Research Article

Combination of Vestibular Rehabilitation and Galvanic Vestibular Stimulation Improves Verbal and Visuospatial Memory: A Randomized Control Trial in Patients with Amnestic Mild Cognitive Impairment

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Highlights

- Vestibular rehabilitation plus GVS enhances spatial memory in aMCI
- A combination of vestibular rehabilitation and GVS is recommended for aMCI patients

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ABSTRACT

Background and Aim: Considering the critical input of the vestibular system to the hippocampus as an area involved in cognition, and vestibular disorders reported in patients with amnestic Mild Cognitive Impairment (aMCI), we aimed to investigate the effects of Vestibular Rehabilitation (VR) with and without noisy Galvanic Vestibular Stimulation (nGVS) on cognitive function in patients with aMCI.

Methods: In a randomized controlled trial, twenty-two patients with aMCI were randomly assigned to two groups receiving: 1) VR for four weeks (VR group); 2) VR for four weeks with nGVS for three sessions (GVS+VR group). Outcome measures were Rey's Auditory-Verbal Learning Test (RAVLT), Corsi blocks, Visual Search (VS), and match to sample tests.

Results: Mean immediate and delayed recalls of RAVLT, all of the outcomes of Corsi blocks and VS tests, and the error rate of the match to sample tests improved significantly after intervention in VR and GVS+VR groups. Between-group differences were observed for learning and delayed recalls of RAVLT ($p=0.001$, $d=0.444$ and $p<0.001$, $d=0.512$ respectively), reaction times 1 and 2 in VS ($p=0.007$, $d=0.325$ and $p=0.001$, $d=0.446$ respectively), the total correct trial of Corsi blocks ($p=0.026$, $d=0.235$), and error rate of the match to sample ($p=0.017$, $d=0.266$) tests.

Conclusion: The synergistic effect of VR and GVS suggested that simultaneous use of both stimulations improves verbal and visuospatial memory in aMCI patients. Study protocol location: https://irct.ir/trial/47249 Trial registration number: IRCT20160131026279N3

Keywords: Mild cognitive impairment; spatial memory; verbal memory; hippocampus; galvanic vestibular stimulation; vestibular rehabilitation

Introduction

Mild Cognitive Impairment (MCI) is a transitional state between normal age-related cognitive decline and dementia, which can delay or prevent the onset of dementia with timely diagnosis and treatment [1]. MCI is divided into two types, amnestic (aMCI) and non-amnestic (nMCI), each of which can be single-domain or multi-domain. It is said that aMCI is more likely to progress to Alzheimer's Dementia (AD), while nMCI is more likely to progress to non-Alzheimer's dementia [2]. The process of developing AD probably begins years and perhaps decades before the appearance of clinical symptoms [3]. The overall prevalence of MCI in people over 60 is estimated 15–20%, and the annual rate of progression of MCI to dementia is different and has been reported between 8–15% per year [4].

Defects in cognitive functions are evident in MCI patients [3]. Cognition includes many intellectual processes, including perception, attention, memory, the ability to problem-solving and decision-making, learning, and language production. Impaired episodic memory is the main key indicator in MCI. In addition to episodic memory, several non-amnestic cognitive domains, such as creative and associative thinking, are also impaired in MCI, but these non-amnestic deficits are smaller than episodic memory impairment [5]. The hippocampus structure, which is involved in patients with AD and MCI, plays a vital role in various aspects of memory processing as a cognitive process [6]. In a review study, the right hippocampus is specifically recognized to play a role in spatial memory, while the left hippocampus is more involved in episodic memory [7]. The vital role of the hippocampus on spatial memory probably leads to visuospatial memory impairment in patients with MCI [8]. Verbal memory disorders have also been reported in these patients. Rusconi et al. showed that the immediate and delayed recall scores of Ray's test were significantly lower in the aMCI group compared to the nMCI and healthy groups [9]. For these reasons, in this study, we used visuospatial memory tests including Corsi blocks, Visual Search (VS), and match to sample and also Rey's Auditory-Verbal Learning Test (RAVLT) as a verbal memory test to determine the effects of interventions in patients with aMCI.

