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REVIEW

Caloric and galvanic vestibular stimulation for the treatment of Parkinson's disease: rationale and prospects

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ABSTRACT

Introduction: Deeply embedded within the inner ear, the sensory organs of the vestibular system are exquisitely sensitive to the orientation and movement of the head. This information constrains aspects of autonomic reflex control as well as higher-level processes involved in cognition and affect. The anatomical pathways that underline these functional interactions project to many cortical and sub-cortical brain areas, and the question arises as to whether they can be therapeutically harnessed.

Areas covered: The body of work reviewed here indicates that the controlled application of galvanic or thermal current to the vestibular end-organs can modulate activity throughout the ascending vestibular network and, under appropriate conditions, reduce motor and non-motor symptoms associated with Parkinson's disease, a disease of growing prevalence and continued unmet clinical need.

Expert opinion: The appeal of vestibular stimulation in Parkinson's disease is underpinned by its noninvasive nature, favorable safety profile, and capacity for home-based administration. Clinical adoption now rests on the demonstration of cost-effectiveness and on the commercial availability of suitable devices, many of which are only permitted for research use or lack functionality. Dose optimization and mechanisms-of-action studies are also needed, along with a broader awareness amongst physicians of its therapeutic potential.

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1. Introduction: the vestibular system as a therapeutic pathway

The peripheral vestibular system is cocooned within the dense temporal bone of the inner ear and comprises two organ types: the semi-circular canals and otoliths. The three semi-circular canals are co-located in a perpendicular arrangement and together detect rotational head movement across the three cardinal depth planes. The otoliths comprise the saccule and utricle and together detect linear head movement and gravitational pull, sensitivities that mean that the vestibular nerve never falls quiet. The dimensions of the vestibular organs seem so well optimized that over roughly seven orders of magnitude of mass variation in mammals, the overall size of the vestibular organs varies over one [1].

Mechanoreceptors within these structures sense extremely fine and brief movements which in turn stimulate action potentials that are propagated along the eighth cranial nerve to the vestibular brainstem nuclei. These nuclei receive and send projections from/to the cerebellum as well as from/to neighboring nuclei involved in limbic (such as the raphe nuclei and locus coeruleus) and autonomic regulation [see 2,3]. Every vestibular nucleus projects to at least several thalamic nuclei (in many cases contralaterally if not bilaterally) which thereon link to numerous cortical destinations including the central parietal and occipital cortices, orbito-frontal, insular and temporal cortices [2]. These areas are principally involved in spatial, interoceptive and egocentric cognition, qualities that underpin the very concept of self. No brainstem fibers appear to project to a primary vestibular cortex or region that shows the domain-specific trademarks of hierarchical or topographical organization associated with other primary sensory areas. In non-human primates, a parieto-insular vestibular cortex has however been identified [4] and in humans, analogous activations can be seen in the temporoparietal junction, posterior insula, and posterior parietal cortex although most cells in this region are bi-modal or multi-modal [5–7]. This multisensory feature is one of several that distinguishes the vestibular system from all other sensory systems, with multimodal interactions (incorporating multi-sensory convergence, transformation and modulation) between visual, somatosensory and vestibular signals occurring in almost all vestibular relays [8].

The multi-sensory and diffuse nature of the vestibular projections point to a pervasive role in brain function that is echoed by the behavioral symptoms that accompany vestibular impairment. In a recent neuropsychological assessment of 101 individuals with a chronic neurotological diagnosis, mostly vestibular migraine, over 60% passed the cutoff for clinical anxiety, 37% fell above the clinical cutoff for depression, 70% exceeded clinical cutoff for fatigue and 44% reported significant daytime sleepiness [9]. Over half the sample reported visuo-spatial short-term impairment and reduced visual processing speed. These findings accord with the outcomes from larger-scale epidemiological studies, including a survey of 20,950 adults in the US which revealed that the 8% who self-reported vestibular vertigo were eight times more likely to have serious difficulty concentrating or remembering, four

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Article highlights

- The diversity of pathways between vestibular brainstem centres and other brain areas, coupled with the strong link between a healthy vestibular system and mental well-being, gives good reason to test whether these pathways can be therapeutically modulated.
- Neuronal activity within the vestibular pathways can be simply and effectively modulated by means of portable stimulation devices that administer transcutaneous caloric or galvanic current to the peripheral vestibular organs of the inner ear.
- Some of the most compelling therapeutic effects have been reported in Parkinson's Disease, a condition of growing prevalence and continued unmet need.
- Laboratory studies and early-phase trials indicate that vestibular stimulation can reduce motor symptoms, including postural instability, rigidity and tremor, as well as non-motor symptoms that impair cognitive and emotional capacity.
- Larger-scale trials are now needed to replicate and further characterise symptom reduction in 'real world' care settings using affordable medical devices that are easy to use and programmed with stimulation protocols optimised for the treatment of Parkinson's disease.

