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Can Galvanic Vestibular Stimulation Be an Effective Management for Bilateral Vestibulopathy?

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Abstract

Background: Vestibulo-ocular and vestibulospinal reflexes contribute to postural stability and gaze stabilization during head and body movements. Thus, chronic disequilibrium, postural imbalance, and oscillopsia occur after bilateral vestibulopathy (BVP). This disorder reduces the daily physical activity and seriously affects the quality of life. Because of its limiting and hazardous consequences, it is necessary to plan an effective therapeutic and rehabilitative strategy for BVP. Recent attempts have used the beneficial effects of stochastic resonance through noisy galvanic vestibular stimulation (nGVS) for this purpose. The present paper aimed to review the effects of nGVS on balance functions in patients with BVP.

Methods: This review article investigated research papers in the field of usefulness of nGVS in the treatment of BVP. In the initial search, a total of 134 articles were found with keywords of this manuscript in the SID, Google Scholar, Science Direct, and PubMed databases, of which 7 articles were considered relevant to our subject.

Results: The results of these articles suggest that nGVS can have ameliorating effects on the static and dynamic balance as well as on the vestibular performance in BVP patients.

Conclusion: In BVP, nGVS may be useful in designing prosthetics for permanent use by the patient, and/or as a method for enhancing the neuroplasticity in combination with other therapies, such as vestibular rehabilitation.

Keywords: Noisy Galvanic Vestibular Stimulation, Stochastic Resonance, Bilateral Vestibulopathy

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Introduction

The peripheral part of the vestibular system is located in the inner ear, including 3 semicircular canals and 2 otolithic organs responsible for angular and linear acceleration, respectively. This system contributes to balance control in association with visual and somatosensory systems. The vestibular system coordinates the head and eyes movements and activates the postural control muscles, thereby maintaining balance, proper head and body orientation, and gaze stabilization during head movements (1).

The loss or absence of bilateral function of the vestibular end organs or nerves, or a combination of the 2 conditions, is known as BVP (2). The prevalence of this disor-

↑What is "already known" in this topic:
Galvanic vestibular stimulation has a therapeutic and ameliorating effect in the improvement of static and dynamic balance functions in healthy people and patients with bilateral vestibulopathy.

→What this article adds:
This study analyzed the available evidence to identify the different dimensions of the efficacy of galvanic vestibular stimulation as a treatment modality for bilateral vestibulopathy. This method can be a complementary method along with other therapies, although it is necessary to study its long-term effects and its maximum degree of therapeutic sustainability.

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der was previously estimated as 28 per 100,000 adults in the United States (3). The etiology of bilateral vestibulopathy (BVP) often remains unknown and the most commonly known causes include the use of ototoxic aminoglycosides, bilateral Ménière disease, meningitis, and genetic mutations (4). It is noteworthy that the vestibular function loss may also occur by aging due to the decrease in the number of vestibular hair cells (5).

Bilateral loss or failures in peripheral vestibular inputs results in a deficiency in vestibulo-spinal and vestibulo-ocular reflexes (VOR), orientation, and navigation (2). Impaired vestibulospinal reflexes (VSR) lead to unsteadiness during walking and standing, which is a characteristic of this disorder. It becomes worse in the darkness and/or uneven surfaces or during head movements (6) and in the presence of a peripheral neuropathy (7). Decreased VOR leads to oscillopsia (8) and reduced dynamic visual acuity during head movements (9). In the absence of visual and somatosensory cues (such as descending from stairs in the darkness), where the subjective verticality perception is reduced, these patients experience impaired orientation and navigation and consequently spatial disorientation, although they typically do not show any symptoms while sitting or lying down in static positions (2). These complications increase the falling risk in patients with BVP (10).

The outcomes of BVP can reduce the level of everyday activities and reduce individual autonomy, social interactions, and quality of life, and finally the patient may be isolated. Therefore, thinking about appropriate preventive or therapeutic approaches to eliminate or minimize these consequences is necessary. One of the preventive approaches is to provide counseling to the patient to identify the potential risks of this disorder to increase their safety, such as turning on the lights at night, avoidance of driving, and also making proper changes in the workplace and at home (11). Therapeutic approaches include optimizing the residual vestibular function or substituting other mechanisms to gaze stabilization and postural stability during head movements. It seems that an ideal therapeutic strategy for these patients is to provide information that is routinely sent to the brain by a healthy vestibular system. However, in some cases, such as the vestibular nerve section, this method cannot be thought of, and alternative means should be considered.