Previous studies have shown several anatomical connections between the vestibular system and cognitive areas, including the hippocampus. In addition, the vestibular system transmits spatial representation information to the hippocampus and has an important role in spatial learning and spatial navigation through head direction and place cells in the hippocampus [6, 10-13]. The association of spatial memory in the hippocampus with the vestibular system has been demonstrated using vestibular stimulation [14]. Various studies indicated vestibular system defects in patients with AD and its preclinical stage, MCI using cervical [15-18] and ocular [16] vestibular evoked myogenic potential, video head impulse test [19], and Dix-Hallpike maneuver [18]. Shamsi et al. showed a significant difference in the absence of ocular vestibular evoked myogenic potentials between patients with aMCI and the healthy control group (63.6% vs. 18.2%, respectively) [16]. According to Wei et al., abnormalities of cervical and ocular vestibular evoked myogenic potentials, and video head impulse test are three to four times higher in patients with MCI than those in healthy control group [17].

The vestibular system has a critical role in cognition and vestibular disorders observed in patients with MCI that can lead to cognitive disorders in these patients [20]. In addition, vestibular loss can be considered as a contributing factor to the Alzheimer's disease, which initially causes the degeneration of cholinergic systems in the posterior parietal-temporal, middle temporal, and posterior cingulate regions [21]. The level of vestibular disorders in individuals with MCI was reported to be between healthy people and AD patients [17]. Therefore, interventions through the vestibular system may improve not only the vestibular functions but the cognitive performance in such patients.

Vestibular Rehabilitation (VR) is an exercise-based strategy for the management of vestibular disorders, and it aims to maximize central nervous system compensation at the vestibular nucleus level and other levels of the vestibular pathways [22]. Sugaya et al. showed using VR three times a day for one to four months improves visuospatial abilities, executive function, attention, and processing velocity in patients with intractable dizziness [23]. Lotfi et al. showed that the use of 45-min VR twice per week for 12 weeks enhances choice reaction time while none of the parameters of the spatial working memory showed improvement, in children with Attention-Deficit/Hyperactivity Disorder (ADHD) [24]. Lack of improvement in spatial working memory could be due to additional hippocampus disorder in ADHD patients and insufficient vestibular interventions.

Galvanic Vestibular Stimulation (GVS) activates vestibular neurons, vestibular nuclei, and several cortical and subcortical areas through electrodes placed on the mastoid [25]. GVS by directly affecting the spike trigger zone of primary vestibular afferents leads to depolarization (cathodal stimulation) or hyperpolarization (anodal stimulation) of vestibular nerve fibers [26, 27]. Functional imaging showed the activation of a network including the multisensory cortex and hippocampus following the use of vestibular galvanic stimulation [28-30]. Moreover, adding an appropriate amount of noise to a nonlinear system enhances the response [31]. The use of low-level electrical noise changes the potentials of the neuron membrane and leads to the discharge of the action potential of the neurons [32]. Wilkinson et al. showed the positive effects of repeated sessions of 25-min GVS on improving cognitive function in patients with unilateral spatial neglect [33]. In an animal study, Ghahraman et al. showed that repeated sessions of 30-min noisy Galvanic Vestibular Stimulation (nGVS) can improve spatial memory in rats with streptozotocin-induced sporadic Alzheimer's disease [34].

Vestibular rehabilitation leads to the improvement of cognitive outcomes in various diseases, although Lotfi et al. [24] did not show improvement in spatial memory. Galvanic vestibular stimulation increases the neurophysiological effects of VR [35] and facilitates the vestibular nuclei through spinal pathways [36]. Therefore, we assumed that the use of nGVS with VR may provide a better overall improvement than VR alone in patients with aMCI. To the extent that we could search, only the effects of the simultaneous use of VR and GVS have been investigated in patients with Unilateral Vestibular Disorder (UVD) and Bilateral Vestibulopathy (BVP) to improve balance function. A significant improvement in body sway [37], reduced canal weakness and increased postural stability, improved quality of life, and decreased dizziness handicap [35] were reported in patients with UVD following the use of VR and GVS simultaneously. The simultaneous use of two vestibular interventions has probably led to more stimulation of the vestibular system and helped the vestibular compensation process in patients with UVD. On the other hand, Eder et al. showed that the combination of VR and nGVS does not lead to synergistic therapeutic effects in patients with BVP [38], probably due to fewer VR sessions or a different group of patients.

