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The influence of vestibular stimulation on metabolism and body composition

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What's new?

- Accumulating evidence suggests that vestibular stimulation may play a role in the regulation of metabolism and body composition.
- This review summarizes current understanding of the relationship between the vestibular system and homeostatic regulation of body composition, metabolism and endocrine function as the basis for discussion of novel therapeutic approaches towards treating obesity and diabetes.
- Vestibular stimulation represents an emerging area of translational research that appears to hold potential for the development of innovative strategies for the effective treatment of metabolic conditions, the incidence of which is increasing rapidly.

Abstract

Obesity, diabetes and metabolic disease represent an ongoing and rapidly worsening public health issue in both the developed, and much of the developing world. Although there are many factors that influence fat storage, it has been clearly demonstrated that the homeostatic cornerstone of metabolism lies within the hypothalamus. Moreover, neuronal damage to vital areas of the hypothalamus can drive reregulation or dysregulation of endocrine function, energy expenditure and appetite, thereby promoting a shift in overall metabolic function towards a state of obesity. Therefore, identification of treatments that influence the hypothalamus to improve obesity and associated metabolic diseases has long been a medical goal. Interestingly, evidence from animal studies suggests that activating the vestibular system, specifically the macular gravity receptor, influences the hypothalamus in a way that decreases body fat storage and causes a metabolic shift towards a leaner state. Given that the macular element of the vestibular system has been shown to activate with transdermal electrical stimulation applied to the mastoids, this may be a potential therapeutic approach for obesity, diabetes or related metabolic diseases, whereby repetitive stimulation of the

vestibular system influences hypothalamic control of metabolic homeostasis, thereby encouraging decreased fat storage. Here, we present an up-to-date review of the current literature surrounding the vestibular influence of the hypothalamus and associated homeostatic sites in the context of current and novel therapeutic approaches for improved clinical management of obesity and diabetes.

<H1>Introduction

<H2>Regulation of body composition

It has long been known that complex central mechanisms, particularly within the hypothalamus and brainstem, regulate the storage of body fat through the process of homeostasis, and that these control mechanisms thereby modify metabolism, feeding behaviour and energy expenditure to maintain body fat within a predetermined range [1]. By default, homeostasis naturally resists deviations in body fat in either direction, with a tightly maintained range of values, sometimes referred to as the 'set-point' [2]. Although the idea of a set-point, which is sometimes compared to a thermostat, does provide a concept that is easily understood, it unfortunately represents a vast oversimplification of the complexity of homeostatic regulation, and fails to appreciate the interplay between the numerous homeostatic effectors that seek to maintain equilibrium within a physiological range [3].

Although external influences can cause body composition to deviate outside the homeostatic range, this process appears to be significantly asymmetric with a tendency towards the direction of chronically increased body mass [1]. What is classically known as a 'western lifestyle', typically a high caloric intake coupled with sedentary activity levels, can readily overcome the normal homeostatic range and therefore promote excess fat storage. Indeed, it has been reported that simple carbohydrates (e.g. glucose and fructose) and saturated fatty acids actually cause neuronal damage to nuclei within the hypothalamus, causing the set-point

for adipose storage to shift upward, and, unfortunately, with time, this increased level of fat storage appears to become the new homeostatic norm, with attempts thereafter to lower body fat triggering rigorous central mechanisms, that cause both metabolic and psychological changes to aggressively resist the reduction in fat storage [1].

It has been known for over 50 years that the vestibular system plays a role in the modulation of body composition (fat, bone and muscle), although the underlying mechanisms are only partly understood. However, as summarized in Table 1, more recent work has indicated that the potential of the vestibular system to affect body composition is in fact highly significant, and appears to be mediated via its extensive connections to brainstem nuclei involved in regulating metabolism and feeding behaviour, i.e. energy homeostasis [5]. As such, this review highlights current understanding of the role of vestibular stimulation in regulating metabolism and body composition with discussion of underlying mechanisms and its emerging potential as a novel therapeutic approcah for the clinical management of obesity and associated diabetes.

