The potential of noisy galvanic vestibular stimulation for optimizing and assisting human performance

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Dr. Carlo Menon has filed a patent for a galvanic vestibular stimulation device.

Abstract

Noisy galvanic vestibular stimulation (nGVS) is an emerging non-invasive brain stimulation technique. It involves applying alternating currents of different frequencies and amplitudes presented in a random, or noisy, manner through electrodes on the mastoid bones behind the ears. Because it directly activates vestibular hair cells and afferents and has an indirect effect on a variety of brain regions, it has the potential to impact many different functions. The objective of this review is twofold: (1) to review how nGVS affects motor, sensory, and cognitive performance in healthy adults; and (2) to discuss potential clinical applications of nGVS. First, we introduce the technique. We then describe the regions receiving and processing vestibular information. Next, we discuss the effects of nGVS on motor, sensory, and cognitive function in healthy adults. Subsequently, we outline its potential clinical applications. Finally, we highlight other electrical stimulation technologies and discuss why nGVS offers an alternative or complementary approach. Overall, nGVS appears promising for optimizing human performance and as an assistive technology, though further research is required.

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1. Introduction

The field of neuroscience has seen a surge of studies investigating the benefits of using a variety of magnetic and electrical non-invasive brain neuromodulation techniques on motor, sensory, and cognitive function (e.g., Adair et al., 2020; Buch et al., 2017; Coffman et al., 2014). Here, we discuss an emerging technique called noisy galvanic vestibular stimulation (nGVS). Our objective is twofold: (1) to review how nGVS affects motor, sensory, and cognitive performance in healthy adults; and (2) to discuss potential clinical applications of nGVS.

The vestibular system, whose end organs—the semicircular canals and otoliths—detect linear and angular acceleration of the head, contributes to postural and gaze stabilization through vestibulospinal reflexes and vestibulo-ocular reflexes (VOR), respectively, as well as self-motion perception and spatial orientation (Cullen, 2019). Recent research suggests that the vestibular system also plays a role in cognitive functions, such as spatial memory and navigation (Cullen, 2019; Hitier et al., 2014). These contributions are possible because the vestibular nuclei project to the spinal cord and other brainstem nuclei and are densely connected to the thalamus and in turn, to various cortical areas (Hitier et al., 2014; Lopez and Blanke, 2011). Thus, vestibular stimulation has the potential to indirectly affect a variety of brain regions and functions.

In this review, we first briefly introduce the principle of galvanic vestibular stimulation (GVS), with an emphasis on nGVS. Next, we focus on the anatomical regions receiving and processing vestibular information. Subsequently, we present a detailed review of the literature on the effects of nGVS on standing balance, gait, upper extremity tasks, vestibulo-ocular function, sensory perception, and cognitive processes. Here, we focus on the effects observed in healthy adults. In the next section, we outline the potential applications for using nGVS for clinical

purposes. Finally, we highlight other electrical brain stimulation technologies, and contrast those with nGVS.

2. Overview of GVS and nGVS

Scientists have used some form of GVS for experimentation for centuries (see Dlugaiczyk et al., 2019; Fitzpatrick and Day, 2004). This technique involves applying weak electrical current through electrodes placed on the mastoid bones behind the ears to activate or perturb the vestibular system. The most common form is direct current stimulation, using a bilateral bipolar configuration, which leads to perceived head rotation primarily in the roll plane and in turn, to actual compensatory movements to counteract the sensation (Fitzpatrick and Day, 2004). GVS is generally considered safe, with few minor adverse events occurring, most notably itching and tingling sensations at the electrode site (Utz et al., 2011; Valdés and Menon, 2019). Devices used for this stimulation are also highly portable and relatively inexpensive.

How does GVS activate the vestibular system? GVS is thought to modulate the activity of vestibular afferents, including those related to both the otoliths and semicircular canals (Goldberg et al., 1984; Kim and Curthoys, 2004; Kwan et al., 2019). Kim and Curthoys (2004) demonstrated in guinea pigs that pulsed GVS, using either a surface electrode placed over the mastoid or electrodes implanted in the tensor tympani muscle, activated vestibular afferents from semicircular canals and otoliths. In squirrel monkeys, GVS applied from an electrode in the perilymphatic space of the vestibule modulated spike discharge activity of vestibular afferents (Goldberg et al., 1984, 1982). In macaque monkeys, (Kwan et al., 2019) found that transmastoid sinusoidal GVS across a broad range of frequencies (0.1 to 25 Hz) caused activation in both semicircular canal and otolith afferents. Recent work using a semi-intact preparation of *Xenopus*

laevis tadpoles also suggests that GVS activates vestibular hair cells (Gensberger et al., 2016). Specifically, complete pharmacological blockage of the transmission between semicircular canal hairs cells and afferent fibers—confirmed by the absence of discharge activity with turntable rotations—significantly reduced sinusoidal GVS-induced activity recorded in vestibular afferents. This is consistent with a report on patients with damage to vestibular hair cells due to Gentamicin vestibulotoxicity and who had no mechanical responses to caloric stimulation, horizontal head rotation, and head impulse tests (Aw et al., 2008): electrically-evoked phasic and tonic VOR amplitude was dramatically reduced. Therefore, GVS (and presumably nGVS) appears to directly activate both vestibular hair cells and afferents.

In this review, we focus specifically on subthreshold nGVS, also sometimes referred to in the literature as subthreshold stochastic vestibular stimulation (SVS). nGVS uses a noisy, alternating electrical current waveform. Typically, Gaussian white noise or pink noise is used, though other noise is possible. A white noise signal has equal energy at the different frequencies included. For a pink noise signal, the energy is inversely proportional to the frequency; the energy is more intense at lower frequencies. Regardless of the type of noise, the intensity is subthreshold in most nGVS protocols and the reader should assume that studies discussed in this review use at least some of the applied intensities in this range unless otherwise noted.

There are two common methods to determine stimulation intensity in humans. In one approach, stimulation intensities are varied in a stepwise manner until the individual perceives it. Intensity is then set to 80 or 90% of this cutaneous threshold (Hilliard et al., 2019; Kuatsjah et al., 2019; Piccolo et al., 2020; Valdés and Menon, 2019; Wuehr et al., 2016a). In the other approach, a sinusoidal waveform is applied when the eyes are closed, where the lowest stimulation intensity to induce perceived or observable sway of the head or body is found.

