GAZE AND POSTURAL STABILITY REHABILITATION

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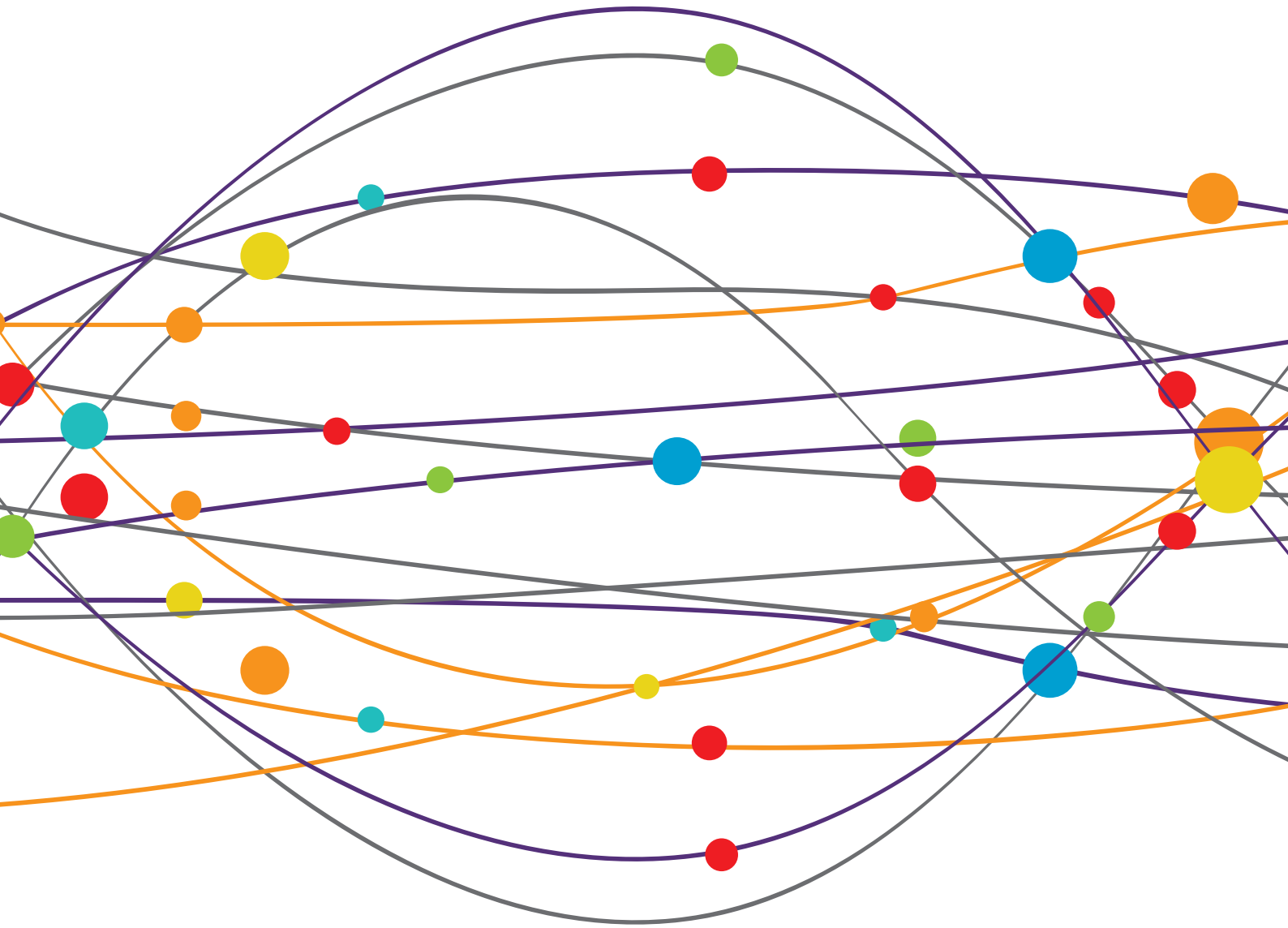

