comparing RVS and Control, § comparing Control and RVS+nGVS, ¶ comparing between RVS and nGVS, ** comparing AD and RVS, †† comparing AD and RVS+nGVS

s, p<0.05) and between the AD and the RVS (22.1±14.3 s, p<0.001) and nGVS+RVS (39±7.01 s, p<0.01) groups (Figure 6).

The results of repeated measures ANOVA of the time spent in the target quarter demonstrated the significant effects of stimulation ($F_{(4,25)}$=13.3, p<0.001) and time ($F_{(1.87,46.8)}$=14.9, p<0.001) in all training days. However, the interaction effect of stimulation and time was not significant (p>0.05). On the first day, a statistically significant difference was observed between the nGVS and nGVS+RVS groups (15.9±4.24 s, p<0.05). On the second day, a significant difference was observed between the control group and the RVS (11.9±2.79 s, p<0.05), nGVS (9.10±2.64 s, p<0.05), nGVS+RVS (10.4±2.29 s, p<0.05) and AD (15.5±3.95 s, p<0.05) groups. On the third day, a significant difference was observed between the AD group and the control (25.8±5.32 s, p<0.01), RVS (12±3.50 s, p<0.05) and nGVS+RVS (11.6±3.10 s, p<0.05) groups (Figure 7).

Regarding the time spent in the target quarter in the

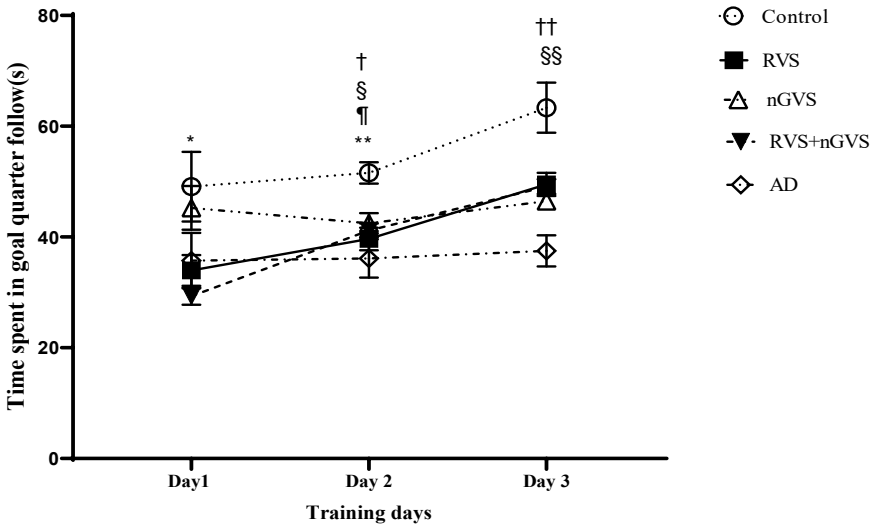

Figure 7. Percentage time spent in goal quarter between groups in the training days. RVS; rotatory vestibular stimulation, nGVS; noisy galvanic vestibular stimulation, AD; Alzheimer disease
* Comparing nGVS and RVS+nGVS. † Comparing AD and Control, § compare RVS and Control. ¶ Comparing nGVS and Control, ** comparing RVS+nGVS and Control, †† Comparing RVS and AD. §§ comparing AD and RVS+nGVS

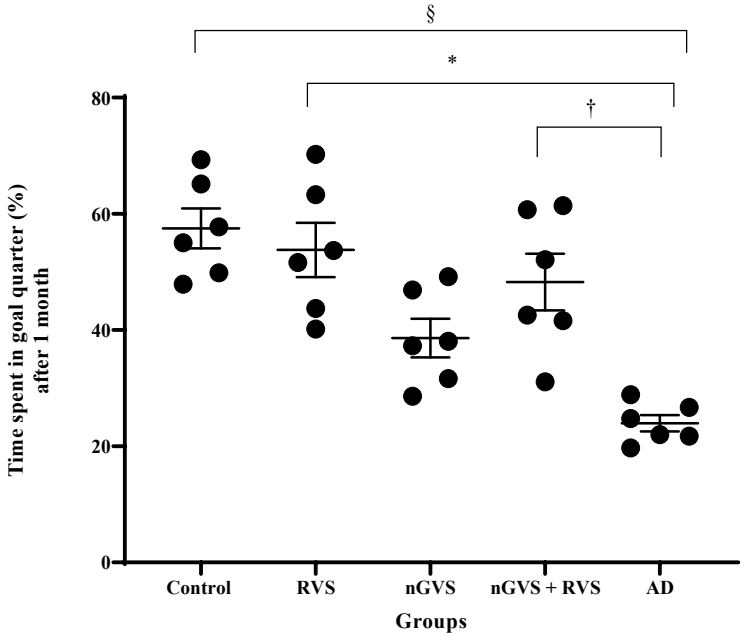

Figure 8. Percentage time spent in goal quarter for each rat in the probe day. RVS; rotatory vestibular stimulation, nGVS; noisy galvanic vestibular stimulation, AD; Alzheimer disease
* comparing AD and RVS groups, † comparing AD and RVS+nGVS groups, § comparing AD and Control

probe day, one-way ANOVA results demonstrated the significant effects of stimulation ($F_{(4,25)}$=11.1, p<0.001). A significant difference was observed between the control group and the AD (33.5±5.61 s, p<0.001) and nGVS (17.2±5.61 s, p<0.05) groups. Also, a significant difference was observed between the AD group and the RVS (29.8±5.61 s, p<0.001) and nGVS+RVS (22.6±5.61 s, p<0.01) groups (Figure 8).