Intensity is then set to 50% of this motion threshold (Goel et al., 2015; Piccolo et al., 2020; Temple et al., 2018). Importantly, a recent study on standing and walking balance found no statistical difference in the effects of nGVS when intensity was determined via cutaneous or motion methods (Piccolo et al., 2020), and studies employing either method have demonstrated benefits. The typical stimulation intensities applied in humans (as set based on one of these threshold procedures or as determined by performance measures to be optimal) are slightly lower than the detection threshold of vestibular afferents—population averages between 0.4 to 0.6 mA across a range of sinusoidal frequencies—assessed using transmastoid GVS in the monkey (Kwan et al., 2019).

Unfortunately, there are currently no standard stimulation parameters for nGVS. This is most evident by the fact that groups have employed a variety of frequency ranges, including 0 to 2 Hz (Keywan et al., 2018), 0 to 30 Hz (Goel et al., 2015; Mulavara et al., 2011, 2015; Piccolo et al., 2020; Wuehr et al., 2016a), 0.02 to 10 Hz (Iwasaki et al., 2018, 2014), 0.1 to 10 Hz (Kuatsjah et al., 2019; Valdés and Menon, 2019), 0.1 to 100 Hz (Hilliard et al., 2019), and 0.1 to 640 Hz (Inukai et al., 2018b). A stimulation range of 0 to 2 Hz was chosen because it captures the frequency range of head motion during standing (Keywan et al., 2018). A range of 0.02 (or 0.1) to 10 Hz captures the bandwidth of typical frequencies of body sway during standing and head rotations during walking (Dakin et al., 2010; Grossman et al., 1988; Loram et al., 2005). This is the case for the range of 0 to 30 Hz as well, which also captures the bandwidth of vestibular reflexes determined by the coherence between SVS and lower limb muscle activity during standing (Dakin et al., 2007; Mulavara et al., 2015, 2011). Finally, (Inukai et al., 2018b) chose to use 0.1 to 640 Hz, in part, since random electrical noise applied over the motor cortex in this higher frequency range increased excitability in this cortical region (Terney et al., 2008).

Nonetheless, benefits of nGVS are present across each of the frequency ranges listed above. Therefore, what is currently needed are studies to determine which frequency ranges are most effective, and how these effects differ depending on the behavior (e.g., standing balance, walking, spatial memory). A greater understanding of how different stimulus parameters alter the effectiveness of nGVS will only serve to enhance this technique.

The effects of subthreshold nGVS are likely mediated through the phenomenon known as stochastic resonance (Keywan et al., 2018; Wuehr et al., 2018). Stochastic resonance refers to the increased ability to detect weak stimuli because of the addition of noise to the original signal or more broadly, as better output signal quality in a nonlinear system with the presence of noise compared to its absence. When output (or performance) is plotted against input noise magnitude, there is a characteristic pseudo bell-like shape to the curve with a clear peak denoting the optimal noise level. For excellent reviews on this concept, see McDonnell and Abbott (2009), McDonnell and Ward (2011), and Moss et al. (2004). Although largely hypothetical in humans, there is evidence of this phenomenon from work in animals. In a pioneering study, Jaramillo and Wiesenfeld (1998) found that noise in the form of mechanical Brownian motion applied to the hair cell bundle of the bullfrog sacculus resulted in enhanced signal-to-noise ratio recorded from isolated hair cells. Later, Indresano et al. (2003) extended this finding: mechanical noise applied to the bullfrog sacculus enhanced the signal-to-noise ratio in sacculus afferents. More recently, Flores et al. (2016) recorded multiunit activity from posterior semicircular canal afferents of chicken embryos and hatchlings during mechanical Gaussian noise in the range of 0 to 250 Hz. An optimal amount of noise led to a greater signal-to-noise ratio in these afferents, particularly for the hatchlings. The researchers suggested that glutamate synaptic transmission between hair

cells and primary vestibular afferents mediated these effects, as they were eliminated by application of NMDA and AMPA/Kainate receptor antagonists (Flores et al., 2016).

To demonstrate the presence of vestibular stochastic resonance in humans, the performance metric of interest (e.g., vestibular perceptual threshold, postural sway, gait measures) must be determined across a range of nGVS intensities. Performance should improve at some intermediate (i.e., optimal) level of nGVS but degrade at intensities above or below this level, following a pseudo bell-shaped response curve. A further (and stricter) criterion to consider is whether the performance change around the curve peak is significantly different from sham-stimulation on an intra-individual level. Galvan-Garza et al. (2018) have most rigorously tested for stochastic resonance with nGVS in humans, though others have shown optimal noise levels—reflected by different performance metrics—testing a range of nGVS intensities (e.g., Goel et al., 2015; Iwasaki et al., 2014; Keywan et al., 2018; Mulavara et al., 2015, 2011; Wuehr et al., 2018). In this study, detection recognition threshold for roll tilts acted as the performance metric, and three blinded judges assessed the response curves of individual participants to determine the presence of stochastic resonance in one of two ways: only requiring it match a typical bell-shaped profile or requiring this characteristic and the additional criterion listed above (Galvan-Garza et al., 2018). Regardless of method, at least 50% of participants exhibited evidence of stochastic resonance.

Thus, nGVS may increase the nervous system's sensitivity to vestibular input via stochastic resonance. For nGVS to impact a variety of functions, it must influence brain areas beyond simply the vestibular hair cells and afferents. Below we provide a brief overview of where vestibular information is processed in the brain.

3.   Anatomical areas receiving and processing vestibular information

Vestibular afferents from both otoliths and semicircular canals terminate in the vestibular nuclei. Output from these nuclei can influence motoneuron activity of the legs and arms for the control of balance via vestibulospinal pathways and through interactions with the corticospinal system at cortical and spinal levels (Dakin et al., 2013; Kennedy et al., 2004; Nepveu et al., 2020). These nuclei are heavily interconnected with oculomotor-related nuclei and the cerebellum, giving rise to the VOR (Bronstein et al., 2015). The vestibular nuclei also have dense connections to the thalamus (Hitier et al., 2014; Lopez and Blanke, 2011). For instance, the medial vestibular nuclei project to the ventral posterior inferior and ventral posterior median nuclei, as well as to the medial and lateral geniculate nuclei via the medial longitudinal fasciculus. Not surprisingly, a variety of neuroimaging techniques have confirmed that vestibular stimulation leads to cortical activation in several regions like the sensorimotor, posterior parietal, temporal, and insular cortices, as well as the visual cortex and related areas (Bense et al., 2001; Lopez and Blanke, 2011). Thus, the vestibular system has the potential to affect a wide range of motor, sensory, and cognitive abilities.

