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RESEARCH ARTICLE

Inhibitory function and sustained attention following galvanic vestibular stimulation in children with attention-deficit/hyperactivity disorder

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Abstract

Background and Aim: In recent years, galvanic vestibular stimulation (GVS) has been used as an effective method in rehabilitation and treatment of psychological disorders in children and adults. This study was designed to evaluate the effect of GVS on response inhibition and sustained attention in children with attention-deficit/ hyperactivity disorder (ADHD).

Methods: Seventeen children with ADHD, within the age range of 9−12 years, participated in this study. All participants were exposed to the go/no-go task. The behavioral outcomes and event-related potentials were recorded at baseline status, in sham condition, and after 20 minutes of exposure to GVS polarities, with an anode on the right mastoid region and a cathode on the left mastoid region.

Results: The results showed that there was a significant difference in reducing the behavioral response of the commission error ($p < 0.05$). But the reduction in behavioral responses to omission error and reaction time were not significant ($p > 0.05$). However, regarding ERPs, reduced latencies and increased amplitudes of N2 and P3 waves were observed in GVS intervention, compared to the baseline and sham conditions ($p < 0.05$).

Conclusion: The present results indicated the potential of GVS in improving of cognition function in children with ADHD and could help us develop a new strategy for rehabilitation of response inhibition disorders in the future.

Keywords: Galvanic vestibular stimulation; attention deficit hyperactivity disorder; go no go task; event-related potentials; motor control

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common behavioral disorders in children that is associated with symptoms of hyperactivity, lack of concentration and attention. The symptoms of this disorder continue into adulthood [1]. The distinctive features of this disorder include difficulty in cognitive functions especially impaired sustained attention and response inhibition. Response inhibition is a set of

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high-level cognitive processes that provide the ability to inhibit and control responses and is supported by extensive brain networks including bilateral frontal, right superior temporal, right thalamic, and mid-brain [2]. Sustained attention is a cognitive activity that involves the ability to focus on a particular subject for a long time and is usually measured by the average reaction time and errors [3]. In attention studies, omission errors (inability to identify the target stimulus) usually measure the symptoms of attention deficit, while commission errors (incorrect response to the non-target stimulus) measure weakness in response inhibition [4]. Numerous fMRI studies in ADHD children show that the activity of inferior prefrontal cortex, striato-thalamic, parieto-temporal and cerebellar regions in these children during attention functions is lower than in the healthy group. [5].

Basically, based on lesion studies in animals and humans, pathophysiology of ADHD is attributed to dysfunction of fronto-parietal and fronto-striatal circuits [6]. Also, approximately 30 to 50 percent of children with ADHD show poor balance during physical activity compared to their peers, which may be due to involvement of the atrial and cerebellar systems [7]. Moreover, brain imaging studies combined with cognitive function in ADHD children in comparison to their normal peers indicated that a) cerebellum, prefrontal cortex and the striatum are smaller b) methylphenidate increase regional brain metabolism in the cerebellum, frontal and temporal lobes and c) caloric vestibular stimulation as well as galvanic vestibular stimulation activates the limbic system and neocortex providing a neuroanatomical link between vestibular stimulation and fronto-parietal-striatal network including, cerebellum, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), anterior PFC, lateral frontal pole, anterior insula, caudate and parieto-temporal [8-11].

Many studies have shown that although the basal ganglia and cerebellum play an important role in the control motor, their neuroanatomical association with the fronto-parietal network causes this complex to play an important role cognitive and attentional function [11,12]. Research in both animals and humans have shown a connection between the vestibular system and the cerebellum and their effect on cognitive function [6,13].

Many studies on behavior and event-related responses show that children with ADHD have cognitive dysfunction and weakness in electrophysiological responses compared to their peers [14,15]. In the behavioral level, children with ADHD perform poorly function in the go/no-go tasks, which are the most commonly used methods to measure sustained attention and response inhibition [16]. In this task, participants are instructed to react quickly to target stimuli and to refrain from responding to non-target stimuli.