<H2>Current weight loss intervention

An almost universal approach to weight management is the target of chronically reducing daily food intake by ~ 500 kcal below the calculated maintenance amount to achieve 0.45 kg (1 lb) per week weight loss [9]. However, although this strategy is capable of generating long-term weight loss, it does not specifically address the established central mechanisms that chronically counteract reduced energy consumption by decreasing metabolic rate and altering appetite and satiety [10].

Given that such mechanisms are mediated at a neurological level, it is not surprising that the recent focus of weight loss drug therapies has moved away from targeting the gastrointestinal tract (such as orlistat, which aims to decrease intestinal fat absorption) to directly targeting the hypothalamus [11]. Currently, lorcaserin, phentermine–topiramate and naltrexone–bupropion

are the only three oral treatments (aside from orlistat) that are approved by the US Food and Drug Administration (FDA) for the sustained management of obesity. These drug combinations act specifically on the hypothalamus to influence the central pathways regulating appetite and adiposity, and when introduced into a weight loss approach that couples increased physical activity with a calorie-deficient diet, they promote significantly more weight loss than diet and increased physical activity alone [11]. However, as a weight loss treatment, important consideration should be given to the reported side effects of these drugs, not only central neurological effects (such as psychosis, suicidal actions and depression), but also systemic effects further to oral ingestion (such as nausea, constipation and vomiting) which may become a barrier to long-term compliance [11].

The FDA has also approved several invasive devices intended for the treatment of obesity that range from well-established gastric bands and gastric balloons, to the lesser known AspireAssist gastric drainage system, which removes food directly from the stomach after eating, and the vBloc electrical nerve stimulator, which acts on the vagus nerve [12]. Unfortunately, as many patients cannot manage their excess body weight with lifestyle interventions alone (even with addition of weight loss drugs), endoscopically placed interventions are often seen as the next step in a multidisciplinary approach [13]. Typically, a patient who receives an intragastric balloon system (of which there are several variants) will achieve between 6% and 10% total body weight loss at 6 months, while the AspireAssist and vBloc devices are reported to achieve ~ 12% and 9% total body weight loss, respectively, but after a 12-month period. It is also important to note that whereas balloon systems are intended for temporary use with removal at 6 months, both the AspireAssist and vBloc systems are considered as long-term solutions so remain *in situ* unless otherwise indicated [13].

<H2>The vestibular system

The vestibular system is a complex structure located within the inner ear in the petrous temporal bone. It conveys sensory information directly to the brainstem which classically determines our 'sense of balance' (often referred to as our sixth sense). However, the vestibular system also contributes significant information in relation to spatial orientation, acceleration and overall physical activity [14]. While this is obviously important in everyday activities that are consciously undertaken (such as walking), it is also vitally important to many autonomic functions (such as the maintenance of blood pressure when transitioning from a supine to standing position).

The vestibular system comprises two distinct elements: the otolith organs (i.e. the utricle and saccule), which detect linear movements relative to gravity, and the semi-circular canals, which detect rotational movements. The vestibular end organs project into the vestibular nuclei in the brainstem (through the vestibular element of cranial nerve XIII) where they continue to many significant autonomic nuclei of both the brainstem and hypothalamus, before linking with a diffuse cortical network across the wider regions of the brain [15].

For many years, stimulation of the vestibular system has been investigated as the focus of physiological research. In experimental animals, centrifugation (where animals are housed in a spinning environment) and caloric stimulation (where warm or cold water is irrigated into the ear canal) are the two most common methods. In humans, along with caloric stimulation, electrical stimulation of the vestibular nerve is commonly used as it is well tolerated with long-established safety [16]. Historically, this technique has been referred to as galvanic vestibular stimulation, and although there are some variations, typically vestibular nerve stimulation is induced by delivering a small electrical waveform to the skin over both mastoid bones, thereby directly activation the vestibular system, with preferentially activation of the otolith component. Electrical vestibular nerve stimulation has a long history in the research setting where the very low-risk nature of this treatment has been established. One particular

study reviewed the long-term effects of electrical vestibular stimulation over 255 individual sessions, and concluded that, even at relatively high current levels of 1.5 mA, there were minimal side effects, with the most significant being skin itching or tingling under the electrode pad [17]. Importantly, this study also reported that neither nausea nor vertigo were experienced by the participants, while highlighting the ability of individuals to manage their own doses up to a maximum tolerable therapeutic level without side effects as a major benefit. Taken together with the fact that electrical vestibular stimulation is a non-invasive, simple and low-risk procedure [18], it seems reasonable to further explore the use of this technology as a novel treatment modality.