So far, there has been no unique and agreed upon treatment for BVP, and based on clinical findings and theoretical foundations, several strategies have been proposed. Here, a brief explanation of different approaches, benefits, and limitations of each one is discussed.

The common option for treatment of BVP is physical therapy. The purpose of physical therapy is to use visual and proprioceptive cues to compensate for the lack of vestibular function (12). However, the majority of patients do not benefit from this kind of intervention (13). Another method is to use sensory substitutive devices based on the principle of replacing lost sensory feedbacks by signs and symptoms of other sensory sources. Accordingly, a sensor connects to the body, controls the balance information, and triggers equilibrium feedbacks by auditory, tactile electrical (tongue) and tactile vibration (trunk) stimulation (14, 15). Limited encoded equilibrium information, compared with the widespread information of an intact vestibular system, and failure to provide comprehensive treatment for all symptoms associated with BVP are among the limitations of this method (16). Artificial vestibular implantations have been inspired by the successful application of cochlear implants (17) and provide vestibular feedbacks by direct electrical stimulation of the nerves. So far, the use of these implants has been limited to restoring the function of the semicircular canals (18), but it is a very invasive method that may lead to a permanent hearing loss (12). Active vestibular rehabilitation (including vestibular adaptation and compensatory strategies) is also performed in BVP patients, which can improve dynamic gait stability and dynamic visual acuity in a group of patients, however, the benefits of rehabilitation for rapid and unpredictable movements are limited. In addition, the combination of some factors or patient characteristics, such as age, onset of the BVP, and usual physical activity of the patients, may affect the effectiveness of treatment (19).

Noisy GVS (Noisy galvanic vestibular stimulation) has been used to study the human vestibular system and its role in postural stability and walking. The results of previous studies have shown that galvanic stimulation has a therapeutic and facilitating role in the improvement of balance functions in healthy people and patients with BVP (20-30). It has been shown that galvanic stimulation stimulates the activity of vestibular hair cells in addition to the effect on early afferents (31). Except for the case of vestibular nerve section, some degrees of vestibular responses may remain in BVP. In such cases, it is logical that therapeutic approaches focus on the optimization of the residual vestibular function. Based on this, efforts have been directed to recruit and strengthen the remaining vestibular function in patients with BVP, using subthreshold electrical noise (nGVS) to vestibular end organ. Galvanic vestibular stimulation is a simple, safe, and tolerable method for stimulating the neuronal activity of the semicircular canals and otolithic organs of the peripheral vestibular system. In this method, a weak electrical current is transmitted subcutaneously to the vestibular hair cells and afferents through the cathode and anode electrodes that are placed on the 2 mastoid processes (32). Since no method is considered as an absolute and unique treatment option, nGVS, in turn, is a complementary method along with other therapies. The objective of this article was to explain and discuss the potentials and efficacy of nGVS as a treatment modality for BVP.

Review of the Literature

To investigate the usefulness of nGVS in the treatment of BVP all related papers in this field were reviewed from January 2000 to May 2020 by searching the following keywords: "noisy galvanic vestibular stimulation (nGVS)," "stochastic resonance," "BVP," "bilateral vestibular hypofunction," "bilateral vestibular areflexia," "bilateral vestibular loss," and "bilateral vestibular failure" in the SID, Google Scholar, Science Direct, and PubMed databases.

In the initial search, a total of 134 articles were availa-

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ble. The inclusion criteria for article selection were as follows: availability of full-text articles in English, studies that used GVS only, and the use of qualitative or quantitative scales to evaluate the effects. The abstracts, case reports, cohort studies, and non-English articles were excluded from the review. Based on these criteria, 7 articles were considered relevant to our subject. In these articles, study groups and number of participants in each group, GVS parameter's (intensity level, frequency, how to determine the level of optimal intensity in studies in which this parameter is measured), type of evaluation and variables, type of subjective improvement assessment in studies in which this parameter is measured, and main results of the article were reviewed. The summary of the literature review is presented in Figure 1.