times more likely to have limitations on daily living, and three times more likely to suffer from depression, anxiety or panic disorder [10]. In a seminal paper [11], Grimm et al. reported cognitive disturbances in 102 patients diagnosed with perilymph fistula syndrome (a peripheral vestibular disorder) that included general forgetfulness, a specific deficit in auditory short-term memory, apraxia, and a general slowing of information processing. Fatigue, anxiety, depression and unexplainable dread were also commonly observed, and contributed to a clinical picture described as functionally devastating. These clinical findings speak to a profound role for vestibular input in brain health and mental well-being. A strong advocate of this view is the renowned developmental psychological therapist Jean Ayres who proposed that the child's relationship to gravity is even more primal than his/her relationship to his/her mother [12]. According to Ayres, knowing which way is up and knowing that we are always firmly connected to the Earth is the foundation to all meaningful behaviors and interpersonal relationships; an individual cannot follow his/her inner drive and develop emotionally or socially if he/she feels lost in space and is afraid to act through fear of spatial disorientation. One might question the foundational status that Ayres attributes to the vestibular system, but the profound effects of vestibular dysfunction suggest that it shapes cognition more pervasively than any other sensory system. In the present context, if (as in case of disease) vestibular signals can impair mental well-being then might there be conditions in which, by means of artificial stimulation, they can be clinically engineered to enhance it?

2. The approach of noninvasive vestibular stimulation

Several approaches have been taken to test whether efferent signals from the peripheral vestibular organs can be therapeutically modified. Parents will be intimately familiar with the calming effects that can be induced by gentle, rhythmic rocking although, as reported below, more compelling benefits can be obtained via the controlled stimulation of the vestibular organs using thermal or galvanic current. Thermal, or caloric, stimulation is traditionally achieved by irrigating the external ear canal with warm or cool water (or less commonly by air) [13]. The method of application is, as it sounds, somewhat crude, and its simplest form requires little more than an ice water bath and some rubber tubing. More sophisticated off-the-shelf devices allow flow rate, volume and temperature to be carefully controlled. Although surprisingly effective, the standard procedure relies on in-clinic administration and can spontaneously elicit a strong, short-lived sense of vertigo which may lead to nausea and sickness. Initially developed by Robert Bárány more than a century ago, the temperature changes introduced to the external ear canal find their way to the endolymphatic fluid of the semi-circular canals within the inner ear where the induced convention currents change the firing rate of the vestibular afferents; cold temperatures decrease mechanoreceptor discharge rate while warm temperatures increase it [14]. By virtue of cupula deflection, Bárány reported that a cold stimulus produces a horizontal nystagmus (i.e. side-to-side involuntary eye movement) with the fast phase directed away from the stimulated ear while a warm stimulus exerts the opposite ocular-motor effect. Debate continues as to whether this thermo-convection model accounts entirely for the physiological effects observed during CVS [15,16] but it is widely taken to account for at least most of them. Although initially applied as a means of diagnosing vestibular deficit, the last 40 years has seen a gradual growth in therapeutic application which has been enhanced by the development of solid-state device technology that allows greater control over the stimulation waveforms and makes the devices more suitable for home-based administration.

The recent emergence of CVS as a neuro-therapeutic is paralleled by progress made with galvanic vestibular stimulation (GVS). The technique involves the application of low amplitude (< ~2 mA), transcutaneous current to the mastoid processes, the bony protrusions located just behind the ears [17]. Several electrode configurations (i.e. bilateral monopolar, unilateral monopolar) are possible (especially when testing for unilateral vestibular impairment) although therapeutic applications most commonly use a bilateral, bipolar arrangement in which the anodal and cathodal electrodes are placed on opposite mastoids. Direct current [18], alternating current [19] and band-limited noise [20] waveforms are commonly applied but the parameter space is large and in the absence of dose response studies likely not yet optimized for clinical use. Many off-the-shelf devices are available, not least because they are also suitable for transcranial direct current stimulation, a more common form of electrode-based, noninvasive brain stimulation. Most, if not all, devices are yet to be indicted for clinical use but are becoming increasingly suitable for self-administration by virtue of their simple user-interfaces and the capacity for researchers to pre-set stimulation programs from a wide range of frequency, amplitude, duty cycle and morphological profiles. The tolerable side effects reported during low-amplitude (i.e. <2 mA) GVS, which mainly comprise mild itching and tingling at the electrode sites and may occasionally extend to vertigo and headache, provide further incentive. Studies indicate that GVS activates the vestibular afferent