Discussion

This study is an investigation of the sub-acute effects of vestibular stimulation on spatial memory in a rat model of AD. We aimed to assess the efficacy of two vestibular stimulations and their combination in mitigating spatial memory deficits associated with AD. Understanding the impact of vestibular rehabilitation on cognitive function

in the sub-acute phase is crucial for developing targeted therapeutic interventions to enhance the quality of life of people with AD. There are clear interactions between the vestibular system and the hippocampus, and the role of this system in spatial memory has already been reported [16]. The hippocampus plays a role in spatial memory and the vestibular system affects the function of the hippocampus. Spatial cognitive impairment, prevalent in both aging and neurodegenerative conditions, has significant clinical and functional implications, such as increased risk of falls and mortality [22]. However, considering that vestibular stimulation often requires active participation of patients and given that some patients may be unable to engage in vestibular exercises [23], especially dynamic exercises, due to their disabilities, alternative interventions seem be necessary.

During the administration of nGVS, the delivery of electrical current through the mastoid affects all components of the vestibular system, including the semicircular canals and otolith organs. However, when rats are subjected to a rotatory chair, only the horizontal semicircular canal is affected. In this study, the MWM test was employed for evaluation one month after intervention [24]. A considerable difference in the length of path traveled one-month after intervention was observed in all three intervention groups compared to the AD group. The rats in the intervention and healthy control groups spent less distance to reach the target platform than the rats in the AD group. The nGVS+RVS group exhibited a significant difference in the velocity required to reach the target platform. Furthermore, a significant difference in the time spent to reach the target platform was found between the control and AD groups. The control group spent a shorter time to reach the platform. Additionally, a significant difference in the time spent in the target quarter in the training days was observed between the AD group and the two RVS and nGVS+RVS groups. therefore, it can be said that these two methods exhibited more specific and stable effects. The time to reach the platform and the time spent in the target quadrant as the two main criteria in the MWM test [10] indicated the improvement of spatial memory. The induction of AD in the rats was confirmed due to the significant difference in mean STL between the AD and control groups. Previous study has highlighted the use of Shuttle box test in assessing passive avoidance memory and confirming AD model [25].

The RVS method, affecting the semicircular canals, can enhance communication pathways between the vestibule and the hippocampus, leading to increased neural activity in this region [8, 26]. Previous study has highlighted the communication role of channels, especially the horizontal channel, in connection with the hippocampus. The RVS contributes to memory and learning improvement, dendrite proliferation, synaptic connection enhancement, and cognitive and spatial memory function improvements [11]. In the study by Devi et al., it was reported that, after 30 minutes of RVS, memory improved and the time of learning decreased in rats [9]. The saccule and utricle have a communication role with the hippocampus [27]. According to a study, stimulation of the saccule causes the activity of multisensory areas involved in spatial processing in the vestibular cortex, and it seems that the saccule plays an important role in cognitive-spatial processing [28]. In the RVS group, one month after intervention, the time to reach the target platform decreased and the time spent in the target quarter increased compared to the AD group. Therefore, RVS had stable effect.

In previous studies, it was observed that nGVS has considerable effects during the presentation and several hours after the intervention; however, these effects were not found to be stable over time [29, 30]. In the present study, the impact of nGVS was not found to be stable, because, one month after intervention, we did not found a significant difference between the nGVS and AD groups. Nakamura et al. reported the significant effects of nGVS both during and after the intervention [19]. In line with previous research, Azzam found that galvanic stimulation combined with vestibular stimulation improved both static and dynamic balances [31]. Hassan et al. reported that the combination of nGVS and exercises did not significantly improve stability compared to the exercise alone [32]. In the present study, the nGVS+RVS group demonstrated considerable improvement in spatial memory, measured by the MWM test, one month after intervention. The time spent in the target quarter and the time to reach the platform improved in this group compared to the AD group. Moreover, the current study observed that the RVS and the nGVS+RVS led to significant improvement in spatial memory of rats compared to the AD group. This suggests the potential benefits of combining the two vestibular interventions

in the fields of cognitive function and spatial memory enhancement.

Conclusion

The rotatory vestibular stimulation alone or in combination with noisy galvanic vestibular stimulation cause stable effects in improving the spatial memory of rats with Alzheimer's Disease (AD). There is no significant difference between these two approaches. Future investigations including longer follow-up periods of 2–3 months are commended. The results can provide valuable insights into the potential of vestibular stimulation for individuals with AD.

Ethical Considerations

Compliance with ethical guidelines

The article is an extract from a PhD thesis of the University of Social Welfare and Rehabilitation Sciences, Tehran, Iran with the ethical code number of IR.USWR.REC.1401.183.

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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.

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