Recent Findings

A total of 95 patients with BVP and 127 healthy people were studied in the reviewed articles. Three studies used the optimal intensity level, and the method of determining the optimal level was different in all of them. In 2 studies, 80% of the cutaneous threshold criterion was used, 1 study considered 80% of the perception (vestibular sensory) threshold, and in another article a fixed "1 mA × 2s" criterion was used. The galvanic stimulation frequency was white noise with 0.02 to 10 Hz in 3 articles, 0 to 30 Hz in 2, and 0.02 to 20 Hz in 1 article. In one article the type of galvanic stimulation was not mentioned (Table 1).

Type of evaluations in 6 articles were different variables of static or dynamic balance functions, including evaluation of the COP (Center of pressure) (velocity, area, and RMS), the VSR threshold, walking performance (gait velocity, stride length, and stride time, base of support, and double support time percentage), variables of bilateral coordination of walking (the coefficient of variation of stride time, stride length, and base of support, also the bilateral phase synchronization by phase coordination index), and whole-body movement, and ground reaction force evaluation. Effects of GVS on cortical responsivity in BVP and healthy people were studied with MRI in just 1 article. Four studies assessed the GVS subjective improvement. In 3 of them, patients reported improved balance function during and even after stimulation, and in 1, patient sensation to a stimulus and its effects on body balance was asked, however, results were not mentioned (Table 2). The main results of 7 reviewed articles are summarized in Table 2.

Discussion

Based on the present review, studies in the field of nGVS have addressed reflexive functions of the vestibular system, and the majority of them focused on the facilitating effects of nGVS on VSRs and static and dynamic balance improvement.

Vestibular Reflexes

A safe and independent movement depends on awareness of the environment features while maintaining the proper body orientation related to support surface and gravity (33). Integration of sensory inputs from visual, somatosensory, and vestibular systems is needed for postural control (34). Balance information, including vestibular, somatosensory and visual inputs, and motor commands, are simultaneously processed and integrated through a central processor, the "vestibular nucleus complex." Although balance control and walking are controlled by many structures in the brain, the vestibular system plays a special role. One of its roles is the detection of the head orientation related to the gravity axis, which is 4 to 5 times more accurate than the vision. This subtle detection of head orientation leads to a proper adaptation to gravity and the prevention of imbalance and falls (35). Since vestibular nucleus sends motor commands to the eyes and the body, timely and directed signals are required to the vestibular reflexes effectors, that is, skeletal and extraocular muscles and extensive communication between the vestibular nucleus complex, cerebellum, ocular motor nucleus, and the brainstem reticular formation sys-

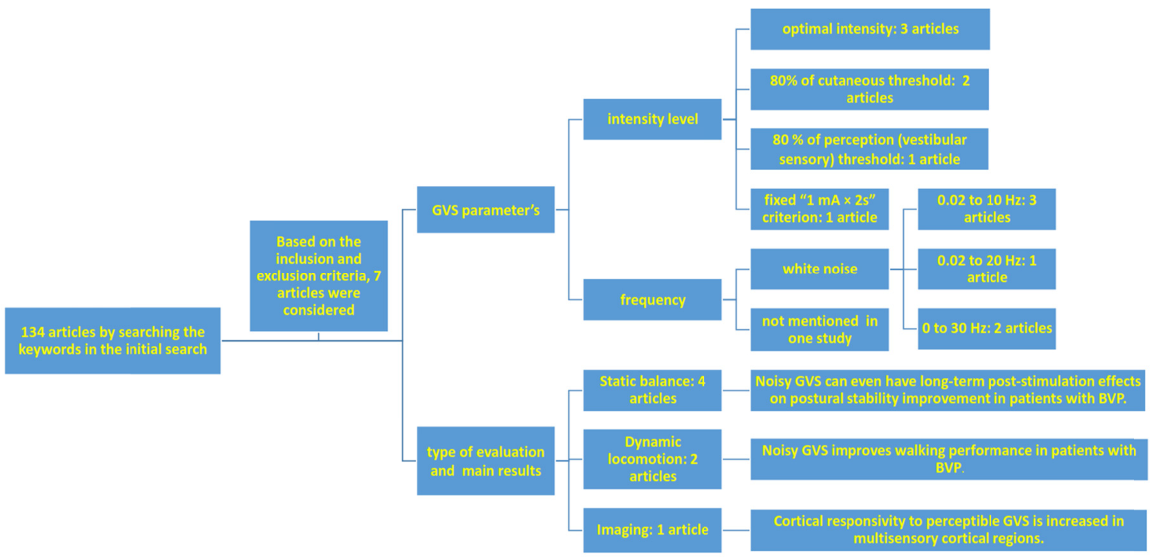

Fig. 1. Graphical abstract of the literature review.