From the perspective of neural responses, event-related potentials (ERPs) are used to examine neural processes in children and adults. These responses clearly show the basic brain processes during cognitive functions [17]. The advantage of the ERP approach is that it can provide information about cognitive processes that are selectively affected by electrical stimulation. In the go/no-go paradigm, two groups of waves with positive and negative amplitudes are formed. The go conditions in cognitive tasks create a wave with a positive amplitude known as the P3 wave. The amplitude of the P3 wave represents the resources allocated to attention activities, while the latency of this wave indicates the information processing time [18,19]. The no-go condition elicits a frontal N2 wave which reflects conflict monitoring and is measured as a marker of response inhibition [20].

There are several ways to rehabilitate cognitive function and motor control in children and adults [21]. Many studies in the field of rehabilitation show that some changes in brain function can be an important factor in changing behavioral activities [21,22]. Direct electrical stimulation to the cortex can lead to positive effects on cognitive and behavioral function in children and adults.

The use of non-invasive electrical stimulation is more important today compared to traditional cognitive and rehabilitation methods and can increase or decrease cortical activity in proportion to the polarity of the stimulation and the duration of stimulation, which ultimately leads to improved cognitive function [23]. One of the methods used in cognitive rehabilitation is GVS method. In this method, the anode and cathode electrodes are applied to the mastoid bone of the right and left ears.

GVS acts through the effects of polarization on the entire vestibular nerve and differs from other methods of vestibular stimulation, for instance caloric vestibular stimulation, which activates only the horizontal semicircular canal, which in turn causes nystagmus [24]. Functional imaging studies in normal subject using GVS stimulation during cognitive tasks show that large areas of brain networks are activated. These areas that receive stimulation mainly including the insular and retroinsular regions, the superior temporal gyrus, temporo-parietal cortex, basal ganglia, anterior cingulate gyrus, cerebellum and hippocampus [25]. This network of cortical regions is also known as the cognitive control circuit because it controls cognitive processes and provides information processing mechanisms.

Electrical stimulation techniques in children and adults have shown that electrical stimulation improves the severity of symptoms in different psychiatric and neurological disorders, such as depression [26], schizophrenia [27] and dyslexia [28]. In this regard, suggested that GVS might be of therapeutic importance as a new approach for ADHD, especially due to its beneficial effects on large-scale brain networks.

Therefore, in this study, we decided to investigate the effect of GVS on improving inhibitory function and sustained attention in children with ADHD. In order to increase the activity in both hemisphere of the cerebral cortex, we used a bipolar bilateral electrode arrangement with anode electrode on the right mastoid and a cathode on the left.

Methods

This study, with non-randomized clinical trial, was conducted after obtaining approval from the Research Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.FNM.REC.1398.081). The study was conducted according to the Declaration of Helsinki by the World Medical Association. The steps of the research as well as the possible risks of the electrical stimulation intervention were fully explained to the parents. The parents completed the consent form prepared for this purpose and they were free to leave the study at any stage.

Study sample

Seventeen children with ADHD (male = 9 and female = 8; mean age: 10.87 ± 1.30 and 9.88 ± 1.35 years) in the age range of 9−12 years (mean: 10.35 ± 1.36 years) participated in this study. The final diagnosis of ADHD was made by a child and adolescent psychiatrist, based on the Diagnostic and statistical manual of mental disorders (DSM-5) criteria [29]. Based on the inclusion criteria in this study, the evaluation of intellectual function was performed by a psychologist using the Wechsler Intelligence Scale for Children-Revised (WISC-R) [30]. The participants' verbal IQ score was within the range of 90−132 (107.29 ± 14.28). All participants were monolingual (native Persian speakers) and right-handed (according to the Edinburgh handedness inventory) with normal hearing (better than 20 dB HL) at 250–8000 kHz frequencies. None of the children had a history of a vestibular disease or accompanying neurological disorders. Also, none of the participants reported any other significant cognitive activity, such as painting or playing music. Any participants who felt dizzy or intolerant of skin irritation were excluded from the study.