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GAZE AND POSTURAL STABILITY REHABILITATION

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Editorial: Gaze and postural stability rehabilitation

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Editorial on the Research Topic
Gaze and postural stability rehabilitation

Proprioceptive, Visual, Vestibular, and Cognitive systems interact in a continuous sensorial re-weighting, ensuring gaze and postural control (1, 2). The central nervous system integrates the information originating from these systems into a continuous sensorial re-weighting that ensures postural control in both static and dynamic conditions (3, 4). The contribution of each sensory system changes depending on environmental conditions and the motor task performed by the person (5–7). To tailor a rehabilitative program for patients with gaze and postural stability disorders, a multidimensional assessment is required. A wide range of both clinical and instrumental evaluations could be performed before the rehabilitative approach in order to obtain quantitative and qualitative information about the patient's balance and gait disorders, supporting the rehabilitative staff in designing the most suitable therapeutic intervention. Instrumental assessment of the vestibular system has made significant progress in recent years. Two protocol tests are available in the clinical practice to evaluate the Vestibular Ocular Reflex (VOR) function through the use of Video Head Impulse Test (vHIT): Head Impulse Paradigm (HIMP) and Suppression Head Impulse Paradigm (SHIMP) (8–10). The head turn stimulus and the eye movement recording are identical. All that is changed are the instructions—from "look at that fixed target on the wall" to "look at the moving target." At the same time, vestibular-evoked myogenic potentials are the most suitable test to evaluate otolith functions in patients with unilateral vestibular hypofunction in the acute and sub-acute phases (11, 12).

An innovative evaluation strategy could be represented by the inertial measurement unit sensors (IMU)-based assessment that provides valid objective metrics able to discriminate, with a higher sensitivity than clinical scores, between healthy people and patients with multiple sclerosis (MS) (Carpinella et al.) and in other neurological conditions (13). This approach would help in tracking these impairments over time and identifying those individuals who may benefit from preventive motor exercise and better tailor the rehabilitative program.

Standard rehabilitation, aimed at the recovery of static and dynamic postural stability, is usually focused on trunk stabilization and on exercises consisting of maintaining the standing position on an unstable platform such as oscillating boards and foam cushions (14). Another useful strategy is to work on postural control excluding the visual feedback and stimulating the sensory reweighting. Moreover, it could be effective to train the dynamic gait stability using a mechanism commonly required in daily life, defined as the dual-task paradigm (5). These exercises consist of combining a walking task with a cognitive one.

The gaze stability exercises consist of holding the gaze on a firm target during active horizontal and vertical head movements (15) or stimulating the refixation saccades (16). Another interesting strategy could be Galvanic vestibular stimulation (GVS) which can increase or decrease the firing rate of vestibular afferents by reversing the polarity. The cathodal galvanic stimulation results in excitation and the anodal galvanic stimulation results in the inhibition of the vestibular afferents through the spike trigger zone of primary afferents (Tohyama et al.). The stimulation of the vestibular system using bipolar GVS has an influence on visual vertical perception and standing posture depending on the polarity of the stimulation and hemispheric lesion side (Tohyama et al.). Furthermore, the noisy GVS (nGVS) can modulate the VOR-gain (Matsugi et al.). This will improve the understanding of the neural mechanisms that underlie balance disorders and the development of effective therapy and rehabilitation in the future.

An interesting contribution was the study of the trunk muscle activation patterns during the turning of patients with stroke. Indeed, the results of this trial (Chen et al.) provide insights into the contribution and importance of the trunk muscles during turning and the association with turning difficulty after stroke, which can guide the development of more effective rehabilitation therapies. Technological devices could be used in support of conventional therapy in the recovery of gaze and postural stability disorders. Different devices were used with a positive effect on postural stability in neurological disorders. Among these, are virtual reality, augmented reality (Cerritelli et al.), and load auditory feedback in people with neurological disorders (Tamburella et al.).