Table 1. Summary of Articles on Galvanic Stimulation in BVP

How to Determine the Level of Optimal Intensity	Galvanic Stimulation Frequency	Galvanic Stimulation Intensity Level	Samples	Authors
Helmchen et al. 2019	26 BVP patients and 27 age matched healthy control	1) Perceptible GVS: low (0.5 mA) and high intensity current (1.5 mA) above the perceived threshold. 2) Imperceptible noisy GVS: with a maximum of 80% of the current at perception threshold.	White noise GVS: 0.02 to 20 Hz	---------------------
Fujimoto et al. 2018	13 BVP patients	The mean of optimal intensity: Session 1: 454 µA Session 2: 462 µA	White noise GVS, ranging from 0.02 to 10Hz	The intensity at which all parameters of the center of pressure was smaller than baseline values.
Schniepp et al. 2018	12 BVP patients in two groups: rBVP (10 patient) and cBVP (2 patient)	sGVS: 0 to 1.9 mA nGVS: 80% of cutaneous threshold	sGVS: 1 HZ nGVS: 0 to 30 HZ	---------------------
Iwasaki et al. 2018	19 healthy subjects and 12 BVP patients	The mean of optimal intensity in healthy subjects: 342 ± 46 µA (subthreshold) and in patient: 725 ± 46 µA (subthreshold)	White noise GVS: 0.02 to 10 HZ	The intensity at which gate velocity was the largest.
Wuehr et al. 2016	13 BVP patients	80% of cutaneous threshold The mean intensity: 381.5 µA	White noise GVS: 0 to 30 HZ	-------------------
Iwasaki et al. 2014	21 healthy subjects and 11 BVP patients	The mean of optimal intensity in healthy subjects: 281.2 ± 39.8 µA (subthreshold) and in patient: 455.6 ± 81.8 µA (subthreshold)	White noise GVS: 0.02 to 10 HZ	The level of nGVS at which the ratio of the variable to the baseline period was smaller than trials with no stimulation (0 µA) for all three parameters (velocity, area and RMS of the COP) simultaneously.
Tax et al. 2013	60 healthy subjects and 8 BVP patients	1 mA × 2s	The type of galvanic stimulation has not mentioned.	---------------

BVP bilateral vestibulopathy, rBVP patients with residual function, cBVP patients with complete loss, sGVS sinusoidal galvanic vestibular stimulation, nGVS noisy galvanic vestibular stimulation, COP center of pressure

tem maintain the needed accuracy. The vestibular system is controlled and regulated by the cerebellum (36).

The motor output of the central vestibular system to eyes and the body are implemented through 3 reflexes: vestibulo-ocular, vestibulocollic, and VSRs. The VOR produces eye movements and allows clear vision during head movements. The vestibulocollic reflex (VCR) affects the neck muscles for fixation of the head. The VSR is composed of several reflexes that are named according to the timing (dynamic versus the static or tonic) and the sensory inputs (canal against the otolith) (36). The function of the VSR is to interact with the neck and antigravity muscles, producing compensatory body movements, thus maintaining the position of the head in space, postural stability, and regulating the upright position (37). The efferent connections between vestibular nucleus complex and spinal cord levels form the anatomical basis of VSRs and on a larger scale, the head and limbs postural control (38). Modulations of this reflex with accurate motor coordination maintain the static and dynamic balance (39).

The results of the previous studies indicate that movement perception and spatial orientation are strongly dependent on the vestibular signals, and the somatosensory replacement and the central compensation itself are not enough to replace them. Thus, weakness in vestibular functions, including poor vestibular reflexes, is associated with numerous problems. For example, poor VSRs lead to balance disorder, decreased gait speed, and an increased risk for falling, and also the low gain of the VOR complicates the clear vision during head movements, especially unpredictable ones (40).

Therefore, due to defective vestibular signals, the weakness of vestibular functions and severe gait and balance disorder are not unexpected in BVP patients (35).