The human vestibular cortex is believed to be centered around the inferior parietal lobule, temporo-parietal junction, and posterior insula (Fasold et al., 2002; Frank and Greenlee, 2018; Lobel et al., 1998; Lopez and Blanke, 2011). The latter two areas are often called the parieto-insular vestibular cortex (PIVC). Studies in both humans (Bense et al., 2001; Fasold et al., 2002) and non-human primates (Chen et al., 2010; Grüsser et al., 1990) have characterized neurons in this area and reported responses to somatosensory and visual stimuli in addition to vestibular activation. In humans, the exact location and extent of a non-human primate PIVC homologue is still unclear. However, neuroimaging studies suggest the posterior insula and retro-insular region

as a potential human PIVC. For instance, Bense et al (2001) showed an increase in blood-oxygen-level-dependent signal in that region following GVS application. Earlier studies using either GVS (Bucher et al., 1998) or caloric stimulation (Bottini et al., 1994) also support these findings. PIVC may be part of a network integrating sensory feedback to form an internal model of body orientation and thus, play a role in the maintenance of postural verticality via cortico-vestibular and vestibulospinal tracts (Takakusaki, 2017).

More recently, Frank and Greenlee (2018) suggested a new organization of the main human vestibular cortex. Specifically, they proposed an area called PIVC+, encompassing PIVC and another region called the posterior insular cortex. Posterior insular cortex differs from PIVC in its anatomical connections and strong activation by visual motion cues (Frank and Greenlee, 2018). In contrast, Kahane et al (2003) argued that the human homologue of PIVC is located more superficially than previously thought and does not include the insula. Instead, area OP2, the parietal operculum, could be a candidate for the human PIVC (Eickhoff et al., 2006). Several studies have also reported activation of the supramarginal gyrus (BA 40) (see Lopez and Blanke (2011) for a review) following GVS (Bense et al., 2001; Stephan et al., 2005) and caloric stimulation (Karim et al., 2013). Galvanic and caloric vestibular stimulation also activate more frontal brain regions. These include the primary motor cortex, the premotor cortex, and the prefrontal cortex (Bense et al., 2001; Emri et al., 2003; Fasold et al., 2002; Lobel et al., 1998). This further supports the role of vestibular input in motor control.

The vestibular system also influences a variety of cognitive functions due to widespread connections of the vestibular nuclei. Hitier et al (2014) and Lopez and Blanke (2011) provide excellent reviews. Animal studies, for instance, demonstrate strong connections between the vestibular nuclei and areas involved in memory and spatial navigation, such as the medial

entorhinal cortex, cingulate cortex, and hippocampus (Hitier et al., 2014; Lopez and Blanke, 2011). Vestibular signals are an important source of input to key neurons related to spatial navigation, including place cells and head direction cells. In rats, floor rotation meant to stimulate the vestibular system can influence hippocampal place cell firing (Sharp et al., 1995). Electrical stimulation of the medial vestibular nucleus can increase activity in complex-spiking CA1 neurons in the hippocampus considered to represent place cells (Horii et al., 2004). In addition, a bilateral vestibular lesion or temporary, bilateral inactivation of the vestibular apparatus via injection of tetrodotoxin in rats eliminates or disrupts location-specific hippocampal place cell firing (Russell et al., 2003; Stackman et al., 2002). These same procedures also disrupt direction-specific postsubicular and anterior thalamus head direction cell firing (Stackman et al., 2002; Stackman and Taube, 1997) and the impact that angular head velocity has on the firing rates of the latter cells (Stackman and Taube, 1997). In humans, caloric vestibular stimulation causes activation of the hippocampus and parahippocampal gyrus (Suzuki et al., 2001; Vitte et al., 1996). Interestingly, studies from patients with vestibular deficits, such as bilateral vestibular loss, show impairments in memory recall, spatial memory, and memory-guided saccades (Brandt et al. 2005; Tian et al., 2000; see Bigelow and Agrawal (2015) for a review). In fact, there is evidence of hippocampal atrophy in patients with bilateral vestibular loss (Brandt et al., 2005).

The vestibular system may also exert an influence on behavior via the basal ganglia (Hitier et al., 2014; Stiles and Smith, 2015). There is evidence that vestibular information may influence cognitive functions through the basal ganglia in animals (Hitier et al., 2014). In rats, anatomical tracing studies demonstrate a possible vestibular-thalamic-striatal pathway from the medial vestibular nucleus (Lai et al., 2000). Electrical stimulation of the vestibular nerve or medial or

lateral vestibular nuclei causes activity in the caudate nucleus is cats and squirrel monkeys (Liedgren et al., 1976; Spiegel et al., 1965). In the rat, vestibular stimulation can also evoke activity in a small number of single neurons of the striatum (Stiles et al., 2018) and elicit changes in blood oxygen level-dependent activity in this region during fMRI (Rancz et al., 2015). Although it is unclear whether such connections are present in humans, neuroimaging studies have shown activation of various basal ganglia regions, such as the putamen and caudate nucleus during caloric stimulation or GVS (Bottini et al., 1994; Della-Justina et al., 2014).

The evidence presented above highlights the widespread connections of the vestibular system at the cortical and subcortical levels. Not surprisingly, vestibular stimulation affects a variety of functions, which we detail in the following section.

4. The effects of nGVS on motor, sensory, and cognitive function in healthy adults

In this section, we review the effects of nGVS on standing, walking, upper limb movements, and vestibular-ocular function in healthy adults. Subsequently, we review evidence of nGVS affecting sensory perception and cognitive functions. Figure 1 provides a summary of key findings.

4.1 Standing balance

During standing, vestibular feedback contributes to the perception of verticality and to balance control via vestibulospinal pathways (Cullen, 2019; Dakin and Rosenberg, 2018; Fitzpatrick and Day, 2004). Several recent studies suggest the potential for nGVS to influence standing balance (Herssens and McCrum, 2019). For instance, Inukai et al. (2018b, 2020) found reduced center of pressure (COP) amplitude and velocity with the eyes open.