Cognitive tasks

Equiprobable auditory go/no-go task

The go/no-go task is generally used to evaluate sustained attention and inhibitory function. In equiprobable auditory task two different auditory stimuli are used, that are presented randomly in equal numbers [31]. In the present study, event-related potentials (ERPs) are investigated for both the go or target stimulus (1000 Hz) and the no-go or standard stimulus (1500 Hz). In this test, the subjects were exposed to 150 tones (75 tones at 1000 Hz and 75 tones at 1500 Hz) of 50 ms duration and 5 ms rise/fall time in a random order, with fixed stimulus-onset asynchrony (1100 ms) presented through sound fields at

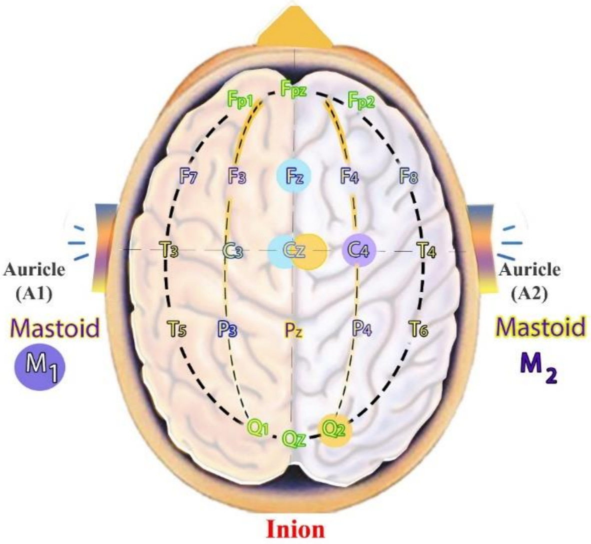

Fig. 1. Schematic representation of brain regions based on the 10−20 system

60 dB SPL. Prior to the experiment, the subjects were familiarized with both tones, and the target was introduced.

When performing the task, the participants were asked to accurately and quickly press the button with the right hand and finger thumb when hearing the target stimulus and to refrain from pressing the button when hearing the standard stimulus. In this task, the error response to the no-go stimuli (commission or no-go error) determines inhibitory function. The error response to the go stimuli (omission or go error), indicates sustained attention. Also, regarding the go reaction time, the speed of response to the go stimulus was assessed, and durations longer than 700 ms were ignored.

Experimental design

All subjects, were examined in three different conditions at one-week intervals. In the first condition (baseline), no intervention was performed; in the second condition (sham), no effective stimulation was provided; and finally, in the third condition (GVS), the anode electrode was placed as the active electrode in the right mastoid region and the cathode electrode was placed as the inactive electrode in the left mastoid region. Stimulation with two electrodes of different polarities (anode and cathode) placed behind the mastoids is known as the bilateral bipolar GVS method. The order of the three conditions, except for the baseline, was randomized. The participants were blinded to the experimental conditions (stimulation or non-stimulation). To avoid bilateral bias, the experimenter was also blinded to the stimulation condition for all participants. Besides, a trained person was asked to apply electrical stimulation to eliminate the examiner's role. Therefore, this study was perfectly blinded. For the GVS intervention, an electrical brain stimulator (Neurostim 2, Co, Iran) and two rubber conductive electrodes (5 cm×5 cm), covered with 9% saline-soaked synthetic sponges, were used.

The electrodes (anodal M1 and cathodal M2 electrodes) were placed over the mastoid region (Fig. 1), according to the 10−20 system for electroencephalogram (EEG) electrode placement by measuring the size of the skull.