Noisy GVS: As a Potential Method for the Treatment of BVP

In patients with BVP, vestibular information processing becomes significantly damaged due to abnormally elevated thresholds of signal detection (41). Besides, during common balance activities, even in normal individuals, a significant amount of vestibular signals resulting from natural head movement remain below the threshold level of the vestibular afferents (30), and therefore no vestibular

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Table 2. Summary of Evaluation Tools and Results of Articles on Galvanic Stimulation in BVP

Results	Subjective Improvement Assessment	Type of Evaluation and Variables	Samples	Authors
Helmchen et al. 2019	26 BVP patients and 27 age matched healthy control	MRI	-------------------	Cortical responsivity to perceptible GVS (both high-intensity and low-intensity) is increased in multisensory cortical regions (visual-vestibular) in BVP patients compared to normal subjects. This incensement is correlated with the vestibular symptoms severity and handicap in daily life. Imperceptible nGVS stimulation does not cause significant cortical activity, which may be due to the lack of wick background vestibular stimulation.
Fujimoto et al. 2018	13 BVP patients	Posturography (COP evaluation)	Subjective improvements of body balance assessments after each posturography testing at predetermined time points	Noisy GVS by reducing the high-frequency components of the postural locomotion can have long-term post-stimulation effects on improving the postural stability in BVP patients.
Schniepp et al. 2018	12 BVP patients in two groups: rBVP (10 patient) and cBVP (2 patient)	Evaluation of VSR threshold	------------------	The results of this study showed that in patients with BVP, there is a potential of facilitating effects of the SR phenomenon, because in patients with residual vestibular function, the addition of nGVS improved the threshold of VSR reflex in 90% of patients.
Iwasaki et al. 2018	19 healthy subjects and 12 BVP patients	Evaluation of walking performance with parameters including gait velocity, stride length and stride time	The patient sensation to stimulus and its effects on body balance was asked, but results have not mentioned.	Noisy GVS improves walking performance in patients with BVP and reaching the levels of variables to normal subjects.
Wuehr et al. 2016	13 BVP patients	1. variables of spatiotemporal gait pattern (stride length, stride time, base of support and double support time percentage) 2. variables of bilateral coordination of walking (the coefficient of variation (CV) of stride time, stride length, and base of support, also the bilateral phase synchronization by phase coordination index (PCI)	Positive correlation between subjective rating of walking balance and objective improvement in walking performance for slow speeds	Noisy GVS has a significant improving effect on walking stability in BVP patients, especially at low speeds.
Iwasaki et al. 2014	21 healthy subjects and 11 BVP patients	COP evaluation (velocity, area and RMS)	All healthy subjects and 7 of 9 patient responsive to stimulation reported the postural balance improvement at optimal intensity (compared with the baseline period)	Imperceptible levels of nGVS have been effective in improving postural function in normal subjects and in patients with BVP.
Tax et al. 2013	60 healthy subjects and 8 BVP patients	Evaluation of whole-body movement and ground reaction force Variables: the displacement, velocity and ground reaction force	------------	In normal subjects, monaural-galvanic stimulation caused the anterolateral sway of the entire body away from the cathode. In patients with BVP, the response was reduced or absent. Body sway induced by galvanic stimulation (galvanic VSR) provides valuable information on the amplitude and symmetry of the vestibulospinal projections, rehabilitation and follow-up of patients.

BVP bilateral vestibulopathy, COP center of pressure, rBVP patients with residual function, cBVP patients with complete loss, VSR vestibulospinal reflex, sGVS sinusoidal galvanic vestibular stimulation, nGVS noisy galvanic vestibular stimulation

reflexes is evoked. Wuehr et al (2017) observed a significant reduction in the threshold of sinusoidal GVS (sGVS) by additional application of nGVS in 90% of participants. The results of this study suggest that nGVS somehow leads to a reduction in the VSR threshold, and consequently the detection and processing of near-threshold signals

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(28). The proposed explanation for the ameliorating effects of nGVS, which is cited in most studies, is the stochastic resonance (SR), a phenomenon wherein the response of a nonlinear system to weak input signals can be optimized by the presence of a certain level of noise (42, 43). In this phenomenon, the optimal level of noise causes the greatest improvement, while further increase in the noise intensity only reduces the detectability or information content (24). For many years, the existence of this phenomenon has been studied in physics, engineering, biology, and medicine. Also, it has been shown that the appropriate intensity of noise can magnify the detection of weak near-threshold signals in a variety of sensory information, such as visual (44) and auditory perception (45, 46). Since vestibular information processing is essentially non-linear (47), the improvement of the vestibular reflexes threshold and the balance functions that have been observed in previous studies can be indicative of the presence of SR in the human vestibular system.