<H2>Vestibular connections to the hypothalamus and brainstem

The brain and nervous system are reported to influence adiposity through the complex and multifactorial process of energy homeostasis [19]. Within the hypothalamus there are many key nuclei, although the main influence on metabolism appears to be the melanocortin-4 receptor, which forms part of the central melanocortin system and is located primarily in the arcuate nucleus, a sub-nucleus of the hypothalamus [19,20]. Although this seems to be the most significant area with regard to metabolism, it is not the sole regulator, and several other important regions in the brainstem have been detailed extensively. The most notable of these homeostatic sites are the nucleus of the solitary tract, the dorsal motor nucleus of the vagus nerve and the parabrachial nucleus [20]. In conjunction with the arcuate nucleus, the dorsomedial hypothalamic nucleus, paraventricular nucleus and lateral hypothalamic nucleus represent the other hypothalamic sub-nuclei that appear to be involved in regulation of metabolic homeostasis [1,19,20]. Indeed, as detailed in Fig. 1, many studies have reported that these key nuclei are influenced by the vestibular system, thereby mediating autonomic control of homeostasis, with this eloquent network being referred to as the vestibuloautonomic relay [21]. Interestingly, as the vestibular system appears to exert

influence over both afferent and efferent autonomic signals, its increasingly evident role in metabolism is likely to involve a twofold approach towards maintenance of homeostasis.

Several experimental studies have highlighted key interplay between the vestibular system and the hypothalamus. It was reported more than 25 years ago that electrode probes placed in the hypothalamus of guinea-pigs detected neuron activation subsequent to electrical stimulation of the vestibular nerve [8], while subsequent studies in rats, rabbits and cats have confirmed that vestibular nerve stimulation induces potent activation of the lateral hypothalamic nucleus and the nucleus of the solitary tract [6,7]. Complementary studies using tracer methods have also demonstrated neuronal connections between the vestibular nuclei and the nucleus of the solitary tract, dorsal motor nucleus of the vagus nerve and the parabrachial nucleus [22].

Other investigators have studied mutant mice that do not possess macular otoconia, and therefore functional otolith organs, to dissect the specific involvement of the otoliths in mediating neuronal activation induced by stimulation of the vestibular system [4]. Gentle centrifugation of these animals for 2 h to stimulate the vestibular system facilitated isolation of the specific effects of vestibular gravity receptors have on the central structures of the brain, particularly the hypothalamic and autonomic nuclei. This study reported that control mice, with normal vestibular activation, demonstrated increased expression of c-Fos (a well-established immunohistochemical marker of neuronal activity) [23] within the hypothalamus in response to centrifugation, with specific localization in the paraventricular nucleus, dorsomedial hypothalamic nucleus, arcuate nucleus, lateral hypothalamic nucleus and parabrachial nucleus [4], while mutant mice with no vestibular gravity receptors demonstrated significantly reduced c-Fos activation in these regions. Thus, it appears that the otolithic element of the vestibular system influences central autonomic control through a complex and multifaceted network of projections into the hypothalamus and brainstem, and that these

regions are not only important in mediating general homeostasis and neuroendocrine control, but are also linked to regulation of both food intake and body mass composition.

<H1>Vestibular influences on metabolic homeostasis

<H2>Body composition

The vestibulohypothalamic connection has been established for ~ 50 years as a major pathway contributing to the marked change in body composition (specifically a reduction in body fat) observed when animals are subjected to experimental centrifugation [4,5]. Although the specific purpose of such studies was to explore the effects of altered gravity, with the results acting as precursors to expected autonomic dysfunction due to space flight, they have also highlighted intriguing effects on body composition with high relevance to potential therapeutic applications for metabolic disease. A more recent study, focused specifically on the influence of vestibular stimulation, reported that wild-type mice subjected to vestibular stimulation via centrifugation for a period of 8 weeks demonstrated an initial decrease in food intake and prolonged body fat reduction, which was not evident in mice lacking macular otoconia [5]. Thus, it would appear that the observed differences between these two groups could be attributed to the vestibular modulation experienced only by the wild-type mice that had normal function of their vestibular otoconia. Therefore, this study appears to identify effects of vestibular stimulation that are specific to the vestibulohypothalamic pathway, so is the first to report direct influence of the vestibular system on metabolism and substrate utilization (particularly fat). It was concluded that vestibular stimulation secondary to centrifugation causes a beneficial metabolic shift resulting in both altered energy storage and feeding behaviour, thereby highlighting that the vestibular system can influence the central mechanisms that control metabolism and feeding.