During the electrical stimulation intervention, the current increases in the first 30 seconds (gradual increase). Then, a constant direct current of 2 mA was delivered for 20 minutes and then gradually reduced to 0 mA in the last 30 seconds.

For the sham intervention, the generated current was applied for only 30 seconds to create the initial stimulus sensation, this duration was adequate for creating a sensation of stimulation. Therefore, the participants could not distinguish whether they had received the actual or sham treatment [32]. The ERP measurements were performed at baseline; immediately after the removal of GVS electrodes in the sham condition (application of electrodes for 20 minutes without effective stimulation); and after 20 minutes of exposure to a 2-mA current from GVS polarities.

Event-related potential recording

The ERP data were recorded using an EEG device (EBI Neuro, Netherlands), with active Ag-AgCl electrodes at three midline electrode sites (Fz, Cz, and Pz). The electrode, placed at the right and left auricles (A1 and A2), was used as the reference. The ground electrode was attached close to the forehead (Fpz), according to the international 10−20 system [33]. False waves caused by eye movements are controlled by a

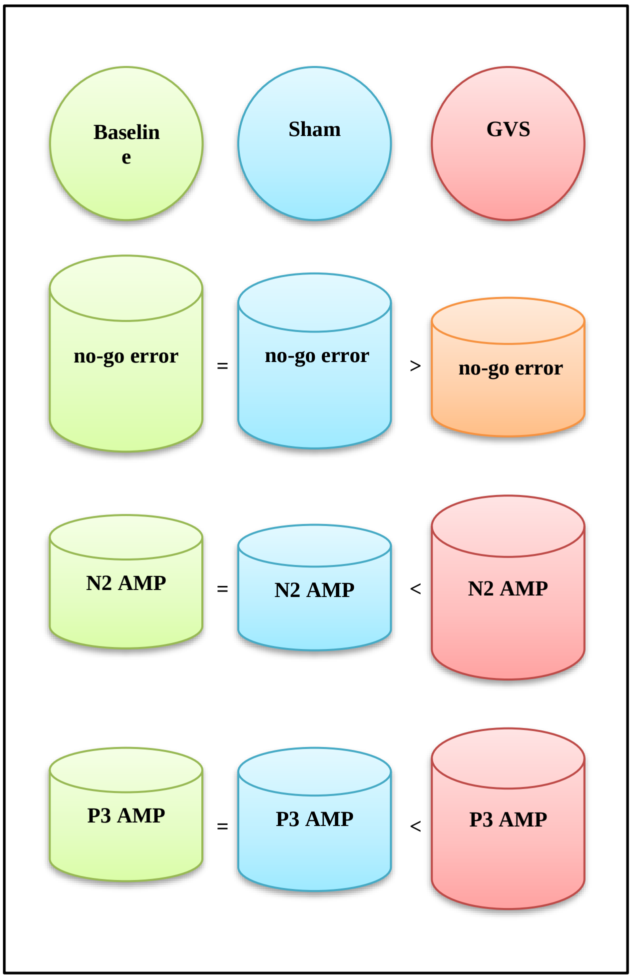

Fig. 2. Schematic representation of three experimental conditions and recording behavioral and electrophysiological results. N2 AMP; N2 amplitude, P3 AMP; P3 amplitude.

bipolar electrode montage (supraorbital to the lateral canthus). Also, an artifact rejection criterion was considered to eliminate unwanted high-amplitude waves. The average recording time of ERP responses for each participant was eight minutes. Electrode impedance less than 5 ohms was considered. ERP responses were performed in a room with soundproofing and without electrical interference.

Data processing

Data processing was performed concurrently with response recording, using Galigo device software. In data processing, bandwidth of 0.1−25 Hz was used. The time window was considered to be 600 milliseconds, calculated from 100 milliseconds before the start of the stimulus and 500 milliseconds after the stimulus. Data were digitized at 512 Hz.