The important note about the facilitating effects of SR is that these effects only occur in sensory systems that have at least partially intact signal processing (43). Given that the mechanism of nGVS effects on the vestibular system is SR, it seems that residual vestibular function is required to benefit from the ameliorating effects of SR. This was observed in Schniepp et al study (2018), in which patients with complete vestibular loss did not show any difference in the threshold of VSR with and without nGVS (26) .

Based on the presence of SR in the human vestibular system, in recent years, nGVS has been used to optimize the residual vestibular function in BVP patients. It has been observed that nGVS improves static postural stability and dynamic locomotion in normal individuals and patients with BVP by augmenting the VSR, and strengthens the VOR function (20-30).

Ameliorating Effects of nGVS on Static Balance

Humans have an unstable physical structure in the standing position, and activities in this position require the ability to stabilize the body to counteract the perturbations and make voluntary movements possible. To contract the effects of gravity and to meet the requirements of body stability during voluntary movements, continuous changes occur in motor activity, especially in antigravity muscles based on continuous changes in sensory information (48). To maintain an upright standing position, both in static and in dynamic situations, antigravity muscles interact with gravitational force, and the center of gravity (COG) is continuously moving to and from around the center of the mass. This movement is called "postural sway" that occurs reflexively through VSR (49). It has been observed in various studies that increasing the velocity and sway of the COG is associated with an increased falling risk and this risk increases in patients with BVP because of the impaired vestibular reflexes (10, 50, 51).

Abnormally increased VSR threshold in patients with BVP leads to a failure to detect a significant amount of vestibular signals from head movements during common balance activities, and consequently the VSR is not excited (41). By reducing the VSR threshold, nGVS can enable the BVP patients to receive and process vestibular stimuli that were previously below the threshold and were not detected; therefore, the patient's vestibular balance regulation is partially returned. It is assumed that the SR is the basis of these corrective effects. This phenomenon improves static balance control by modifying vestibular information processing. The physiological basis of these effects is likely to be small changes in the transmembrane potentials and the canal and otolith afferent firing rate, which improves the detectability of weak inputs below the threshold of vestibular neurons (32). In Iwasaki et al study (2014), the patient's performance while receiving nGVS at the optimal intensity level was comparable to the condition of normal people standing on a foam; that is, nGVS had improved patients' function to some extent towards normal levels (25). Fujimoto et al (2018) observed that nGVS can even have long-term poststimulation effects on the improvement of postural stability in patients with BVP by reducing individual sways during standing, and only after a 30 minute application of nGVS patients showed improvement in the postural stability, especially at the velocity of the center of pressure (COP) displacement, that lasted for several hours (20). Thus, it is expected that nGVS effects postural stability, decreasing falling risk through the SR phenomenon.

Static balance improvement can be due to the change in the function of vestibulospinal pathways, which is a good indicator of behavioral adaptation to vestibulospinal disorders (52). Hence, the long-term facilitating effects of nGVS on static balance, especially only after a 30 minute nGVS application, is a promise that supports its use as an approach for the treatment of BVP.

Ameliorating Effects of nGVS on Dynamic Locomotion

Spatial orientation and the ability to walk upright are critical human functions (36). Walking is one of the most complex functions and the vestibular system participates in controlling it, allowing for the harmonious and coordinated movement of the body into the environment (48). Walking requires dynamic changes of vestibular inputs to motor neurons. Phase dependent changes in vestibular signals are observed during the walking cycle and these signals contribute to balance control in any point of stride cycle (53). Vestibular feedbacks through VSRs regulate the locomotion pattern in a phase-dependent manner and smooth the stride-to-stride sways while walking (54). Vestibular inputs form the timing (55) and the range of muscular activity (56) during locomotion. Also, the vestibulospinal system creates an appropriate level of tonicity in the extensor muscles in collaboration with the reticulospinal system during locomotion (57). The maximum effect of VSR on locomotion is on the slow speed walking and as the speed increases, this effect becomes weaker (53, 58). Thus, walking disorders in BVP patients generally increases in slow walking speed and increases the risk of falls (58, 59).