The articles in this Research Topic are focused on but not limited to the evaluation of the gaze and postural function in both static and dynamic conditions, and on the new rehabilitation strategies for balance disorders. These studies provide a snapshot of issues relevant within the neuro-otologic field. They provide new small, but essential, steps in advancing knowledge to better design further studies for the evaluation and treatment of balance disorders.

As editors of all these articles, we would like to encourage the readers to take their time to read these articles and to update their knowledge on these topics.

Author contributions

Writing—original draft preparation: MT. Writing—review and editing: LM and NP-F. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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The Challenges and Perspectives of the Integration Between Virtual and Augmented Reality and Manual Therapies

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Virtual reality (VR) and augmented reality (AR) have been combined with physical rehabilitation and psychological treatments to improve patients' emotional reactions, body image, and physical function. Nonetheless, no detailed investigation assessed the relationship between VR or AR manual therapies (MTs), which are touch-based approaches that involve the manipulation of tissues for relieving pain and improving balance, postural stability and well-being in several pathological conditions. The present review attempts to explore whether and how VR and AR might be integrated with MTs to improve patient care, with particular attention to balance and to fields like chronic pain that need an approach that engages both mind and body. MTs rely essentially on touch to induce tactile, proprioceptive, and interoceptive stimulations, whereas VR and AR rely mainly on visual, auditory, and proprioceptive stimulations. MTs might increase patients' overall immersion in the virtual experience by inducing parasympathetic tone and relaxing the mind, thus enhancing VR and AR effects. VR and AR could help manual therapists overcome patients' negative beliefs about pain, address pain-related emotional issues, and educate them about functional posture and movements. VR and AR could also engage and change the sensorimotor neural maps that the brain uses to cope with environmental stressors. Hence, combining MTs with VR and AR could define a whole mind-body intervention that uses psychological, interoceptive, and exteroceptive stimulations for rebalancing sensorimotor integration, distorted perceptions, including visual, and body images. Regarding the technology needed to integrate VR and AR with MTs, head-mounted displays could be the most suitable devices due to being low-cost, also allowing patients to follow VR therapy at home. There is enough evidence to argue that integrating MTs with VR and AR could help manual therapists offer patients better and comprehensive treatments. However, therapists need valid tools to identify which patients would benefit from VR and AR to avoid potential adverse effects, and both therapists and patients have to be involved in the development of VR and AR applications to define truly patient-centered therapies. Furthermore, future studies should assess whether the integration between MTs and VR or AR is practically feasible, safe, and clinically useful.

Keywords: balance, cybersickness, head-mounted display, multisensory integration, presence, simulation, touch

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INTRODUCTION

Virtual reality (VR) and augmented reality (AR) have recently drawn professionals and patients' attention in several fields, including psychology, physical, and neurological rehabilitation, and surgery. In particular, the development of low-cost head-mounted displays (HMDs), which can be associated with smartphones, gaming consoles, personal computers, or workstations, brought VR and AR outside research laboratories toward a vast audience of users (1, 2). VR and AR typically use input devices to gather information about the user (e.g., the position of the body and its kinetic information) and the surrounding environment, and output devices to send the user sensory information (e.g., images, vibrations, and sounds) (1).

VR aims to create an environment that the users feel as realistic and coherent: they should experience "presence"—the illusion of "being there" in the simulated environment and the feeling that what is happening is plausible. Indeed, the simulated events have to follow precise physical laws, satisfy psychosocial expectations, and synchronize with the user's actions (2). AR aims to superimpose virtual information on the physical world: just like VR, AR should synchronize the virtual simulation with the real world to give a fair degree of realism and a sense of presence (1). Since the virtual objects extend the real environment (the users "are already there"), the sense of presence in AR could be better defined as "informed continuity."