Due to the aging of the population and the increasing prevalence of age-related diseases including MCI, the possible hypothesis of Alzheimer's vestibular disease and vestibular disorders reported in patients with aMCI [16, 19], and the presence of verbal and visuospatial memory disorders in these patients, this study aimed to investigate the effect of VR with and without nGVS in aMCI patients' verbal and visuospatial memory.

Methods

Participants

This study is a Randomized Controlled Trial (RCT) conducted on patients with aMCI diagnosed by a neurologist based on Petersen and the National Institute on Aging (NIA) and Alzheimer's Association criteria including self-reported memory impairment, no problems with daily activities, and no dementia [39]. The inclusion criteria were a Clinical Dementia Rating<0.5 [40]; a Mini-Mental State Examination (MMSE) score of 19-21 for patients with primary school education [41], and 22-26 for patients with higher education [42, 43]; a Montreal Cognitive Assessment (MoCA) score of 19 to 24 [44]; near-normal or corrected visual acuity; lack of color blindness, neck pain, limited range of motion of the neck, and obvious lower limb deformities; no history of rheumatic, metabolic, and orthopedic disease in the last 6 months; and no history of drug or alcohol addiction. Out of 32 volunteer patients, four patients were excluded due to a lack of inclusion criteria, 28 patients were recruited and 22 patients (9 male and 13 female, mean age: 62.87±8.83) completed training sessions. All recruited patients signed informed consent. Participants were not in any other rehabilitation program during the study and were asked to adopt a healthy lifestyle according to Alzheimer's Association recommendations.

Patients were randomly allocated into two groups using Random Allocation Software. The statistics consultant and patients were blinded to the groups. Patients in the VR group received vestibular rehabilitation only, and patients in the GVS+VR group received both galvanic vestibular stimulation and vestibular rehabilitation. Figure 1 shows the flow chart of the study from enrollment to statistical analysis.

Outcome measure

Before and after interventions, we administered Rey's Auditory-Verbal Learning Test (RAVLT) as a verbal memory test, and three visuospatial memory tests of the Psychology Experiment Building Language (PEBL) test battery includes Corsi blocks, VS, and match to sample tests. To avoid the order effect, all tests were performed in random order.