<H2>Melanocortin-4 receptor

The central melanocortin system has been well defined as a key regulator of energy homeostasis, with specific interest in the role of the melanocortion-4 receptor, which is reported to regulate feeding behaviour and body weight in both humans and animals [24]. An apparent link between the medial vestibular nuclei and melanocortin-4 receptor has been established using several different approaches. For example, transgenic mice that specifically defined the distribution of melanocortin-4 receptor-expressing cells, highlighted the medial vestibular nuclei as an area of high expression, with a later study indicating that ~ 80% of medial vestibular neurons expressed the melanocortin-4 receptor [24]. Although the viral tract tracer studies discussed above demonstrated direct connections between brown adipose tissue and the medial vestibular nuclei in Siberian hamsters [25], a similar study also using viral tracers injected in to the kidney identified renal melanocortin-4 receptor expression and direct melanocortinergic circuits extending between the medial vestibular nuclei and the kidney [26]. Taken together, these studies highlight the emerging importance of the melanocortin-4 receptor with regard to the vestibular system, which should be considered in the context of future therapeutic approaches for metabolic disease based around vestibular stimulation.

<H2>Bone and muscle metabolism

The influence of the vestibular system on metabolism of bone and muscle is a well-established and documented phenomenon. Specifically, the vestibular system displays diffuse projections into the central drivers of sympathetic outflow which appear to directly regulate bone metabolism and remodelling by increasing sympathetic outflow, thereby inhibiting bone formation through reduced osteoblast activity and promoting bone resorption by stimulation of osteoclasts [27]. Similarly, activation of the sympathetic nervous system may indirectly influence muscle mass through modulation of the vestibular system. For example, animal studies have reported that vestibular modulation specifically alters expression of both FK506 binding protein 5 and follistatin, key regulators of muscle protein synthesis [27]. Consistent

with these findings, clinical studies have highlighted modulation of muscle sympathetic nerve activity as a direct target of electrical stimulation of the vestibular nerves [28]. One such study reported increased muscle sympathetic nerve activity, recorded by electrodes placed at the common peroneal nerve, in response to a range of frequencies of vestibular nerve stimulation, induced by electrical stimulation bilaterally, up to 156% baseline [28]. With specific regard to metabolism, muscle sympathetic nerve activity, which is known to regulate energy expenditure and adipose storage, is reported to positively correlate with weight loss in response to a hypocaloric diet [29]. Put simply, individuals with higher muscle sympathetic nerve activity are more likely to succeed with diet-based weight loss interventions compared with those who have lower muscle sympathetic nerve activity.

<H2>Brown adipose tissue

Recent focus has turned to investigating the particular influence of specific subtypes of fat on metabolism. In addition to white adipose tissue, which has a well-defined role in lipid storage and undergoes pathological expansion during obesity, mammals also possess brown adipose tissue, a less-characterized subtype that plays an important role in thermogenesis and may protect against diet-induced obesity and type 2 diabetes [30]. Both white and brown adipose tissue are subject to regulation by the sympathetic nervous system, with sympathetic activation driving lipolysis and mobilization of lipids from white adipose tissue and thermogenesis in brown adipose tissue [30]. Interestingly, a study of Siberian hamsters to assess direct connections between brown adipose tissue and the central nervous system, detected infiltration of viral tract tracers injected into specific areas of brown adipose tissue in the medial vestibular nuclei, highlighting a direct sympathetic pathway linking the medical vestibular nuclei and brown adipose tissue [25].