It has been shown that nGVS improves the dynamic walking stability in normal people and in BVP patients and it is most pronounced at slow rather than medium and fast speeds (29, 30). In a study by Iwasaki et al (2018), the effect of an imperceptible level of nGVS on dynamic locomotion was investigated in normal people as well as in patients with BVP; nGVS had significant facilitating effects on gait velocity, stride length, and time in both groups, and none of these parameters became worse under the stimulus conditions. The values of those parameters in BVP patients during nGVS application reached similar levels for healthy people (23). Wuehr et al (2016) evaluated the effect of nGVS on walking performance at slow, preferential, and fast speeds in patients with BVP. The results of this study showed improvement in walking stability, especially at low speed and it was concluded that nGVS was effective on bilateral coordination in walking and reduced the stride-to-stride fluctuations (29).

It seems that the rationale behind these effects is the SR. Possibly the sensitivity of the residual vestibular afferents increases and enhances the vestibular functions, including reflexes both in normal people and in BVP patients.

Subjective Effects of nGVS

Some studies have investigated the subjective effects of nGVS in addition to objective examination. In these studies, patients reported improved balance function during and even after stimulation (20, 25, 29). In Fujimoto et al study (2018), subjective improvement of body balance was maintained during the poststimulation period in addition to the objective improvement of static postural stability (COP movement) (20). These effects can be evidence for the efficacy of nGVS in improving the postural stability in patients with BVP during everyday activities.

Post stimulus Effects of nGVS on Balance Functions

Fujimoto et al (2018) have assessed the efficacy of long-term effects of nGVS on static postural stability in patients with BVP, showing that galvanic stimulation improved the posture for several hours (20). In another study, they observed these effects on postural stability in healthy elderly adults. They attributed the results to the synaptic plasticity of vestibular nuclei and cerebellum, and consequently poststimulation effects on body balance (21). In Inukai et al study (2018), the effect of nGVS on the center of pressure (COP) sway of static standing posture was examined in normal people. Interestingly, the findings of this study showed that only after 5 seconds of nGVS application, noise-induced improvement was observed and the COP sway was decreased. The authors attributed the results to the after effects of stimulation and the possibility of neural plasticity, such as LTD and LTP in vestibular nuclei potentials due to high-frequency vestibular nerve stimulation (22).

According to previous studies, vestibular neural plasticity is based on the synaptic plasticity of the vestibular nuclei and cerebellar circuits. Experimental studies have shown that learning in the vestibular system is primarily dependent on the activity of Purkinje cells in the cerebellum flocculus lobe in such a way that LTD in the synapses between Purkinje cells and parallel fibers represent the early stages of vestibular learning (60), while memory accumulation appears to be stored in vestibular nuclei. High-frequency stimulation of the vestibular nerve can cause LTP and LTD in the vestibular nuclei (61). These plastic changes in the vestibular nuclei represent memory storage in the vestibular system. Vestibular nuclei through the lateral vestibulospinal tract stimulate the ipsilateral extensor and contralateral flexor motor neurons (62). The gain and spatiotemporal characteristic of VSRs is controlled by the activity of the cerebellum (63).

Since the reorganization of neural connections is the basis for behavioral improvement (64) and as this behavioral improvement is more pronounced, neurogenesis will also be more likely (65); thus, behavioral improvements can be a sign of neurogenesis at the level of the vestibular nuclei. In this regard, Shaabani et al (2016), with a 30-minute galvanic stimulation per day for 14 consecutive days in unilaterally labyrinthectomized rats, examined the effectiveness of this intervention on the rebalancing of the vestibular nuclei. The assessment of static and dynamic balance functions as well as cell counting in the medial vestibular nucleus (MVN) indicated that in addition to significantly improving the balance functions of the rats under intervention, the percent of marked cells in the lesion side MVN was also significantly higher than that of the healthy side and also more than the percentage of these cells in other groups indicating neurogenesis in the MVN. The behavioral and immunohistochemical assessments of this study showed that this intervention can be effective in facilitating the static and dynamic vestibular compensation. The researchers attributed findings to cellular proliferation at the lesion side, reweighing inputs, and augmenting synapses in the vestibular nucleus, and finally their constructive implications on the motor outcomes of the nucleus (66).

The Effects of nGVS on Vestibular Functions

So far, there has been little research on the direct effects of nGVS on vestibular function and most studies by GVS have looked at the effects of this approach on balance functions representing the final motor output of the vestibular system. However, in a study on healthy people, low-intensity nGVS significantly increased the oVEMP amplitude to bone-conducted vibration, and the authors attributed the findings to the SR (24). Helmchen et al (2019) in an MRI study observed that vestibular cortical responsiveness to GVS in BVP patients is similar to normal people. Despite the severe damage to vestibular inputs in BVP patients, this responsiveness is promising and supports the potential use of vestibular implants or portable GVS pacemakers (67).