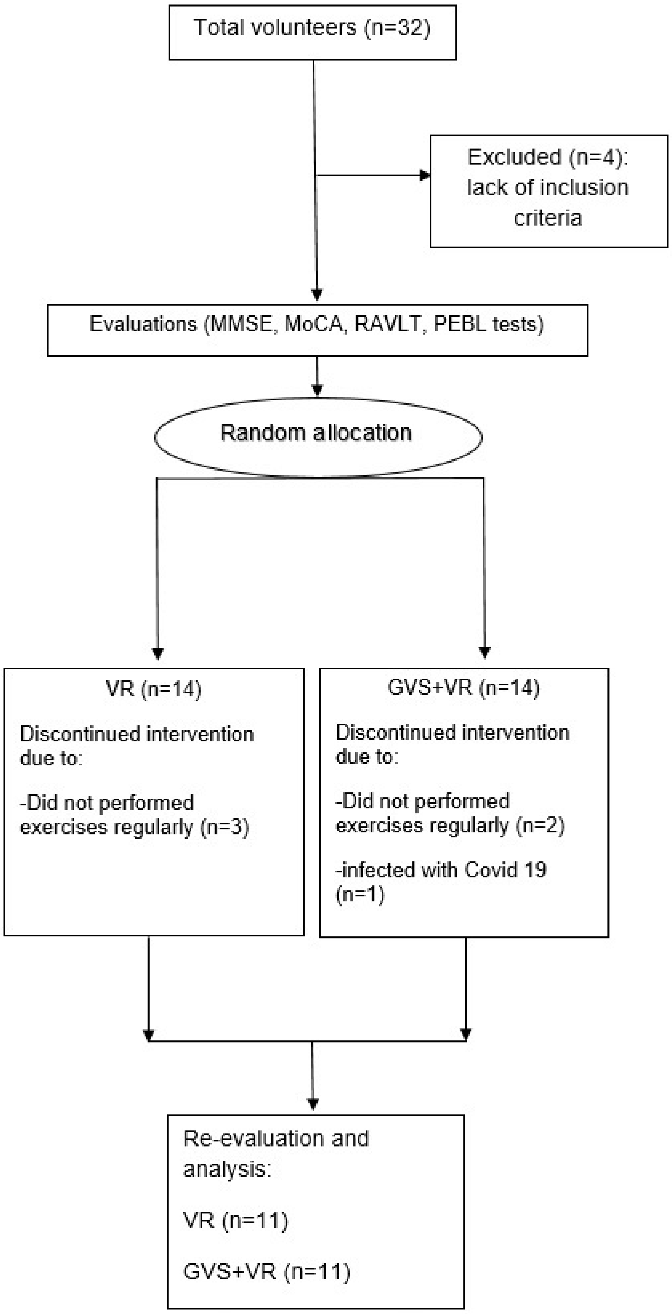

Figure 1. Flowchart of the study. MMSE; mini-mental state examination, MoCA; montreal cognitive assessment, RAVLT; Rey's auditory-verbal learning test, PEBL; psychology experiment building language, VR; vestibular rehabilitation, GVS; galvanic vestibular stimulation

Procedure

Rey's auditory-verbal learning test

The Persian version of RAVLT [45] was administered. A 15-word list A was read orally to the patient, and we asked him to repeat as many words as possible. We repeated this process 5 times, and each time we recorded the number of words that were repeated correctly; then, we obtained the learning score by subtracting the score of step 5 from step 1. In the next step, we read list B as a distracting tool, and without repeating list A, we asked him to repeat as many words as he could remember from list A, then we calculated the immediate recall score. We asked the patient to repeat as many words as he could remember from list A 20 minutes later, and we recorded the delayed recall score.

The psychology experiment building language tests

In the present study, we used three tests of visuospatial memory of the PEBL test battery, including Corsi blocks, VS, and match to sample tests.

Corsi blocks-nine blocks appeared in the center of the screen, some of which were lit at each stage. At first, three steps were performed to familiarize the participant with the test process. In the first sequence, two blocks were lit, and the number of lit blocks gradually increased depending on the participant's ability. In each block sequence, two experiments of the same length were administered. If at least one of them was repeated correctly, the next sequence would be longer. The blocks lit up at a rate of about one per second. The participant must click on the blocks in the correct order. If the subject incorrectly identified two sequences of the same length, the test would end. At the end of the test, four variables of block span, total correct trials, total score, and memory span were calculated. The block span was the longest length that was repeated correctly at least once. Total correct trials were the number of trials total that was correctly repeated. The total score was obtained by multiplying the block span by the total correct trials. The memory span was calculated by summing the minimum list length plus the total number of corrects divided by the number of lists in each length [2, 46, 47].

Visual search- A letter or a geometric shape with white or green color was displayed in the center of the screen. After a few seconds, a field of letters and spatial shapes appeared on the screen. The subject was asked to recall and click on the location the target was displayed. By the first click, all letters and shapes were displayed as empty circles, and the participants must click again on the empty circle that was previously the target. 120 trials were performed, and at the end, the percentage of correct responses, the mean Reaction Time 1 (RT1; search time), and the mean Reaction Time 2 (RT2; move the mouse to target) were calculated [48, 49].

Match to sample test- A complex pattern was displayed on the monitor screen. Then, with a few seconds delay, two patterns were displayed, and the participant must press the right or left shift key to select the pattern he/she had seen before. Thirty trials were performed for each subject, and finally, the error rate and reaction time were calculated [48, 50].

Noisy galvanic vestibular stimulation

Disposable electrodes placed on the mastoid bone behind both ears in a binaural-bipolar manner provided the electric currents of the noise. The patients were seated on the chair in a relaxed state with their eyes open. The skin behind the ear was completely cleansed using Nuprep gel (Weaver and Company, USA). For proper contact of the electrode with the skin, a suitable amount of Skintact ECG electrode gel (Leonhard Lang, Austria) was applied to the electrodes. The electrodes were attached to the mastoid in the hairless area. The impedance of the electrodes was continuously kept below 1kΩ. We first determined the participant's sensory threshold for stimulus initiation. To do this, patients were asked to close their eyes. The threshold was obtained by slowly increasing the current intensity in 0.1 mA steps until the person reported itching or tingling (first threshold). Then the current intensity decreased so that the subjects had no sensation (second threshold), the same process is repeated once more and the median of the four thresholds obtained is considered as the sensory threshold of each patient [51]. The mean sensory threshold of patients was 0.9 (range: 0.3-1.8). Then, the patients were asked to open their eyes and sit quietly on the chair until the end of the electrical stimulation while the examiner was next to them. noisy GVS was provided by Neurostim 2 electric current generator (Medina Teb Company, Iran) with a random frequency bandwidth of less than 30 Hz, bipolar current, and an intensity of 0.1 mA below the threshold level. The GVS and GVS+VR groups received three 20-minute GVS sessions once a week for three consecutive weeks [37, 51].