Data analysis

A negative amplitude wave, with a latency of about 180 ms, appeared after the stimulus was presented (marked as N200). Within 300 ms after stimulation, a wave with a positive amplitude and forehead propagation appeared (labeled as P3). The peak amplitudes were quantified by measuring the baseline-to-peak amplitudes at the midline electrodes. The absolute latency was also defined as the interval between the onset of the stimulus and a change in the waveform of the auditory evoked potential [34]. The peak of response to the go task were referred to as go-P3. Also, the peak of response to the no-go task were referred to as no-go N2. The behavioral performance on the task was determined by calculating the reaction time to the go stimuli, omission response (go error) to the go stimuli, and commission response (no-go error) to the no-go stimuli [35].

Statistical analysis was performed in SPSS version 24. Continuous variables are presented as mean ± standard deviation (SD). The normal distribution of data was assessed, using Shapiro-Wilk test. The amplitude and latency data were evaluated using repeated-measures ANOVA (RM-ANOVA), with task (go and no-go) and condition (GVS, baseline, and sham) as the within-subject factors. Moreover, post-hoc pairwise comparisons, adjusted by Fisher's least significant difference (LSD) test, were performed. Mauchly's test of sphericity was also used to assess the sphericity assumption. If this assumption was violated, the Greenhouse-Geisser correction was performed. All statistical tests were two-sided, and $p < 0.05$ was considered as significant for the RM-ANOVA test. Also, partial eta squared (η^2p) effect sizes were measured (Fig. 2).

Results

Table 1. Means and standard deviations of the behavioral outcomes in three experimental conditions

	Mean ± SD						
	Baseline	**Sham**	**Right anode/ left cathode**	**F**	**p**	**Effect size (η2p)**	**Pairwise comparisons***
Omission (go error)	13.3 ± 1.4	13.2 ± 1.3	12.52 ± 1.12	2.64	0.111	0.141	RL < S = B
Reaction time	521.6 ± 71.7	523.2 ± 72.1	482.6 ± 32.9	1.80	0.195	0.101	RL < S = B
Commission (no-go error)	14.3 ± 3.2	13.7 ± 3.1	12.1 ± 2.7	16.74	< 0.001	0.511	RL < S = B

RL; anode electrode in right mastoid/cathode electrode in left mastoid in galvanic vestibular stimulation intervention, S; sham, B; baseline
*Fisher's LSD test

Behavioral data
The mean and standard deviation of behavioral outcomes (omission errors, commission errors, and reaction time) were calculated in the sham, baseline, and GVS conditions (Table 1).
The results of RM-ANOVA indicated a significant difference between the three experimental conditions in terms of commission response (no-go error). The results of post-hoc test also showed a significant difference in the no-go error between the GVS and sham conditions. In other words, the no-go error decreased following the GVS intervention, compared to the baseline ($p < 0.00$). Despite some indications of the reduced number of go omission errors and reduced mean go reaction time with GVS, the differences were not statistically significant ($p > 0.05$). Also, the results of the analysis showed no significant difference between the baseline and sham conditions in terms of behavioral outcomes in the go and no-go tasks.

Event-related potential data
The mean and SD of peak amplitudes and latencies are presented in Tables 2 and 3.

N2 amplitude
Regarding the N2 amplitude, RM-ANOVA indicated the significant main effect of stimulation factor on N2 amplitude in the no-go task $F(_{1.45,15}) = 9.86$, $p < 0.002$, $\eta 2p = 0.381$). Also, the results of bonferroni test revealed no significant difference between the baseline and sham conditions N2 amplitudes following GVS in no-go task.

N2 latencies
The results of RM-ANOVA indicated the significant main effect of stimulation on the N2 latencies in the no-go task ($F(_{1.06,16}) = 13.70$, $p < 0.002$, $\eta 2p = 461$) which were shorter in GVS condition. The results of bonferroni pairwise test showed no significant difference between the baseline and sham conditions regarding N2 latency in the no-go task.