Studies have shown that subthreshold nGVS can improve postural stability when standing on foam with the eyes closed (Goel et al., 2015; Iwasaki et al., 2014; Keywan et al., 2020, 2019, 2018; Mulavara et al., 2011; Nooristani et al., 2019a). For instance, nGVS applied during this task affects a variety of standing balance measures, such as reducing COP amplitude and velocity (Iwasaki et al., 2014), as well as reducing the root-mean-square of linear medial-lateral head and trunk acceleration and anterior-posterior head acceleration (Goel et al., 2015; Mulavara et al., 2011). Interestingly, the positive effects seen in Nooristani et al. (2019a) were only evident when nGVS was applied with 3 cm^2 electrodes and not 35 cm^2 electrodes. Higher current density or greater focality may explain these results. Recently, Piccolo et al. (2020) investigated the effects of nGVS when participants stood quietly with their eyes open with and without wearing inflated rubber hemispheres attached to the bottom of their shoes that altered the ability to shift the COP to maintain balance. They reported a decrease in medial-lateral trunk velocity root-mean-square with nGVS compared to sham stimulation in the balance-challenged condition only, suggesting that nGVS may be particularly effective when balance is challenged. It is reasonable to expect a heightened response of nGVS during balance-challenging standing conditions, as there is a re-weighting of sensory feedback such that vestibular input has a greater contribution, particularly if vision is absent (Peterka, 2018).

Not all standing-based studies have demonstrated positive or convincing results. Although 30-minute exposure to nGVS led to improvements in postural stability immediately after and one-hour later, Nooristani et al. (2019b) showed a similar effect with sham stimulation. These researchers argued that the lack of difference between conditions was likely due to the stimulation parameters or the presence of a ceiling effect for individuals with an intact vestibular system. In addition, Pal et al. (2009) found no effects of nGVS on postural sway in healthy

individuals with the eyes either closed or open, although a trend towards decreased postural sway was observed. In both studies, all participants received identical stimulation intensities. In contrast, most of the earlier-mentioned studies tailored the stimulation intensity to each participant by either determining the optimal value or using methods thought to provide the optimal value.

Taken together, however, there is substantial evidence to indicate that nGVS could be used to improve balance function in individuals with an intact vestibular system. Nonetheless, the choice of stimulation parameters and electrode surface area should be considered for the design of future technology meant to optimize or assist human performance in this task.

4.2 Gait

Although studying static standing balance provides insight into how nGVS affects postural control, humans are often in a state of motion. During walking, vestibular feedback is used in a phase-dependent manner to regulate foot placement for balance, and to control head movements to ensure stable gaze (Bent et al., 2005; Crane and Demer, 2000; Cullen, 2019; Dakin et al., 2013). This section looks at the application of nGVS during walking. The paradigms used in this work can be divided into two broad categories: treadmill walking and over-ground walking. We describe each in turn.

Early work examining the effects of nGVS on walking relied on the use of a treadmill. For example, Mulavara et al. (2015) investigated the effects of subthreshold levels of nGVS while individuals walked on a treadmill mounted on a six-degrees-of-freedom motion platform. The platform moved laterally in a sinusoidal motion and participants walked while looking at a screen in front of them. Results showed a decrease in the variability of gait cycle timing and

trunk acceleration in the plane of perturbation during stimulation. This suggests an improvement in dynamic stability. Wuehr et al. (2016a) also showed positive effects of subthreshold nGVS on several gait metrics during primarily slow treadmill walking with the eyes closed, including a reduction in the coefficient of variation of stride time and stride length. It is unclear whether the effects would still be present with the eyes open, as the lack of vision during walking can make maintaining balance more of a challenge and increase the contribution of the vestibular system.

Why is nGVS most effective at slow walking speeds? This may relate to the fact that slow walking already negatively affects dynamic stability (England and Granata, 2007). Alternatively, recent work proposes that internally-generated feedforward commands suppress vestibular feedback at higher locomotor speeds (Dietrich et al., 2020; Dietrich and Wuehr, 2019a, 2019b). This is based on the idea that head motion predictability drives a change in the contribution to balance control of efference copy signals versus vestibular feedback, where more predictable head motion during walking causes a down-weighting of the latter (Dietrich et al., 2020). The feedforward motor command, or efference copy, may stem from collaterals of descending pathways or via ascending spinal locomotor pattern generator signals directed to the cerebellum (Kiehn and Dougherty, 2013). Indeed, neurons in the vestibular nuclei of monkeys are suppressed during active head motion where an efference copy signal is present compared to passive head motion (Cullen et al., 2011). Compatible with this proposal, Dietrich et al. (2020) showed greater head motion predictability accompanied by a decrease in SVS-COP coupling with increasing locomotor speed. Interestingly, periods of low head motion predictability during the gait cycle correlated with the peaks of local vertical angular VOR gain (Dietrich and Wuehr, 2019a) and SVS-COP coupling (Dietrich et al., 2020). This mechanism is thought to explain the observed decrease in vestibular-muscle coupling (Dakin et al., 2013) and decrease in vertical

angular VOR gain—where there is a switch from the eyes compensating for head rotation to working in phase with head rotation (Dietrich and Wuehr, 2019a, 2019b) with increased locomotor speed.

While treadmill walking offers a more controlled environment in which to study dynamic stability, results may not transfer to over-ground walking, a task that represents more realistic environments. Recent work has examined the effects of nGVS in healthy young adults in this condition. For example, Iwasaki et al. (2018) observed an increase in gait speed and stride length, as well as a decrease in stride time, across a wide range of stimulation intensities when participants walked on level ground with their eyes open and at their preferred speed. In Temple et al. (2018), participants completed a modified version of the Functional Mobility Test with and without nGVS. This test, which is regularly performed on astronauts returning from prolonged space flight (Mulavara et al., 2010), consists of an obstacle course on foam, such that cutaneous and proprioceptive input from the feet/ankles are unreliable. In addition, participants walking the course in Temple et al. (2018) wore vision reversing prism googles, which flipped the visual field upside down and effectively created a situation where vision is also unreliable. Therefore, the participants' vestibular system provided the only accurate source of sensory information for stability. Their results showed that nGVS led to faster adaptation rates to the sensory discordant environment, indicating that this technique might allow certain individuals to improve their reliance on modalities other than vision to maximize dynamic stability. Recently, Piccolo et al. (2020) investigated the effects of nGVS in an over-ground walking task where participants had their eyes open and in one condition, wore inflated rubber hemispheres attached to the bottom of their shoes. These researchers observed significant changes in walking performance, including

an increase in gait speed and a decrease in step-width variability with nGVS in both balance conditions compared to sham stimulation.