Vestibular rehabilitation

Cawthorne and Cooksey proposed vestibular rehabilitation exercises in the 1940s [52, 53]. Since these exercises improve the patient's symptoms, it can be concluded that they cause changes in the vestibular function only, and there is no doubt about the effectiveness of such exercises [54]. Cawthorne-Cooksey's exercises were used as vestibular rehabilitation in groups VR and GVS+VR. These exercises include repetitive movements of the eyes, head, and trunk in positions of lying down, sitting, standing, and moving with eyes open and closed [52, 55]. After baseline evaluations were completed, instructions were given to the patients on how to perform and gradually increase the exercise speed at the home. The instructions for performing the exercises in four situations were: 1) lying down: eye movements by focusing on finger movement at a distance of 30 cm, and head movements first with eyes open and then closed, 2) sitting: performing head and eye movements situation 1 along with trunk movement to the right-left and bending forward, 3) standing: eye and head movements situation 1, trunk movements situation 2, with a change of position from sitting to standing and vice versa and rotation left and right in this situation, and throw a small ball from one hand to the other (above the horizon level), and 4) moving: in the room with head movement with open eyes and then with closed eyes and walking on a soft surface with head movement with open eyes and then with closed eyes. Each exercise was performed five times with eyes open and five times with eyes closed. The patients performed Cawthorne-Cooksey exercises for 30 minutes twice a day (morning and afternoon) for four weeks [22, 56-58]. To ensure that the exercises were performed, we contacted the subjects every week. We asked them to fill out a checklist daily and provide it to us after four weeks.

Statistical analysis

Descriptive statistics were conducted to examine the distribution of all variables and the demographic characteristics of the subjects. In this study, we had 12 cognitive outcomes (three for RAVLT, four for Corsi blocks, three for VS, and two for the match to sample). The Shapiro-Wilk test was used to check the normal distribution of the data, which showed that all outcomes have normal distributions except the block span of Corsi blocks and correct responses of VS. Independent sample T-test or its nonparametric equivalent, Mann-Whiney U test, was used to compare demographic characteristics and cognitive outcomes between groups in the baseline. The chi-square test was used to compare the sex distribution as a demographic characteristic between groups.

ANCOVA test was used for between-group comparison of each variable with normal distribution and pre-intervention measures were adjusted as covariances. Partial Eta squared (η2; small=0.01, medium=0.06, and large=0.14) was used to measure the effect size for between-group comparisons [5]). Mann-Whiney U test was used to compare changes in outcomes (subtracting the results after the results before the intervention) without normal distributions between groups. Paired t-test was used to within-group comparison variables with normal distribution before and after the intervention and the Wilcoxon test was used for data that do not have a normal distribution. Cohen's d (d) (small=0.2, medium=0.5, and large=0.8) was used to measure the effect size for within-group comparisons [60]. All analyzes were performed using SPSS version 17. The significance level of the tests was considered 0.05. The power of the study was reported when there was no statistically significant difference.

Results

From the total of 28 patients participating in the study, three patients in the VR group including two females and one male with a mean age of 68.33±4.5, three patients in the GVS+VR group (two females and one male with a mean age of 72.66±4.16 were excluded from the study due to infection with Covid-19, not performing exercise regularly. Statistical analysis was performed for 22 patients. Demographic characteristics of participants, including age, sex, MMSE, and MoCA mean scores, were not significant between groups before the intervention (Table 1).

There were no statistically significant differences between groups at the beginning of the study for 12 cognitive outcomes related to RAVLT, Corsi blocks, VS, and match to sample tests using independent sample T-test or Mann-Whiney U test ($p>0.05$). In the following, we showed the between-groups difference as well as the difference between the results before and after the interventions in these four tests.