P3 amplitudes
The significant main effect of stimulation on P3 amplitudes was observed in the go task ($F(_{1.85,15}) = 26.87$, $p < 0.001$, $\eta 2p = 0$ .627).

P3 latencies
The results of RM-ANOVA indicated the significant effect of experimental conditions on the P3 latencies in the go task ($F(_{1.6,15}) = 8.12$, $p < 0.003$, $\eta 2p = 0.$ 0.337). Bonferroni test showed no significant difference between the baseline status and sham condition regarding the P3a amplitudes and latencies in the go task ($p = 0.721$).

Discussion
In the present study, we investigated the effect of GVS on cognitive function in children with ADHD using behavioral outcomes and ERP responses. It has been hypothesized that vestibular stimulation using the GVS method with extensive effects on the brain network can improve response inhibition and sustained attention. We

Table 2. Means and standard deviations of peak amplitudes and latencies for the N2 component in the no-go task at Fz electrode in three experimental conditions

	Mean ± SD						
	Baseline	**Sham**	**Right anode/ left cathode**	**F**	**p**	**Effect size (η2p)**	**Pairwise comparisons***
N2 Afz (μV)	−7.76 ±0.79	7.53 ± 0.7	−8.4 ± 0.76	9.86	< 0.002	0.381	RL < S = B
N2 LFz (ms)	261.1 ± 19.1	259.2 ± 17.8	244.9 ± 13.9	13.70	< 0.002	0.461	B = S > RL

N2 Afz; N2 amplitude (Fz electrode), RL; anode electrode in right mastoid/cathode electrode in left mastoid in galvanic vestibular stimulation intervention, S; sham, B; baseline, N2 LFz; N2 latency (Fz electrode)
*Fisher's LSD test

found a significant reduction in the commission response to the no-go task in the behavioral assessment. GVS effectively increased the participants' ability to inhibit themselves and not to press a button in exposure to the no-go stimuli. However, the omission error and reaction time in the go task after GVS stimulation compared with sham condition showed signs of reduction but were not statistically significant.

As expected, we found a larger P3 amplitudes and shorter latency in go condition. The amplitude of the P3 wave in cognitive processes and attention functions reflects the amount of resources allocated to these processing activities.

Furthermore, larger N2 amplitudes and shorter latency were found in no-go conditions after GVS condition compare to sham status. This finding confirms the hypothesis that GVS can induce the modulation of cognition function in children with ADHD. However, even though omission error and reaction time following GVS was not significantly different relative to the baseline session, the P3 amplitude was larger and latency was shorter than during the baseline session and sham status. This is remarkable, because previous studies have shown that behavioral performance of attention decreases when aspects of inhibitory task are added [36]. In addition, behavioral outcomes in stimulus-response processes are influenced by various factors including stimulus evaluation, response selection, and response execution. However, the latency and amplitude of ERP responses are thought to reflect the timing of stimulus evaluation and the amount of resources allocated to the stimulus, and are generally independent of response processes [37]. Numerous studies have also shown that electrophysiological responses are more sensitive than behavioral responses, and the resulting changes in these responses are more pronounced [34,38].

The effect of GVS on cognitive functions in humans is possible based on the findings of existing studies and hypotheses. Allen et al., in a study stated that the association of the cerebellum with limbic structures and prefrontal cortex is influential in cognitive and attention functions [39]. One of the most important sensory inputs to the cerebellum is the vestibular system. The neuro-anatomical relationship of the cerebellum with the cognitive center in the frontal cortex as well as the limbic system is effective in increasing the level of consciousness and attention [40,41]. Vestibular stimulation gradually calms children by creating uniformity in the autonomic nervous system, which leads to a significant effect on hyperactivity and attention of children in treatment sessions [40]. Vestibular connections to the fronto-parietal network and subcortical brain structures such as the thalamus can describe the role of the vestibular system in human cognitive functions, especially attention [42]. On the other hand, according to several studies, the neuro-anatomical connections between the vestibular and limbic systems, as well as the fronto-parietal network, hypothesize that these systems function as a unit [42,43]. Therefore, stimulation of the vestibular system activates the fronto-parietal network, which improves attention and increases the level of consciousness.