Taken together, the above evidence suggests a positive effect of nGVS in healthy young adults during walking. These findings may relate to nGVS lowering the threshold of vestibulospinal reflexes (Wuehr et al., 2018).

4.3 Upper limb tracking

The contribution of the vestibular system to lower limb movements and walking is well known (Bent et al., 2005). Although less extensively studied, it also plays a role in reaching and upper limb movements (Keyser et al., 2017; Mars et al., 2003; Moreau-Debord et al., 2014; Smith and Reynolds, 2017). For example, Moreau-Debord et al. (2014) showed that unexpected direct current GVS during reaching movements to remembered targets leads to perturbations in reach trajectories, and that this was dependent on head orientation. Similarly, pointing movements to a target fixed in space during concurrent whole-body rotations are perturbed during the application of direct current GVS (Smith and Reynolds, 2017).

Unfortunately, few studies have examined the effects of nGVS on performance during upper extremity paradigms. In one such study, healthy young participants performed a visuomotor tracking task, using a joystick to follow a path on a computer screen (Kuatsjah et al., 2019). nGVS led to improvements in visuomotor tracking performance compared to sham trials, including a decrease in root-mean-square error and an increase in signal-to-noise ratio. In contrast, Valdés and Menon (2019) found no effects of nGVS on bimanual tracking performance when participants used two robotic arms to track the vertical movements of a target on a

computer screen. Given the scarce and conflicting evidence, further investigation with different upper limb tasks and stimulation parameters is warranted.

4.4 Vestibulo-ocular function

The vestibular system is tightly linked to oculomotor circuity. Input from both otoliths and semicircular canal ensure gaze is stabilized during head motion (Cullen, 2019). Two recent studies have tested how subthreshold nGVS affects the function of this circuity. Specifically, Iwasaki et al. (2017) determined how nGVS—ranging from 0.02 to 10 Hz—affected ocular vestibular-evoked myogenic potentials (oVEMPs), which reflect the function and integrity of the otolith-ocular circuitry (Curthoys et al., 2012). To elicit an oVEMP, bone conduction vibration is applied to the midline of the forehead at the hairline. nGVS in healthy adults led to an increase in the amplitude of the n10—the first negative (excitatory) potential of the ocular muscle response. (Serrador et al., 2018) determined how nGVS—ranging from 0 to 2 Hz—affected ocular counter-roll (OCR) gain in response to passive roll-tilts in the dark. At the low frequencies of motion applied in this study (<0.02 Hz), the otoliths are thought to contribute to the OCR gain (Merfeld et al., 2005; Serrador et al., 2009). nGVS increased the OCR response in older adults, particularly those with the lowest gain at baseline, but not young adults (Serrador et al., 2018). Taken together, nGVS appears to facilitate vestibulo-ocular function.

4.5 Sensory perception

Sensory perception of the body and environment is critical for interacting with the world around us. Can nGVS, which modulates one of the body's senses, improve sensory perception?

nGVS may facilitate vestibular-based motion perception (Galvan-Garza et al., 2018; Keywan et al., 2020, 2019, 2018). In a direction-recognition paradigm, Keywan and colleagues (Keywan et al., 2019, 2018) studied the effects of nGVS versus sham stimulation on the perception of roll-tilt perturbations. In these studies, participants sat in a chair mounted on a six-degrees-of-freedom platform, with their head fixed, and vision blocked by dark glasses. nGVS led to an improvement in motion perception in the roll plane, albeit this seemed to depend on the frequency of the perturbation. It is worth mentioning that for each participant, the optimal stimulation intensity was previously determined when standing on foam with eyes closed. The minimum intensity at which two out of three COP measures improved with respect to baseline for each person was chosen for the stimulation intensity in the direction-recognition task. To differentiate whether the effects of nGVS on direction perception were mediated via otolith organs or semi-circular canals, Keywan et al. (2019) had participants change head positions in certain trials. Results showed that the stimulation improved mostly inter-aural translational motion perception, and only slightly improved rotational perception, suggesting a greater impact on otolith-mediated perception. However, Keywan et al. (2020) observed no after-effects of nGVS on motion perception thresholds, indicating that longer or continuous application might be needed to produce sizable long-term benefits. It is also possible that there are no long-term benefits, independent of the duration of application. Regardless, there is preliminary evidence to suggest that nGVS may improve motion perception.

4.6 Cognitive aspects

Growing evidence suggests that the vestibular system contributes to a variety of cognitive functions (Bigelow and Agrawal, 2015; Hitier et al., 2014; Smith and Zheng, 2013).

Interestingly, individuals with vestibular loss or dysfunction exhibit impairments in spatial memory, as assessed using a virtual Morris water maze task (Brandt et al., 2005; Kremmyda et al., 2016; Schautzer et al., 2003). These individuals also demonstrate impairments in executive function and short-term memory (Dobbels et al., 2019; Popp et al., 2017), as well as an impaired ability to perform egocentric mental transformations involving images of bodies and body parts (Grabherr et al., 2011). Thus, it is reasonable to consider whether nGVS can facilitate these abilities in healthy individuals.

Preliminary research suggests that nGVS may facilitate cognitive abilities. For instance, Wilkinson et al. (2008) showed faster recall in a face imagery task with application of nGVS compared to sham and direct current GVS. In addition, Hilliard et al. (2019) examined the potential effects of nGVS during a VR-based visuospatial navigation task. Specifically, participants had to determine the remembered position of an object by navigating the virtual environment. During the transfer phase, to assess learning, either the boundary of the environment or the location of the object within the environment was changed. Results indicated that nGVS benefited spatial memory tasks in both males and females but seemed to enhance different aspects based on sex. For example, there was increased sensitivity to both boundary and location-based cues in male participants. In females, nGVS only enhanced sensitivity to boundary-dependent spatial information. Ultimately, more research on the effects of nGVS on different cognitive abilities is required.