The efficacy of both VR and AR lies, thus, in the creation of a coherent simulation: the users must experience the same physical laws during the whole simulation and perceive synchronicity between their (re)actions and the virtual stimuli. Once accustomed to the simulation, the users must see congruence between what is happening and their expectations (1). If the simulated environment lacked coherence, users would feel it as non-realistic: they would live a poor experience, the simulation would fail to induce positive effects, and adverse effects such as cybersickness (i.e., the feeling of discomfort and malaise due to the mismatch between observed and expected sensory signals) could occur. Note that some forms of sickness, e.g., motion sickness, can occur even if users experience presence: in fact, for both presence and cybersickness to occur, the patients have to feel the simulation as realistic (1, 3).

In the last decade, VR and AR applications in the medical and psychological fields have increased: they are used for educational purposes, surgical training and procedures, neuromotor rehabilitation, and anxiety treatments (1, 4). However, more high-quality research is required to include these technologies in healthcare curricula efficiently (5).

Manual therapies (MTs) are touch-based approaches, such as various types of massage or osteopathic manipulative treatment (OMT), that involve the manipulation of tissues (6). Although more rigorous research is required, several papers showed MTs might influence the body's myofascial system, affect local and systemic circulation, improve sleep, and reduce pain (6–9). Despite VR and AR involvement in physical therapy, the literature lacks papers assessing the relationship between MTs and VR or AR, to the best of our knowledge. The published trials about VR and AR in the context of manual approaches discuss VR and AR integration with physical rehabilitation (e.g., physiotherapy for stroke patients) (10, 11), which goes beyond touch or manipulation *per se*. Hence, the interaction of MTs with VR and AR remains somehow unknown.

Therefore, after briefly reviewing the effects of MTs, VR, and AR in healthcare, the present paper aims to propose how these approaches, in particular, MTs and VR, could be combined for improving patient care. Indeed, integrating the tactile, proprioceptive, and interoceptive sensations elicited by MTs with the (mainly visual-auditory) simulated VR experience could harness the benefits and overcome the limits of both. Their integration's positive effects could occur especially in fields like pain, whose treatment needs a comprehensive approach that involves physical, biochemical, and psychosocial factors (12–14).

In order to obtain a comprehensive analysis of the literature, the current review used the following search strategies in Pubmed:

- for VR and AR, the basic query was ["systematic review" (Publication Type)] AND ("virtual reality" OR "augmented reality");
- for manual therapies, the basic query was ["systematic review" (Publication Type)] AND [bodywork OR ("manual therapy") OR ("osteopathic manipulative treatment") OR ("osteopathic treatment") OR ("high velocity low amplitude") OR ("muscle energy") OR (counterstrain) OR ("myofascial release") OR (craniosacral) OR ("cranial field") OR ("lymphatic pump") OR ("rib raising") OR ("spinal manipulative") OR ("suboccipital decompression") OR ("fourth ventricle") OR (CV4) OR ("trigger point")].

For both queries, we repeated the search by adding condition-specific keywords, such as pain, chronic pain, balance, dementia, depression, quality of life, phobia, and surgery. We then selected the papers involving adult people (18+ years old), from inception to February 2021.

THE CURRENT STATE OF THE USE OF MTs, VR, AND AR

MTs, VR, and AR are used to manage several pathological conditions and improve patients' health-related quality of life (HRQoL) and disability. Over the last few years, several systematic reviews investigated their efficacy and safety. Despite the need for more rigorous research—more significant samples, better description of randomization, allocation concealment, interventions, and control group, follow-up assessment, better statistical analyses, standardized methodology, uniform choice of the outcomes to easily pool the results in meta-analyses—for MTs (15–17), VR and AR (2, 10, 18), these interventions have shown

Abbreviations: ACTH, adrenocorticotropic hormone; ADHD, attention-deficit hyperactivity disorder; AR, augmented reality; ARET, augmented reality exposure therapy; ASD, autism spectrum disorder; HMD, head-mounted display; HRQoL, health-related quality of life; LBP, low back pain; MT, manual therapy; OMT, osteopathic manipulative treatment; PD, Parkinson's disease; PTSD, post-traumatic stress disorder; RHI, rubber hand illusion; VR, virtual reality; VRET, virtual reality exposure therapy.

positive effects on several conditions as reported in the next paragraphs. VR and AR also helped augment medical education and training (5, 19–22).