The Side effects of nGVS

In most studies, it has been explicitly pointed out that patients did not report pain or any other unpleasant sensation during or after the stimulation (20, 23, 25, 26, 29). Only in the study of Tax et al (2013), many participants reported mild pinprick sensations and a metal taste in the mouth, and 2 experienced nausea without vertigo, probably due to the suprathreshold intensity of nGVS (1 mA) (27). In other studies, no unpleasant sensations were reported.

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The Current Place of nGVS in our Clinical Practice in This Field

Based on our knowledge, the current place of nGVS in the management of BVP is still at the research level, and comprehensive studies on the parameters of nGVS stimulation and evaluating methods for the efficacy of treatment is necessary.

Overall, reviewing articles on the effects of nGVS in BVP suggests that this intervention can have ameliorating effects on the static and the dynamic balance as well as vestibular performance. In particular, the long-term effects of nGVS support its effectiveness in reducing the outcomes of BVP in everyday life, preventing falls, and enhancing the quality of life. However, it is necessary to pay attention to a few points regarding the studies performed in this area: (1) in reviewed studies, the underlying mechanism for vestibular reflexes function improvements to nGVS has been attributed to the SR; however, further studies on the precise mechanism in this field are needed. To understand the exact mechanism of these effects, it may be necessary to conduct more animal studies from the level of vestibular hair cells up to the cortical regions. (2) Facilitating effects of nGVS have been observed only in laboratory conditions and further studies are needed to assess the effects of galvanic stimulation on the wide range of symptoms associated with BVP in everyday life conditions (3). So far, the majority of studies have focused on the effects of nGVS on vestibular reflexes in BVP, but the potential role of higher structures in the central vestibular system has not been taken into consideration. Based on our knowledge, only in 1 study by Helmchen et al (2019) the cortical responses to GVS have been investigated in BVP patients. In their study, no response was observed to imperceptible noisy GVS in healthy participants and in BVP patients, despite the similar strong activation to perceptible GVS in both groups. According to the authors, these results may be due to the lack of weak background vestibular stimulation. However, the remaining question is that whether cortical mechanisms play a role in the nGVS-related improving of balance in previous studies (67). Since a large portion of the cortex receives vestibular signals, the stimulation of multisensory cerebral regions may also be involved in nGVS induced improvements. In this regard, Helmchen et al (2019) observed that the responses of some multisensory visual and vestibular cortical areas in BVP patients were increased compared with normal individuals, and this excitability was consistent with the severity of vestibular symptoms and dizziness-related handicap in the everyday life (67). However, it is still unclear whether galvanic stimulation can correct this increased excitability. Investigation of the effects of nGVS on higher regions of the central nervous system can provide useful information about possible noise-induced changes in these areas. (4) Considering the nature of the SR, the uselessness of nGVS in patients without residual vestibular function is not unexpected, but it is important to determine the criteria for residual vestibular function. Since each vestibular test evaluates only a part of the vestibular end organ, except in cases of vestibular nerve section, it is necessary to investigate the effects of nGVS on a vestibular test battery, including caloric, Video Head Impulse Test (VHIT), Dynamic Visual Acuity (DVA), Subjective Visual Vertical (SVV), and Subjective Visual Horizontal (SVH). The correlation between residual vestibular function based on the results of various tests, such as caloric, VHIT, oVEMP, and cVEMP, and the level of nGVS-induced improvement is essential (5). If the sustainability of the effects of this intervention becomes desirable, it can be used as a treatment or complementary approach for BVP.

Conclusion

The direct effects of nGVS on vestibular performance suggest that this intervention can be an effective method in vestibular disorders, including bilateral vestibular weakness. It is necessary to examine the long-term effects of this method on static and dynamic balance and also the maximum degree of its sustainability should be studied. Finally, to answer the main question of this article, it can be said that nGVS may be useful in BVP from 2 viewpoints: it can be the basis for designing prosthetics for permanent use by the patient; and/or as a method that increases neuroplasticity along with other methods, such as vestibular rehabilitation.

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Conflict of Interests

The authors declare that they have no competing interests.

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