5. Potential applications of nGVS

The portability and affordability of electrical stimulation devices are advantageous for their implementation across a range of settings and in different populations. In the following section,

we discuss possible applications of nGVS and whether there is evidence to support its use. We first describe its potential use in different clinical populations, then we consider its potential role for astronauts. We conclude this section with some ethical considerations of using this technique outside of a research environment.

5.1 Clinical applications

Many neurological disorders impair movement. nGVS may serve as an effective assistive technology for these clinical populations given its effects on motor function. What is the evidence to support this claim?

Bilateral vestibulopathy refers to chronic bilateral loss or reduction in vestibular function. It results in reduced or absent angular VOR as well as postural imbalance and gait unsteadiness, and individuals suffering from this condition are at a high risk of falls (Schlick et al., 2015; Strupp et al., 2017, 2016; Wuehr et al., 2017). Because of its effect on vestibular afferents, researchers have explored the use of nGVS to enhance residual vestibular function in individuals with incomplete bilateral vestibular hypofunction (Schniepp et al., 2018; Wuehr et al., 2017). Multiple studies have shown beneficial effects of nGVS. Specifically, during eyes-closed standing on stable ground, Fujimoto et al. (2018) found that nGVS led to a decrease in mean COP velocity and the high-frequency component of COP movement for several hours after stimulation. Ko et al. (2020) also showed nGVS reduced root-mean-square COP displacement when standing on stable ground. During eyes-closed standing on foam, nGVS decreases mean COP velocity, sway area, and root-mean-square COP velocity (Iwasaki et al., 2014). However, Sprenger et al. (2020) recently reported that nGVS caused a small increase in sway speed with eyes-closed standing on foam and had no effect with eyes-open or on stable ground compared to

sham and no stimulation. Nonetheless, during walking, individuals with bilateral vestibulopathy also appear to benefit from nGVS, as reflected by increased gait speed and stride length, a decrease in the coefficient-of-variation of stride time and stride length, and improved ability to match a 2-Hz metronome signal with head yaw movements (Iwasaki et al., 2018; Ko et al., 2020; Wuehr et al., 2016b). The benefits of nGVS in this population are likely mediated by a lowering of vestibulospinal reflex thresholds (Schniepp et al., 2018). Taken together, these results suggest a positive effect of nGVS in individuals with bilateral vestibulopathy. It is important to note that other stimulation techniques to improve vestibular function in this population are currently under investigation. This includes electrical stimulation via vestibular implants, which is thoroughly reviewed in Sluydts et al. (2020).

Individuals with Parkinson's disease exhibit a variety of deficits in standing balance and gait, including trouble initiating compensatory steps to recover from a standing perturbation, difficulty turning, and reduced gait speed, and are at a high risk of falls (Boonstra et al., 2008; Mirelman et al., 2019). Recent work has also recognized the presence of vestibular dysfunction in this population (Smith, 2018). Not surprisingly then, researchers have explored the use of nGVS to ameliorate these deficits. For instance, Tran et al. (2018) found decreased anterior-posterior sway frequency during eyes-closed standing with nGVS. Pal et al. (2009) showed decreased anterior-posterior root-mean-square COP displacement during eyes-closed standing on foam. In addition, Samoudi et al. (2015) found decreased COP sway path during eyes-closed standing, which was most apparent when standing on foam. This latter study also reported improvements in balance corrective responses (i.e., decreased response time and decreased COP displacement) following unexpected balance perturbations. Interestingly, subthreshold nGVS also facilitated performance on a sinusoidal visuomotor tracking task in Parkinson's disease

patients (Lee et al., 2015). Even suprathreshold direct current GVS improved finger tapping performance in this population (Khoshnam et al., 2018). In addition, two studies that included individuals with Parkinson's disease, as well as individuals with either cerebellar- or Parkinsonian-type multiple system atrophy, showed reduced bradykinesic-like rest-to-active transitions in trunk and wrist behavior with nGVS (Pan et al., 2008; Yamamoto et al., 2005). Collectively, the positive effects of nGVS in individuals with Parkinson's disease are promising.

Individuals with stroke may also derive benefit from nGVS. This is because these individuals, as with those populations above, show impairments in standing balance and gait (Marigold and Eng, 2006a, 2006b; Sheffler and Chae, 2015; Weerdesteyn et al., 2008), which contribute to an increased risk for falls and fall-related injuries (Harris et al., 2005; Weerdesteyn et al., 2008). In addition, evidence suggests that individuals with stroke have difficulty re-weighting sensory information during standing (Marigold et al., 2004). We are not aware of studies using nGVS to improve these functions following stroke. However, this technique has proved effective at reducing the effects of spatial neglect, an attentional disorder that is characterized by a failure to acknowledge or respond to visual information on one side of space and is most commonly caused by right hemispheric stroke (Wilkinson et al., 2014).

Natural aging results in changes to the vestibular system. Research shows age-related vestibular hair cell loss, neuronal cell loss in brainstem vestibular nuclei and cerebellar regions involved in processing vestibular information, and possible slowing of brainstem signal processing, as evident by increased latency of VEMPs (Allen et al., 2016; Zalewski, 2015). Age-related vestibular hypofunction is now considered an independent disease entity referred to as presbyvestibulopathy (Agrawal et al., 2019). Thus, older adults, particularly those who are at a high risk of falls, may also benefit from nGVS (White et al., 2019). Three studies have recently

demonstrated support. In one, nGVS applied during eyes-closed standing on foam led to a reduction in mean COP velocity, sway area, and root-mean-square, which lasted for several hours beyond the stimulation period (Fujimoto et al., 2016). In another, nGVS applied during eyes-open standing on stable ground resulted in reduced sway path length and both anterior-posterior and medial-lateral mean velocity compared to baseline (Inukai et al., 2018a). Finally, as discussed in Section 4.4, nGVS increased OCR gain in older adults (Serrador et al., 2018).

In summary, nGVS shows great promise as an assistive technology for those with a variety of neurological impairments or older adults at risk of falling. Determining the optimal stimulation frequency range and type of noise for these populations will be critical. In addition, it will be necessary to determine how long potential benefits last.