fibers (mostly of the irregular type) at the spike trigger zone although there is debate as to whether only the otoliths are activated or whether the semi-circular canals are too [17,21]. In any case, primary modulation appears to have occurred by the level of Scarpa's ganglion within the internal auditory meatus because the effects can be recorded in these vestibular-cochlear neurons [22]. Anodal currents inhibit the firing rates of all responsive vestibular afferents regardless of their directional specificity, while cathodal currents excite them [17]. Similar to CVS, GVS elicits a complex whole-body response with a bilateral bipolar configuration inferring an unexpected head rotation toward the cathodal side which elicits compensatory postural and oculomotor responses toward the opposite anodal side.

The compensatory ocular-motor, postural and perceptual behaviors initiated by vestibular stimulation are associated with diffuse hemodynamic responses across cortical, striatal, cerebellar and thalamic structures, some of which show deactivation rather than activation during PET and fMRI [5,23–25]. Meta-analysis of fMRI and PET studies shows activation overlap across bilateral peri-sylvian regions, especially in the media and posterior insula, parietal operculum and retro-insula cortex all of which receive converging afferents from the otoliths and semi-circular canals [6]. Divergent patterns of activation are difficult to interpret because caloric and galvanic waveforms draw from different parameter spaces, differentially activate somatosensory, vagus, visual and auditory systems, do not share a common metric by which the 'intensity of stimulation' can be equated, and cannot be easily calibrated to send the same information about head position and movement. Focusing on the two techniques separately, pervasive neurophysiological effects are nevertheless apparent. In the case of time-varying CVS, transcranial Doppler sonography of the basilar artery shows a significant increase in cerebral blood flow velocity that is consistent with modulation of brainstem centers [26]. In the case of GVS, there are changes in EEG power spectra and P300 morphology [19,27–29] and in rats, there are reports of hippocampal cell proliferation [30] striatal reductions in c-FOS expression, and serine and threonine release [31,32].

The bottom-up, endogenous manner in which CVS and GVS stimulate the brain contrasts with transcranial magnetic stimulation and transcranial direct current stimulation. These more common, transcranial techniques are inherently localizationist in how they seek to modulate brain function, cannot easily modulate activity in deep lying areas, and are constrained by needing to identify both the correct part of the scalp to stimulate and the optimum stimulation frequency to apply (although the latter requirement likely also applies to vestibular stimulation). By activating the same ascending pathways as natural head movement the GVS/CVS signal, although artefactual in origin, is able to be processed in the same innate manner [33,34]. As physiological recording studies show, this 'bottom-up' mode of transmission allows the signal to reach many levels of the central nervous system and brings opportunity to entrain a wide variety of brain oscillations [33,34].

Given the anatomical and physiological reach of the vestibular system, it is perhaps unsurprising that a growing number of researchers conceptualize it as a therapeutic pathway. Initial impetus for this viewpoint came from reports of spontaneous, albeit temporary, recovery from the lateralized attentional disorder of hemi-spatial neglect during CVS irrigation [35–37]. Subsequent studies have shown therapeutic benefit in a number of other acquired brain disorders and neurological conditions (see [38]) as seemingly diverse as minimally conscious state [39] and episodic migraine [40]. As described below, perhaps the most striking reports, given the rigorous clinical trials methodology and the breadth and longevity of improvement observed, are in people with Parkinson's disease.

3. Vestibular stimulation in Parkinson's disease

Parkinson's disease is a form of neuro-degeneration that causes tremor, slowness of movement, muscle rigidity and postural instability as well as debilitating non-motor symptoms including insomnia, speech and memory loss, chronic pain, incontinence, excessive sweating, eating and swallowing difficulties, depression and anxiety [41]. Although of only passing relevance here, emerging evidence suggests that the difficulties with posture, gait, and in making saccadic and smooth pursuit eye movements partly reflects an underlying vestibular disorder [42]. The disease is the fastest growing neurological condition; from 1990 to 2015 the number of people with Parkinson's doubled to 6 million and is expected to double again by 2040 [43]. The disease is incurable although the motor symptoms can be partly managed pharmacologically, especially in the early stages. The non-motor symptoms are much more difficult to manage, both because of their pharmacological complexity and because they may not be disclosed by patients and/or are not fully recognized or appreciated by clinicians [41]. Yet emerging evidence suggests that for many individuals the non-motor symptoms are the major determinant of quality of life, incurring significant health and social care costs [44,45].