Rey's auditory-verbal learning test

Using the ANCOVA test, the difference between groups was statistically significant for mean learning and delayed recall scores, there was no difference between groups for mean immediate recall score ($p>0.05$, power was 0.258; Table 2).

Table 1. Demographic characteristics of the participants (n=22)

Characteristics	VR (N=11)	GVS+VR (N=11)	p
Age (Mean±SD)	62.73±10.28	62.82±7.62	0.981
Sex (Male/Female)	4/7	4/7	1.000
MMSE (Mean±SD)	22.82±1.77	23.55±1.29	0.286
MoCA (Mean±SD)	21.64±1.80	22.64±1.43	0.166

VR; vestibular rehabilitation, GVS; galvanic vestibular stimulation, MMSE; mini-mental state examination, MoCA; montreal cognitive assessment, using the paired t-test, the mean score of the RAVLT learning task significantly improved in the GVS+VR group (p<0.001, d=2.28) after the intervention compared to before the intervention, while the VR group did not show any difference from before the intervention (p>0.05, power was 0.68). In addition, mean scores of the immediate recall and delayed recall of RAVLT improved after the intervention in both VR (p=0.024, d=0.80; and p=0.024, d=0.80 respectively) and GVS+VR (p=0.001, d=1.46; and p=0.001, d=2.36 respectively) groups.

Corsi blocks

Using the ANCOVA test, the difference between groups was statistically significant for mean total correct trials, while not seeing any difference between groups for mean total score, and memory span (p>0.05, power was 0.418 and 0.333 respectively; Table 2). Change in block span using the Mann-Whiney U test was not statistically significant between groups (p>0.05, power was 0.071).

Using the paired t-test, mean scores of total score, total correct trials, and memory span subtests improved after the intervention compared to before the intervention in both VR (p=0.002, d=1.27; p=0.026, d=0.78; and p=0.026, d=0.77 respectively) and GVS+VR (p=0.001, d=1.50; p<0.001, d=1.76; and p=0.001, d=1.31 respectively) groups. Using the Wilcoxon test, the score of block span significantly improved in both VR (p=0.014, d=1.09) and GVS+VR (p=0.008, d=1.25) groups.

Visual search

Using ANCOVA analysis, differences between groups were statistically significant for mean RT1 and RT2 (Table 2). Change in the percentage of correct responses using the Mann-Whiney U test was not statistically significant between groups (p>0.05, power was 0.249).

Using the paired t-test, the mean of RT1 and RT2 improved after the intervention compared to before the intervention in VR (p=0.03, d=0.76; and p=0.048, d=0.91 respectively) and GVS+VR (p=0.001, d=1.33; and p=0.002, d=1.23 respectively) groups. Using the Wilcoxon test, the percentage of correct responses improved after the intervention compared to before the intervention in VR (p=0.015, d=1.01) and GVS+VR (p=0.018, d=0.98) groups.

Table 2. Comparisons of Rey's auditory-verbal cognitive, Corsi blocks, visual search, and match to sample tests between vestibular rehabilitation and galvanic vestibular stimulation+vestibular rehabilitation groups

Tests		VR Group		GVS+VR group		p^a	η^2
		Before Mean±SD	After Mean±SD	Before Mean±SD	After Mean±SD		
RAVLT	Learning	4.73±2.24	5.18±1.72	4.73±1.48	6.64±1.78	0.001	0.444
	Immediate recall	6.73±1.90	7.64±2.37	7.73±1.27	9.36±9.50	0.184	0.091
	Delayed recall	6.00±1.61	6.73±1.73	6.82±1.83	9.27±1.67	<0.001	0.512
Corsi blocks	Total correct trial	6.64±1.28	7.27±1.91	6.55±1.36	8.00±1.34	0.026	0.235
	Total score	32.18±10.15	38.45±10.53	31.82±10.95	43.09±11.24	0.081	0.152
	Memory span	4.31±0.64	4.63±0.59	4.36±0.80	4.90±0.62	0.124	0.120
Visual search	RT1	2988.16±568.02	2848.76±578.59	2987.01±540.42	2510.57±419.49	0.007	0.325
	RT2	2213.93±407.78	2109.63±380.03	1973.39±327.56	1617.83±190.77	0.001	0.446
Match to sample	Error rate	19.08±9.32	14.84±10.98	18.17±7.79	8.78±5.82	0.017	0.266
	Reaction time	2755.29±669.28	2652.17±767.58	2646.39±635.33	2282.39±672.03	0.140	0.111