Table 3. Means and standard deviations of peak amplitudes and latencies for the P3 component in the go task at Fz electrode in three experimental conditions

	Mean ± SD						
	Baseline	**Sham**	**Right anode/ left cathode**	**F**	**p**	**Effect size (η2p)**	**Pairwise comparisons***
P3 Afz (μV)	3.92 ± 0.88	4.01 ± 0.58	5.22 ± 1.2	26.87	< 0.001	0.627	RL < S = B
P3 LFz (ms)	320.8 ± 10.1	323.7 ± 11.2	303.4 ± 17.6	8.12	< 0.003	0.337	B = S > RL

P3 AFz; P3 amplitude (Fz electrode), RL; anode electrode in right mastoid/cathode electrode in left mastoid in galvanic vestibular stimulation intervention, S; sham, B; baseline, P3 LFz; P3 latency (Fz electrode)
*Fisher's LSD test

This could be another reason for increased level of attention function in the intervention group in comparison with sham condition. In the present study, inhibitory role of vestibular stimulation in children with ADHD was affected by increasing the amplitude of the N2 wave and decreasing the commission error in the go/no-go test. Organized and ongoing balance training programs in children improve high-level cognitive functions, including response inhibition [44]. Balance training programs at various levels can stimulate the vestibular, neuromuscular and proprioceptive system. The perception of self-motion and balance is coded by vestibular detection of inertial motion, in conjunction with proprioceptive and visual signals [45]. Neuroanatomical communication between the vestibular system and the cerebellum, hippocampus, as well as prefrontal and parietal cortices increases the activity of these areas and improves cognitive functions, including spatial functions, memory and inhibitory function [12,44]. It has been speculated that an increased stimulation of the vestibular system during self-motion might be an essential mediator between physical exercise and cognitive functioning [46].

GVS procedure, like physical exercise and balance training, can be used to externally stimulate the vestibular system, which is vital for motor control and spatial self-motion perception. Afferents from the otolith organs and the semicircular canals converge with optokinetic, somatosensory and motor-related signals in the vestibular nuclei, which are reciprocally interconnected with the vestibulo-cerebellar cortex and deep cerebellar nuclei [12]. Physiologically, regular and repetitive balance exercises have positive effects on the neurotrophic system. After balance training, the production of brain-derived neurotrophic factor and the function of its receptors in the cere bellum and limbic system is activated. The neurotrophic system plays an important role in nerve flexibility and cognitive function, and is considered a biomarker of the cognitive benefits of exercise. GVS, similar to physical exercise, stimulates the vestibulo-cerebellar circuit [47]. Based on the contents mentioned in the previous sections, it can be concluded that stimulation of the vestibular system by the GVS method can lead to changes in cognitive functions, including inhibition of response and attention. Consistent with the results of our study, many studies in the field of electrical stimulation have examined the effects of GVS on cognitive function. Findings show that GVS has positive effects on some cognitive aspects such as face perception and visual facial memory [48,49]. GVS has also been applied to patients with hemispatial neglect [50] and Parkinson's disease [51].

Conclusion

Today, the use of new and creative methods to increase nerve flexibility and improve cognitive function is increasingly observed in research studies. Among a wide range of intervention programs including cognitive therapy, mind training and magnetic therapy, galvanic vestibular stimulation (GVS) intervention seems to be an effective way to stimulate the atrial system and improve cognitive function. Based on the findings of the study, it can be concluded that GVS approach in children with attention deficit/hyperactivity disorder has positive effects on response inhibition and sustained attention.

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Conflict of interest

No conflict of interest was stated by the authors

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