The case for trialing vestibular stimulation as a treatment for Parkinson's disease is premised on the results of human and animal physiological studies. Tracer studies have uncovered both cortical and subcortical pathways (some only disynaptic) connecting vestibular brainstem nuclei to the striatum, a midbrain structure heavily implicated in Parkinson's disease and comprising nuclei involved in movement planning (see [46]). Other studies indicate that unilateral vestibular loss affects the expression of striatal dopamine receptors [47] and, perhaps most compellingly, Samoudi et al. [48] showed in hemi-parkinsonian rats that noisy GVS not only improved locomotor activity, as measured by performance on a rotarod, but also enhanced GABA release in the substantia nigra. fMRI and PET studies in humans also show physiological changes within the striatum (notably in dorsal areas) during vestibular stimulation [5,24], although the hemodynamic response is evident in many other brain regions including the cerebellum and cerebral cortex which are not only linked to the motor symptoms of Parkinson's disease but many non-motor symptoms too [5,49]. In one recent study, Cai et al. showed with fMRI that both noisy and sinusoidal GVS

increases functional connectivity between the pedunculopontine nucleus, a structure involved in the supra-spinal control of locomotion, and left inferior parietal regions which are also involved in gait as well as visuo-spatial processing and motor planning [50]. Although few in number, preliminary EEG studies suggest that GVS may also normalize aspects of the abnormal-phase coupling seen in Parkinson's disease [51] and help restore inter-hemispheric connectivity [52].

The case for clinically trialing vestibular stimulation in Parkinson's disease is further strengthened by a handful of laboratory studies which have shown that a single session of GVS can temporarily reduce motor symptoms, mostly those associated with posture and gait (which interestingly may partly stem from damage to the vestibular system itself). For example, Kataoka et al. [53] showed a reduction in postural instability soon after a single session of DC GVS in 3 out of the 5 individuals assessed, while Pal et al. [54] showed a small reduction in backwards-forwards and side-side sway in 5 individuals with Parkinson's during subsensory, noise stimulation. Samoudi et al. [55] showed in 10 individuals that a single session of subsensory, noisy GVS was also associated with shorter postural corrections after being unexpectedly pulled backwards. Other studies have found improvements in finger tapping and on a Timed Up and Go Task (which involves moving from sitting to walking and then walking to sitting) during DC GVS [56], faster rest to active transitions during noisy, subsensory GVS [57] and improved visuo-motor tracking during receipt of low, zero-mean pink noise [58].

Prompted by the need to translate the above findings into clinically relevant outcomes, Wilkinson and colleagues recently set out to determine, by means of randomized controlled trial methodology, if repeated sessions of vestibular stimulation, self-administered at home, could both prolong and diversify the motor improvements observed within the laboratory. They chose to use CVS instead of GVS given their recent, positive experiences with a solid-state caloric stimulation device that administers thermal waveforms via aluminum earpieces housed within an easy-to-use headset; in other neurological populations the device has shown high patient compliance during home administration and an impressive treatment and safety profile [40,59]. Unlike other caloric stimulators which typically discharge a constant temperature, the device is able to deliver different temperatures overtime, in the present case oscillating gently from ear canal temperature to ~17℃ every 2 mins in one ear (cold currents primarily activate contralateral cortex), and from ear canal temperature to ~42^{o}c every 1 minute in the other (warm currents primarily activate ipsilateral cortex) for a total period of ~20 minutes [26]. The waveform assigned to each ear can be periodically switched to prevent any vestibular-induced hemispheric bias. The time-varying feature of the waveform is especially important because it is believed to mitigate both semi-circular canal adaptation and the side-effects that accompany the sudden temperature change induced by traditional irrigation methods. Allied study also indicates that, unlike constant temperature CVS, a time-varying temperature profile can elicit a distinctive entraining effect on the Gosling Pulsatility Index, a measure of cardio-vascular resistance [26].