VR; vestibular rehabilitation, GVS; galvanic vestibular stimulation, RAVLT; Rey's Auditory-Verbal Learning Test, RT; reaction time;

[a] ANCOVA with pre-intervention measures adjusted as covariances

η^2 Partial Eta squared effect size (small=0.01, medium=0.06, and large=0.14)

Bold numbers: p<0.05

Match to sample

Using ANCOVA analysis, the difference between groups was statistically significant for the mean error rate (Table 2), while not seeing any difference between groups for mean reaction time (p>0.05, power was 0.309; Table 2). Using the paired t-test, the mean error rate after the intervention compared to before the intervention improved in VR (p=0.026, d=0.78) and GVS+VR (p<0.001, d=2.41) groups. In addition, mean reaction time after the intervention compared to before the intervention only improved in group GVS+VR (p=0.032, d=0.74), while in the VR group, there was no statistically significant difference between the results before and after intervention (p>0.05, power was 0.63).

Discussion

The present study showed a difference between VR and GVS+VR groups for the mean of learning and delayed recall of RAVLT, the total correct trial of Corsi blocks, RT1 and RT2 of VS, and the error rate of the match to sample in patients with aMCI. In addition, the mean of immediate and delayed recall of RAVLT, block span, total score, total correct trial, and memory span of Corsi blocks, the correct responses, RT1 and RT2 of VS, and the error rate of the match to sample improved in the VR group following the intervention. In the GVS+VR group, all cognitive test outcomes improved after the intervention. The effect sizes were larger in the GVS+VR group than in the VR group for all outcomes. Therefore, our study showed the enhancement of verbal and visuospatial memory performance in both VR and GVS+VR groups, although, in the GVS+VR group, we observed more improvement than the VR group, which indicated a synergistic effect of using these two vestibular interventions simultaneously. In line with our study, Roh and Lee showed that gaze stability exercises as a vestibular intervention positively affected the MoCA test as a cognitive test in the elderly with MCI [61]. In the study of Lotfi et al., VR improved choice reaction time cognitive test results in children with ADHD and concurrent vestibular disorder [24]. Sugaya et al. showed VR improved the Dizziness Handicap Inventory score, and Trail Making Test score as a test for assessing attention, executive function, visuospatial scanning, and processing speed in patients with intractable dizziness [23]. Although these studies investigated different populations and used different tests, vestibular rehabilitation improved cognitive performance. In addition, synergistic effects have been investigated in other populations. A few studies also investigated the simultaneous use of VR and GVS. As in our study, Carmona et al. showed that the simultaneous use of VR and GVS significantly improved body sway in patients with UVD [37]. Ahmed et al. showed that adding galvanic stimulation to VR reduces canal weakness in the videonystagmography test and increases postural stability and Vestibular Disorders Activities of Daily Living Scale scores in patients with UVD [35]. Unlike our study, Eder et al. showed that the combination of VR and nGVS does not cause synergistic therapeutic effects in patients with BVP [38]. This discrepancy could be due to different patient populations, outcome measures, and the number of VR sessions. For example, in Adar's study, patients underwent VR for 2 weeks, while in our study for 4 weeks.