<H2>Blood lipids

Dyslipidaemia is a typical metabolic feature of obesity and represents an established risk factor for associated cardiovascular disease [31]. Although improving obesity will likely cause secondary improvement in blood lipid profiles, direct approaches to treating dyslipidaemia are also employed. Interestingly, vestibular stimulation has been demonstrated to confer beneficial effects on the blood lipid profiles of adult male albino rats exposed to high-fat diet for 28 days [32]. Specifically, total cholesterol, triglycerides, HDL and LDL were found to be reduced by vestibular stimulation with comparison to a control group received high-fat diet alone, suggesting that vestibular stimulation may promote direct actions on dyslipidaemia, in addition to its better characterized metabolic actions discussed earlier in this section.

<H1>Vestibular influences of the neuroendocrine system

<H2>Cortisol and stress

Cortisol is known to encourage redistribution of adipose tissue to the abdominal region and to increase appetite with a preference for energy-dense food [33]. Unfortunately, many factors in modern society, such as poor sleeping patterns and chronic stress, can directly influence the hypothalamic–pituitary–adrenal axis, and thereby contribute to metabolic disease [33]. Interestingly, vestibular stimulation is reported to exert positive influence on salivary cortisol levels in adults, infants and animals [34–37]. For example, a study of 240 college students subjected to vestibular stimulation for ~ 5 months demonstrated significant reduction in both cortisol and subjective stress scores compared with controls, together with decreased pulse rate and blood pressure [35]. Similarly, another study of 79 preterm infants receiving vestibular stimulation for 10 days by means of a waterbed, reported reduced urinary cortisol levels vs. controls, which prompted the authors to recommend that vestibular stimulation should be used in preterm infants in intensive care to decrease stress [36]. Furthermore, a small study of 12 female students diagnosed with peptic ulcers reported decreased levels of

anxiety and stress in response to daily vestibular stimulation for 3 months, which was still evident at 6 months vs. baseline [34]. Interestingly, it appears that it is not only humans that may benefit from decreased cortisol levels following vestibular stimulation. African elephants, who tend to display stereotypic behaviour in captivity, particularly involving swaying, demonstrated reduced signs of stress, indicated by salivary cortisol levels, coincident with periods of swaying-induced vestibular stimulation [37].

<H2>Thyroid function

Thyroid hormone plays a significant role in energy homeostasis, body weight and feeding behaviour through its direct influence on the central mechanisms involved in the regulation of energy metabolism [38]. One of the major central targets of thyroid hormone is the arcuate nucleus of the hypothalamus where it promotes alterations in gene expression of neuropeptide Y and proopiomelanocortin, whereas a decrease in thyroid hormone appears to reduce the appetite-suppressing effect of circulating leptin [39]. Indeed, dysregulation of the thyroid system (typically hypothyroid or hyperthyroid) is known to significantly modulate not only energy expenditure and appetite, but also thermoregulation, insulin resistance and torpor, leading to altered body composition and a shifted metabolic state [40,41].

Given the apparent links with the arcuate nucleus and the paraventricular nucleus of the hypothalamus, vestibular stimulation has been suggested as a supplementary therapy for thyroid disorders [42]. Indeed, vestibular stimulation is reported to positively influence thyroid hormone secretion in both animals and humans in response to environmental stress [43,44]. For example, it was shown that daily vestibular stimulation for a period of 2 months in female participants with premenstrual syndrome, not only decreased and increased secretion of thyroid-stimulating hormone and thyroxine, respectively, but also reduced perceived stress [44]. It has been demonstrated that stress can induce negative effects on thyroid secretion, much like cortisol, through interactions with the hypothalamic–pituitary–

adrenal axis, so it is interesting that vestibular stimulation not only negated the expected actions on thyroid function, but also reduced the subjective feeling of stress as reported by study participants. Indeed, vestibular stimulation in rats subjected to a stressor environment induced by cold water swimming is reported to prevent stress-mediated changes in thyroid function, cholesterol and body weight over a period of 15 days [43]. Taken together, it appears that the mechanism by which vestibular stimulation influences the thyroid therefore is twofold, comprising both direct and indirect actions. While the primary driver of vestibular nerve stimulation on the arcuate nucleus and the paraventricular nucleus may exert direct influence on thyroid homeostasis, secondary mitigation of stress-induced changes in thyroid hormone secretion mediated by the hypothalamic–pituitary–adrenal axis may represent an important complementary regulatory mechanism.