5.2 Considerations for astronauts

Spaceflight negatively affects multiple sensorimotor functions (Bloomberg et al., 2015; Clark, 2019; Paloski et al., 2008). Relevant to this review is its specific impact on vestibular function, and in particular, the otolith organs. The otoliths signal an estimate of net gravito-inertial acceleration, which is the vector difference between gravity and linear acceleration (Clark, 2019; Dakin and Rosenberg, 2018). They cannot distinguish between head tilt (relative to gravity) and head translation alone. This requires more central integration of angular velocity signals provided by semicircular canals, visual input, and/or neck proprioceptive information (Dakin and Rosenberg, 2018). In microgravity, there is a lack of normal otolith stimulation. Thus, head tilt creates a sensory conflict between vestibular, visual, and neck proprioceptive signals in which astronauts must adapt, possibly by a sensory re-weighting process that emphasizes vision and proprioceptive information. This adaptation is inappropriate when returning to Earth, and re-

adaptation must occur. Disrupted vestibular function (and sensorimotor function in general) is a particular concern when returning to a gravity-rich environment and piloted manual landing or emergency egress of the vehicle is required. It is also a concern during the post-flight recovery phase, which can take days or weeks.

Post-flight vestibular-related impairments are numerous. Astronauts exhibit alterations in the VOR (Clarke et al., 2000; Paloski et al., 2008), which rotates the eyes to compensate for head movements and stabilize gaze. Astronauts often report tilt-illusions post-flight, such as feeling as though the head is tilting more than it is, or the perception of translation with head tilt (Clark, 2019; Paloski et al., 2008). A range of motor behaviors are also affected, which are either directly or indirectly related to vestibular dysfunction. For instance, impairments are seen post-flight in standing balance (Ozdemir et al., 2018; Paloski et al., 1992; Wood et al., 2015) and walking (Bloomberg and Mulavara, 2003; Miller et al., 2010; Mulavara et al., 2010). These sensorimotor impairments can last for several days.

Effective countermeasures are still under investigation (Bloomberg et al., 2015; Clark, 2019) and will likely involve multiple techniques in combination. However, the application of post-flight nGVS may facilitate recovery of vestibular (and sensorimotor) function. nGVS may also assist sensorimotor adaptability pre-flight training, as suggested by Bloomberg et al. (2015), or speed up adaptation when transitioning to a different gravitational environment, as suggested by Clark (2019). Although we are not aware of any study that has used nGVS on astronauts in a realistic situation, there is preliminary evidence that this technique may assist adaptation to sensory conflict. In Temple et al. (2018), participants performed a modified functional mobility test, which involved walking on foam—to make somatosensory input unreliable—while stepping over and around obstacles. Participants also wore up/down reversing prism goggles to create

visual discordance. A group receiving nGVS had faster completion times compared to a control group, suggesting that nGVS can improve walking adaptation under sensory conflict.

5.3 Ethical considerations

There are many ethical considerations when planning and deciding to develop or use nGVS technology. It is not our intent in this review to discuss in detail the ethical, legal, and regulatory issues surrounding the use of electrical stimulation. Rather, we refer the reader to several other reviews of this nature (e.g., Antal et al., 2017; Davis and Smith, 2019; Hamilton et al., 2011). However, here we raise a few issues for the reader to consider. First, the long-term effects of repeated exposure to electrical stimulation is unknown. Second, device developers must determine whether and how stimulation parameters are controlled and can be modified by the end user, especially if such user is not a trained scientist or clinician. Third, and related to this concern, do-it-yourself electrical stimulation devices are becoming more prevalent and thus, there is a real risk associated with self-experimentation. Fourth, there is the possibility of unanticipated or unpredictable alterations in the personality or behavior of the end-user. This also relates to determining exclusion criteria based on pre-existing medical conditions, given that the impact of nGVS on many different medical conditions is largely unknown. It is also possible that using nGVS to enhance some abilities may be deleterious to others. Thus, nGVS should be used for a specific, well-defined, and well-justified purpose. Finally, regulations to prevent organizations from being able to coerce individuals into having nGVS administered should be developed before widespread adoption of this technique.

6. How nGVS compares to other neuromodulation techniques

Neuromodulation is a promising approach for optimizing and assisting human performance. Several techniques—in addition to nGVS—are available, including transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (transcranial direct current stimulation, or tDCS; transcranial alternating current stimulation, or tACS; transcranial random noise stimulation, or tRNS). However, no neuromodulation technique is optimal. Factors such as portability, temporal and spatial resolution, electrode placement and size, as well as the degree of invasiveness require consideration when selecting a technology. Below, we briefly discuss each of these approaches, then we discuss why nGVS may be a suitable alternative for real-world applications.

Although TMS—which directly triggers action potentials in neurons by sending a focused magnetic pulse through the scalp—is widely used in fundamental and clinical research, its higher cost, low portability, strong magnetic field, and potential to induce seizures greatly limits its use outside the lab or clinical environment. For these reasons, we will not discuss this technique further, but there are a number of reviews on TMS in the literature. Electrical stimulation techniques offer the most versatility in terms of stimulation parameters and location. They are also more affordable, portable, and safer than TMS and more invasive brain stimulation techniques (Cinel et al., 2019).

6.1 Transcranial direct current stimulation

tDCS uses saline-soaked electrodes to deliver an electrical current to the scalp. Unlike TMS, tDCS does not directly cause the firing of action potentials in neurons under the electrode. Instead, it acts by changing the resting membrane potential, such that neurons become more

likely to respond to external stimuli with anodal stimulation or less likely to respond with cathodal stimulation (Nitsche et al., 2008; Nitsche and Paulus, 2000). This technique is particularly popular, as it is highly customizable and also relatively safe (Bikson et al., 2009). There is substantial evidence that tDCS applied to the scalp over different brain regions can improve motor learning, visual perception, memory, and attention, to name a few (for reviews, see: Antal and Paulus, 2008; Buch et al., 2017; Coffman et al., 2014). There are also studies demonstrating that tDCS can improve threat detection efficacy (Clark et al., 2012; Falcone et al., 2012; McKendrick et al., 2015) and skill acquisition related to surveillance and intelligence analysis (see Parasuraman and McKinley, 2014), abilities that are important for a variety of professions.