The potential mechanisms underlying the improvement in cognitive outcomes following VR might be the presence of at least four major pathways between the vestibular system and the cortex regions involved in cognition, including the hippocampus [6]. The RAVLT test is strongly correlated with hippocampal volume and cortical thickness in the frontoparietal [62]. Areas such as the posterior parietal cortex [63], amygdala and hippocampus [64], and parietal cortex along with the intraparietal sulcus and superior parietal lobe [65] are involved in Corsi blocks, match to sample, and VS tests, respectively. Considering the vestibular system is more diffusely projected to a variety of cortical and subcortical areas than any other system, as well as a special and important vestibular pathway that seems to originate mainly from the semicircular canals and terminated in the medial temporal cortex, including the hippocampal and parahippocampal gyrus [21, 66], we expected the use of Cawthorne-Cooksey exercises as a vestibular intervention improved memory performance in patients with aMCI. The hippocampus is highly sensitive to exercise-induced changes through neurogenesis and cell proliferation [67]. Physical exercises, of which VR is a part, reduce neuroinflammation and oxidative stress, increase the expression of BDNF (a brain-derived neurotrophic factor that plays a role in cell growth, survival, and memory enhancement), increase the level of calcium messenger RNA, improving transmission speed, and stimulating neuroplasticity [68-70]. Jee et al. showed physical exercises (running on the treadmill) increased c-Foss expression in the hippocampus as a marker of neural activity in rats with streptozotocin-induced Alzheimer's disease [71]. Using MRI, it has been demonstrated that a multi-component exercise program increases the volume of the hippocampus and maintains the maximum oxygen intake in patients with aMCI [72], which contributes to improving memory in these patients. All outcomes assessed in this study improved the VR group, except the mean learning score of RAVLT and the mean reaction time of the match to sample. No improvement in these outcomes could be the low power of the statistical tests (<80%) which probably needed a larger sample size or a higher dose of the intervention.

The possible mechanisms of improving cognitive outcomes following the simultaneous use of VR and nGVS as non-pharmacological methods could be greater stimulation of the vestibular system followed by the hippocampus. Functional neuroimaging studies indicated galvanic stimulation through the mastoids activates the vestibular nerve and, subsequently, all the vestibular centers, including the vestibular nuclei, the thalamic nuclei, the parietoinsular vestibular cortex, and adjacent regions, including temporoparietal junction and the parietal cortex [25]. Ghahraman et al. showed that nGVS leads to enhanced visuospatial tasks and an increase in the expression of c-Foss in the hippocampus in rats with the streptozotocin-induced Alzheimer's disease probably because of the repeated activation of vestibular neurons [34]. The use of GVS improves the performance of visual, vestibular, and somatosensory functions [35]. Therefore, the simultaneous use of two interventions has higher effects on the performance of cognition.

We used RAVLT and three visuospatial memory tests of PEBL to examine verbal and visuospatial memory in patients with MCI. The RAVLT is a verbal memory assessment test that is commonly used in scientific and clinical research because it is easy to administer and measures the encoding, integration, storage, and retrieval of verbal information by presenting two lists of 15 words (List A for five times and interference list B). The Persian version of the RAVLT is a reliable instrument for repeated neuropsychological tests [45]. In addition, RAVLT is sensitive to differentiating conversion from MCI to dementia [73]. PEBL is a new computer software that includes a test battery (a set of approximately 70 clinical tests) to evaluate cognitive performance in healthy people and for clinical evaluations [48, 74]. PEBL is sensitive to the reduction of cognitive function and the level of familiarity with it does not affect performance [75]. Piper et al. compared four PEBL executive function tests with non-PEBL versions and found a clear correlation between the results of the tests; these findings indicated the high validity of PEBL tests for evaluation decision-making, sustained attention, and short-term memory [76].

One of the limitations of our study was that we could not evaluate the durability of the effectiveness of the interventions because the study took place during the Covid-19 pandemic and patients were reluctant to travel to the clinic many times. In addition, we didn't use an individualized vestibular rehabilitation program since we tried to investigate the effect of a uniform program on patients with aMCI.

Conclusion

Our study supports the synergistic effect use of vestibular rehabilitation and noisy galvanic vestibular stimulation interventions simultaneously to improve verbal and visuospatial memory performance in patients with amnestic mild cognitive impairment, possibly due to multiple activations of vestibular neurons and subsequent stimulation of hippocampal regions associated with these neurons. As a safe and non-invasive stimulation, noisy galvanic vestibular stimulation can be beneficial to be used in combination with vestibular rehabilitation for patients with such cognitive disorders.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethical Committee of Tehran University of Medical Sciences, Tehran, Iran, Code No. IR.TUMS.FNM.REC.1398.186.

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Authors' contributions

BK: Acquisition of data, drafting the manuscript, analysis, and interpretation of data; MAG: Study concept and design, study supervision, drafting/critical revision of the manuscript for important intellectual content; RH: study supervision, technical and material support; VA: Study design, technical and material support; SJ: Study design, statistical analysis, and interpretation of data; RK: Technical and material support, analysis, and interpretation of data. All authors read and approved the manuscript.

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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