In an initial proof of effect study, Wilkinson et al. [60] recruited a single participant, aged 70, who had been diagnosed with Parkinson's disease 7 years earlier. Although in stable receipt of anti-parkinsonian medication, he presented with a wide range of motor and non-motor difficulties. The individual continued to receive his drug medications while receiving CVS twice per day, initially under sham conditions for 1 month and then under active stimulation for 2 months. By end of active treatment, clinically-meaningful improvement, akin to a ~ 50% reduction in symptoms, was observed across nearly all outcome measures during the active compared to sham phase, encompassing symptoms related not only to mobility but also cognition, executive function, sleep, mood and activities of daily living. Most remarkably, many of these gains were still evident at 5 months follow-up.

Buoyed by the success of this single case study, Wilkinson and colleagues sought to replicate the outcomes in a larger-scale, double-blinded study that incorporated separate active and control arms [61,62]. The volunteer sample had a mean age of ~70 years and comprised individuals with a wide symptom and severity profile and who were once again in stable receipt of anti-parkinson's medication. As before, active CVS was associated with a diverse and durable pattern of clinically-meaningful gain at both the end of the 2 month treatment period and, most strongly, at 5 weeks follow-up. Persistent, albeit weaker, improvement was still evident 5–6 months later. The minimum clinically importance difference was exceeded on the 'gold standard' scales of the MDS-UPDRS I (which probes non-motor aspects of daily living including sleep, pain, urinary and constipation problems, light headedness, and fatigue,) MDS-UPDRS II (which probes motor aspects of daily living including speech, salivation, chewing, swallowing, eating dressing, hygiene, hobbies, tremor, walking, balance, and freezing) and MDS-UPDRS III (which is a motor exam that includes assessments of speech, facial expression, rigidity, upper and lower limb movement, gait, posture and tremor). Allied non-motor improvements were seen in 14 of the 16 active participants across multiple sub-domains of the Non-Motor Symptom Scale (which capture symptoms related to sleep/fatigue, mood, hallucinations, memory, gastro-intestinal, urinary and sexual function), Montreal Cognitive Assessment (which is especially sensitive to short-term memory, attentional/executive and visuo-spatial problems), and the Hospital Anxiety and Depression scale which is sensitive to emotional well-being. Further evidence of a more general enhancement in quality of life and functional independence was apparent in the PDQ-39 (which interrogates the ability to perform activities of daily living such as getting around in public, avoiding certain situations and interacting with people) and Modified Schwab and England scale (which measures how independently daily chores can be completed).

These striking improvements were obtained with good treatment concealment (as indicated by post-study questionnaire) which was achieved by informing participants that they may or may not receive stimulation throughout the 2 month treatment period and that any unusual temperatures felt in the ears were not indicative of 'active' treatment but rather signaled normal device operation that people sometimes

reported and which did not indicate whether it was in treatment or sham mode.

Equally as important, the striking improvements were not associated with any serious adverse events related to device use. Thirty-four adverse events were reported in the 46 randomized subjects; 24 in the active group and 10 in the placebo group. Three adverse events were classified as 'serious', but none was deemed by independent clinical adjudication to be related to device use. Four adverse events (i.e. ear discomfort, dizziness/motion sickness and migraine) were considered to be 'possibly' related to device use; however, none was considered to be severe, and all resolved after the cessation of device use. All other adverse events were minor and were most likely attributable to Parkinson's disease rather than to study involvement. An end-of-study device questionnaire revealed that the majority of participants found the device 'easy to use at home' and found the actual time receiving stimulation as 'enjoyable' or 'acceptable'.

4. Conclusion

Taken together, the experimental evidence base provides good, albeit preliminary, evidence that vestibular stimulation can provide a valuable adjuvant therapy for individuals with Parkinson's disease. The handful of small laboratory studies conducted have shown compelling improvements in specific motor functions, mostly focused on posture and gait, during GVS. There is however need to link these observations to broader symptomatic improvement and quality of life measures (both motor and non-motor) and to administer longitudinal stimulation within more formal trials protocols to better leverage and assess carry over. Progress made with CVS contrasts to that for GVS in that far fewer mechanistic and laboratory studies have been conducted but a double-blinded, randomized controlled trial has been completed. The high level of efficacy shown in this trial now needs to be replicated in a larger sample that is drawn from a wider geographical region and with treatment administered through established 'real world' care pathways by healthcare staff rather than via a university research team. The inclusion of cost effectiveness measures will help determine the value of integrating the procedure into current, routine clinical practice.

5. Expert opinion

Although early stage, no other Parkinson's therapy has yet demonstrated the same durable and diverse pattern of gain seen with vestibular stimulation. In fact very few neurological medicines continue to work so effectively once withdrawn, not least those of a non-pharmacological nature. The optimism prompted by the laboratory and clinical research so far conducted is therefore understandable. As discussed below and in addition to those mentioned directly above, many challenges and questions must nevertheless be addressed before the intervention can be considered for routine care.