<H2>Metabolic peptides

Homeostatic regulation of body composition is a complex and multifactorial process, with recent interest focusing on several orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) peptide hormones [45]. In this regard, two particularly significant peptides have been identified, adropin and irisin, which may play a central role. The primary function of adropin is insulin-dependent promotion of carbohydrate, lipid and protein utilization, whereas irisin, which is secreted from muscle following exercise, regulates adipose tissue and glucose metabolism by mediating the conversion of white adipose tissue to brown adipose tissue. Interestingly, recent studies have highlighted links between the vestibular system and these two hormones, although the exact nature of this relationship is not fully understood [46,47]. Adropin is encoded by the Enho gene, which is typically found in the liver and the brain, with one study reporting dense Enho expression in the medial vestibular nuclei along with other regions that are known influence metabolism through regulation of the autonomic nervous system [47]. Another rat study demonstrated the

presence of irisin immunoreactivity markers specifically in Purkinje cells projecting from the cerebellum directly into the vestibular nucleus [46], supporting the concept that irisin-responsive Purkinje cells may innervate the vestibular nucleus. Although the precise functional role of this relationship is not known, it has been suggested that these projections may regulate sympathetic outflow to brown adipose tissue, thereby modulating thermogenesis.

<H2>Diabetes mellitus

To date, only two small pilot studies, with somewhat limited findings, have directly assessed vestibular stimulation in the setting of diabetes mellitus. First, a single-person case study of an 83-year old man with a 20-year history of type 2 diabetes receiving a standard drug regimen of glibenclamide and metformin, and exposed to daily linear vestibular stimulation by ~ 3-min periods of simple swinging for 6 months, reported acute improvement in fasting blood glucose coupled with significant reduction in both systolic and diastolic blood pressure [48]. Second, a rat study (n = 24) of experimental type 1 diabetes induced via alloxan injection (which is used routinely to destroy pancreatic β cells, thereby stopping insulin production), found that daily caloric vestibular stimulation for 1 month induced by irrigation of the external auditory meatus with cold water (but not warm water), resulted in a significant reduction in blood glucose vs. controls [49]. Although these studies have clear limitations and are preliminary in nature, it is still interesting to note that both reported improvements in blood glucose in response to vestibular stimulation, suggesting potential benefits in the setting of diabetes. Indeed, given the more established benefits of vestibular stimulation on body composition and metabolism, it seems likely they may be at least partly extrapolated to people with diabetes, although further detailed studies are required before stronger conclusions can be made.

<H1>Conclusions and future directions

There is accumulating evidence demonstrating that the vestibular system influences key autonomic centres within the hypothalamus and brainstem. Indeed, as summarized in Fig. 2, it would appear that this complex relationship is extensively integrated within the internal physiological milieu that maintains body composition through modulation of metabolism, feeding and substrate utilization. Although vestibular stimulation has yet to be assessed directly as a potential therapeutic intervention for clinical obesity, the reported positive outcomes of vestibular stimulation suggest that this approach may prove beneficial in the area of weight loss. Remarkably, in many animal models, vestibular stimulation has been reported to not only influence energy regulation, but also directly decrease adipose storage and feeding, which is associated with an important shift in substrate utilization, indicating that it may play a role in the configuration of metabolism towards an entirely new homeostatic range.

Why stimulation of the vestibular system may play a role in metabolic homeostasis has yet to be determined. One hypothesis is that the hypothalamus, and other central nuclei, use the vestibular system as an actimeter, providing feedback in relation to both the acute and chronic physical state of the body. In a scenario of long-term physical activity (i.e. chronic vestibular activation), reducing fat storage while simultaneously increasing substrate utilization towards muscle and bone, may confer evolutionary advantage. Conversely, in a period of limited physical activity (such as hibernation), creation of a homeostatic state whereby fat storage is maintained, may be beneficial from an evolutionary standpoint. If this were true, then the vestibular system would, among other sensory feedback mechanisms, act as a reference point for body composition, with increased vestibular activity promoting metabolic homeostasis towards decreased adiposity.