6.2 Transcranial alternating current stimulation and transcranial random noise stimulation

tACS involves the application of (typically small amplitude) sinusoidal alternating current between scalp electrodes, where the flow of current changes between the anode and cathode in a cyclic manner (Bland and Sale, 2019). This stimulation pattern allows for entrainment of brain oscillations in a manner that is both frequency and phase-specific. Neuronal networks in the brain oscillate at specific frequencies, and it is believed that those that oscillate at the same frequency can communicate with each other better (Fries, 2005). Studies have shown positive effects with attention, sensory perception, motor function, and memory consolidation following tACS (Ketz et al., 2018; Tavakoli and Yun, 2017). tACS may also reduce the perception of pain (Ahn et al., 2019; Arendsen et al., 2018).

tRNS also involves the application of alternating currents, but over a broad frequency spectrum (Fertonani and Miniussi, 2017). Similarly to nGVS, the concept of stochastic resonance applies to tRNS (Fertonani and Miniussi, 2017; van der Groen and Wenderoth, 2016). Application of high-frequency tRNS (e.g., 100 to 640 Hz) can improve visual perception, including better stimulus detection, orientation discrimination, and facial identity (Fertonani et al., 2011; Pirulli et al., 2013; Romanska et al., 2015; van der Groen and Wenderoth, 2016). It can also increase corticospinal excitability (Jooss et al., 2019; Terney et al., 2008) and facilitate motor learning, as determined using a tracing task (Prichard et al., 2014). However, its effect on corticospinal excitability and motor performance appears to depend on the task (Jooss et al., 2019). Overall, tRNS has received less attention than the other transcranial electrical stimulation techniques.

6.3 Advantages of nGVS

Each of the techniques we have discussed above in this section can impact human performance. In addition, some of these techniques, like tDCS, have been studied considerably more than nGVS. Thus, why use nGVS to optimize or assist human performance? What are the advantages?

The electrode placement for nGVS—behind the ears over the mastoid processes—provides several advantages. First, hair, which can interfere with electrical conductance (Horvath et al., 2014), is generally not an issue. Typical transcranial electrical stimulation techniques use saline-soaked sponges to conduct the electrical current. To deal with thick hair, sponges may be saturated with saline to a greater extent. Excessive moisture from saline-soaked sponges can cause shunting across the scalp. Thus, current is more likely to penetrate the skull with nGVS.

Second, there is no need to locate a specific brain region, thus making this technique simpler than others. Third, nGVS electrodes are easily secured. Fourth, nGVS electrodes are less conspicuous in that they are thin and can be more easily hidden behind a person's hair. Both of these latter two advantages potentially makes for easier integration into a wearable device and would likely improve user adherence. These aspects are important given that brain stimulation studies suggest the need for constant or frequent stimulation for sustained effects (Keywan et al., 2020; Pirulli et al., 2013). In contrast, transcranial electrical stimulation often requires bulky, unsightly, and/or uncomfortable headgear to secure two or more electrodes on the scalp over top of the hair.

There is also at least one disadvantage of using nGVS. Specifically, this technique targets activity in vestibular hair cells and afferents and thus lacks the versatility in terms of the ability to target different brain areas with different electrode montages that other techniques offer. In the end, however, nGVS provides an alternative approach to optimizing and assisting human performance that may be more suited to a particular application than other approaches. It appears particularly promising for uses related to improving standing balance and walking in healthy and clinical populations.

7. Conclusions

Here, our objective was to review how nGVS affects motor, sensory, and cognitive performance in healthy adults, and to discuss its potential applications. Overall, subthreshold nGVS appears promising as a technique to optimize human performance in a variety of ways. It has the potential to serve as an effective assistive technology for several clinical populations that suffer from balance and gait deficits. It also may facilitate astronauts returning from space missions. As

with other similar electrical stimulation techniques, including tDCS, tACS, and tRNS, nGVS is considered generally safe (Antal et al., 2017; Utz et al., 2011; Valdés and Menon, 2019) and devices to administer it are highly portable. Both factors make it particularly suitable for use outside of a research environment.

To move forward with nGVS as a technique to optimize or assist human performance, there are a number of considerations to take into account. For instance, there are no standards for stimulation parameters (e.g., type of noise, frequency range), which makes it difficult to provide recommendations for future uses. In addition, there is still minimal research on the effects of nGVS on different aspects of sensory perception and cognitive function, though preliminary work is promising. Furthermore, there are no studies administering nGVS in real-world and occupation-specific settings. This is currently a major hurdle in drawing any conclusions regarding the effectiveness of this technique outside of a research environment. Work to establish standardized stimulation parameters and protocols, as well as additional research, particularly in relation to sensory perception, cognitive function, and in clinical populations, is now required.

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Figure Captions:

Figure 1: Summary of the positive effects of nGVS on motor, sensory, vestibulo-ocular, and cognitive function in healthy adults. BC = balance-challenged condition (e.g., standing/walking on foam); BU = balance-unchallenged condition (e.g., standing/walking on normal ground); COP = center of pressure; EC = eyes closed; EO = eyes open; OCR = ocular counter-roll; oVEMP = ocular vestibular-evoked myogenic potential; RMS = root-mean-square; RMSE = root-mean-square error.

Motor Function

Standing
- ↓ COP sway path length; EO, BU & EC, BC
- ↓ COP sway area; EC, BC
- ↓ COP velocity; EO, EC, BC & BU
- ↓ COP RMS; EC, BC
- ↓ Trunk velocity RMS; EO, BC
- ↓ Head & trunk linear acceleration RMS; EC, BC

Gait
- ↑ Gait speed; EO, BC & BU
- ↓ Step-width variability; EO, BC & BU
- ↑ Stride length; EO, BU
- ↓ Stride time; EO, BU
- ↓ Stride length CV; EC, BU
- ↓ Stride time CV; EC, BU
- ↓ Gait cycle timing variability; EO, BC
- ↓ Trunk linear acceleration RMS; EO, BC

Upper limb
- ↓ RMSE with visuomotor joystick tracking

Vestibulo-ocular Function
- ↑ OCR gain
- ↑ oVEMP n10 amplitude

Sensory Function
- ↓ Direction-recognition threshold for roll-tilt perception
- ↓ Direction-recognition threshold for inter-aural translation

Cognitive Function
- Faster visual memory recall
- ↑ Spatial memory in virtual navigation

nGVS

Figure 1