From a device perspective, it is still unclear how much it matters if the vestibular periphery is stimulated via galvanic or thermal currents. It also unclear by how much it matters if the stimulus waveform has an unchanging morphology, is sinusoidal or noisy, and by how much stimulus amplitude and frequency regulate effect. Studies show that these different stimulation protocols have both overlapping and separable effects on neural response (both haemodynamically and electro-physiologically), but their clinical relevance has yet to be demonstrated. Coupled with uncertainty about how long each stimulation session should last, how many sessions should be given and how long to wait between sessions, the need for dose optimization across an unforgivingly wide parameter space is clear. To some degree these methodological uncertainties stem from the good safety profile (which although features short-lived, minor adverse reactions does not seem to carry a significant risk of serious adverse reaction), and noninvasive nature of vestibular stimulation which has enabled human efficacy studies to progress swiftly without the prior dosing and mechanism-of-action studies that typically precede drug trials. One challenge for dose optimization study will be to identify reliable biomarkers of clinical effect that can be swiftly and easily acquired; while vestibular stimulation elicits reliable autonomic responses [13,17] it is unknown whether these accurately predict symptomatic reductions in Parkinson's disease. The means by which vestibular stimulation improves neurological function is varied, likely affecting a range of domain-global processes involved in cerebrovascular regulation, central inflammation, and electrical oscillatory rhythm, as well as more domain-specific processes associated with self-motion and egocentric processing. In terms of identifying and understanding the underlying drivers of effect, this rich diversity of effect may prove both a blessing and a curse.

Despite the enthusiasm of people with Parkinson's to make use of vestibular stimulation devices, further demonstrations of device effectiveness are needed before regulators will grant clinical adoption, clinical commissioners will pay for devices and doctors will prescribe them. The pace of downstream development will continue to rely on the mutual collaboration of academics (perhaps most notably neuroscientists and bioengineers), clinicians, industry and of course, lay advocates. These 'translational' collaborations are not only needed to further demonstrate the safety and efficacy of vestibular stimulation but also to develop the next generation of devices which would benefit from being more portable, cheaper and, in the fullness of time, incorporate telemetry to enable physicians to remotely monitor treatment compliance and response and thereon download repeat or revised prescriptions from clinic to home. Alongside these technical developments, it will be important to assess vestibular stimulation within a multi-interventional context to establish the degree to which it reduces reliance on other Parkinson's medications and/or magnifies their effects. As highlighted by Lee et al. in an allied review [63], impact will also likely be constrained by a host of clinical and demographic factors including disease sub-type, co-morbidity, age, and peripheral vestibular response.

At this stage it is difficult to recommend one form of vestibular stimulation over the other. Unlike CVS, GVS is contra-indicated in people with electronic implants or metal in their head (although both techniques tend to be with-held in

the presence of particular ear pathology) and presently relies on fastening electrodes to the mastoid processes which is a challenge for self-administration, portability and maintaining a low electrical impedance. It also tends to activate only the irregular afferents which make up just one-third (approximately) of all primary afferents [17]. Compared to CVS, GVS has a smaller clinical evidence base, although much of the CVS literature lies within the field of acquired brain injury and neuropsychiatric disorder than within the field of neurodegeneration considered here. On the other hand, GVS is easier to blind (by virtue of being sub-sensory and therefore imperceptible), simpler to miniaturize, and can accommodate a much wider range of stimulus waveforms, some of which are more clearly linked with neural restoration. Direct comparisons are also difficult because neither approach is yet optimized for efficacy, usability or cost of manufacture and supply, a frustration that is not helped by very few research groups actively investigating both techniques.

In closing, it would be remiss to allow the challenges that lie ahead to overshadow the therapeutic promise brought by vestibular stimulation. The equipment needed to deliver stimulation can, in rudimentary form, be found in most domestic households and applied with relatively little expertise. Yet surely few would link the bewildering sensations brought about by lending thermal or galvanic currents to the ears with their profound clinical potential. The technological innovations reviewed above bring an ease, safety and potency that make this potential realizable within the next few years. A key next step is to demonstrate cost effectiveness, a process that with funding should take no more than 5 years. In the longer-term, the intriguing question arises as to whether vestibular stimulation, be this CVS and/or GVS, can replace as opposed to merely supplement existing drug treatments for features of Parkinson's disease.

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