Taking the current supporting evidence, it seems reasonable to hypothesize that stimulation of the vestibular system may represent a potential therapeutic avenue for obesity and type 2 diabetes. Furthermore, because vestibular nerve stimulation is a well-established and safe method for activating the vestibular system, this potential therapeutic approach may realistically be deployed in the form of a wearable device that applies an electrical stimulation waveform to both mastoids on a daily basis. Notably, this technique, unlike weight loss drugs, also has the potential to mitigate side effects by having the ability for the participant to self-adjust, and if required, immediately cease stimulation delivery. Indeed, we will test this hypothesis in a randomized double-blind sham-controlled trial designed to assess the therapeutic potential of daily vestibular nerve stimulation as a practical treatment for obesity [50]. As per recommendations from the US FDA, this clinical trial will be based on creating a calorie-restricted environment in both an active vestibular nerve stimulation group and a sham control group (both with daily calorie restriction of 600 kcal below the calculated maintenance) where a primary end-point of difference in body weight will be assessed at 6 months. Given the accumulating evidence considered in this review, it seems reasonable to assume that addition of repeated vestibular nerve stimulation, to an appropriate calorie-restricted environment, holds potential to facilitate increased reduction in body fat, not only through direct influence on body composition, but also through positive influence on feeding behaviour. As such, similar to weight loss drugs, vestibular nerve stimulation may promote decreased appetite in a way that allows greater compliance with a chronic caloric deficit, thereby supporting its intriguing potential as a novel therapeutic avenue for improved clinical management of obesity and type 2 diabetes.

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Competing interests

Dr Jason McKeown is a founder and CEO of Neurovalens Ltd. Dr Paul D McGeoch is a co-founder of Neurovalens Ltd but does not hold an executive role. Neurovalens Ltd aims to commercially develop vestibular stimulation as a treatment modality for a range of conditions including obesity and diabetes. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. Professor David J Grieve, as an academic researcher at Queen's University Belfast and principal supervisor of Dr McKeown's PhD degree, has no conflict of interest. He has taken a lead role in reviewing and revising the manuscript to ensure that it represents an unbiased, objective and up-to-date appraisal of the relevant literature.

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FIGURE 1 Cross-sectional diagram highlighting the location of the medial vestibular nuclei in the brainstem and corresponding connections to the autonomic nuclei of the hypothalamus and brainstem that are known to influence metabolic homeostasis.

FIGURE 2 Autonomic regulation of metabolic homeostasis is a complicated and multifactorial process that involves several parallel efferent pathways descending from the hypothalamus and brainstem, coupled with complementary afferent pathways that are mediated via both hormonal feedback and the direct action of the vagus nerve. This schematic diagram highlights three proposed areas of influence that the vestibular system may exert on the regulation of metabolic homeostasis.

Table 1. Summary of key articles reporting beneficial outcomes of both hypergravitational activation and electrical activation of the vestibular system.

Author	Year	Method	Summary of major findings
Fuller *et al*. [4]	2004	Acute vestibular stimulation via hypergravitational centrifugation	A 2-h period of 2G centrifugation caused robust activation of autonomic and hypothalamic nuclei known to regulate metabolic homeostasis. This activation appears to be mediated through the macular gravity receptor of the vestibular system.
Fuller *et al*. [5]	2002	Chronic vestibular stimulation via hypergravitational centrifugation	An 8-week period of 2G centrifugation caused a significant change in body composition, most notably a reduction adipose tissue, suggestive of a metabolic-shift. This metabolic-shift appears to be mediated through the macular gravity receptor of the vestibular system.
Grigoryan *et al*. [6]	1999	Electrical vestibular stimulation	Electrical stimulation of the vestibular nerve was shown to cause neuronal activation within the posterior hypothalamus.
Bates *et al*. [7]	1994	Electrical vestibular stimulation	Electrical stimulation of the vestibular nerve was shown to cause neuronal activation within the nucleus of solitary tract.
Azzena *et al*. [8]	1993	Electrical vestibular stimulation	Electrical stimulation of the vestibular nerve was shown to cause neuronal activation within the paraventricular nucleus.