MTs, VR, and AR are generally safe—just some minor transient adverse effects were reported, particularly muscle stiffness and symptoms worsening for MTs (23, 24), and musculoskeletal pain, fatigue, and dizziness for VR and AR (25–28). However, due to the limitations mentioned above, authors had difficulties in drawing firm conclusions or recommendations for MTs (17, 29), VR, and AR (11, 18, 30, 31) as valid and reliable treatments.

The Effects of MTs: A Summary

Evidence shows that MTs could help improve fatigue, sleep, and well-being (32–35). MTs seem to increase functionality and HRQoL, while reducing pain in pregnant and postpartum women with LBP, pelvic pain and dysmenorrhea (36–38). MTs might also positively affect maternal antenatal depression (39).

MTs could be useful in caring for individuals with acute and chronic pain. In particular, MTs (e.g., spinal manipulation and mobilization, massage, OMT) showed clinical effects in acute and chronic LBP, neck pain, lateral epicondylitis, headaches, pain due to surgical and non-surgical adhesion, and pain-related disability (17, 23, 24, 40–45). A recent meta-analysis found that OMT, in particular, myofascial release, is effective in reducing pain and improving functional status (even through the reduction of fear-avoidance beliefs) in case of non-specific LBP, even when assessed after 12 weeks (46). MTs seem to reduce pain even in other conditions such as temporomandibular disorder (47), irritable bowel syndrome (48), and fibromyalgia (49, 50).

Nevertheless, there are mixed results on the effectiveness of MTs in reducing pain: for instance, in some cases MTs such as spinal therapies seem to be ineffective in treating mild to moderate chronic LBP (51), whereas in other cases the effects remain clinically significant only in the short-term (e. g., weeks) (49, 50). Although the clinical significance of the result seems small, a recent randomized controlled trial found that, compared to sham therapy, OMT induced a higher reduction in LBP-specific activity limitations at 3 and 12 months (52).

Some weak evidence shows that MTs, for instance, OMT, might help prevent falls and ameliorate objective measures of mobility and balance (e.g., sit-to-stand, gait speed) in the case of dizziness (53) and cervical vertigo (54). MTs might also improve gait in the case of Parkinson's disease (PD) (55). However, in the elderly MTs seem to improve balance function only together with vestibular rehabilitation (56).

Lastly, some evidence shows MTs might help manage essential hypertension as an adjunctive therapy to drugs (15, 16), an effect that could be due to the potential ability of MTs to positively affect the autonomic nervous system regulation (57).

The Effects of VR and AR: A Summary

Table 1 briefly summarizes the main findings that arise from the systematic reviews published during the years about VR and AR.

As an educational tool, VR and AR enable students to better understand anatomical structures and their spatial relationships through interactive 3D images or models (5, 19, 20, 22). AR also catches the attention of students with disabilities or special educational needs, enacting inclusive education (21).

Specific surgical-oriented VR/AR systems [such as the Da Vinci remote surgical system (79)] improve manual dexterity, surgical skills, and intraoperative time in several surgical fields (e.g., dental implantology, neurosurgical operations, and hepato-biliary surgery), in particular, together with interfaces for haptic feedback (4, 5, 58–64). Viewing the 3D reconstructions of the patient's tissues (previously assessed through imaging techniques) during the operations through AR, surgeons could be more accurate and avoid harming delicate tissues (5, 58, 60, 61, 63).

In the field of psychology, both VR and AR have been combined with exposure therapy—recreating the fear/anxiety-inducing stimuli (Virtual Reality Exposure Therapy, VRET, and Augmented Reality Exposure Therapy, ARET); and cognitive therapy—using a virtual coach voiced by a real therapist—to augment the treatment of different kinds of phobias and anxiety, cravings for various substances (e.g., cigarettes, cocaine), post-traumatic stress disorder (PTSD), depressive symptoms, and distorted body image in case of anorexia nervosa. The effects are often transferred successfully in everyday life and maintained for months or years, maybe because AR and (mostly) VR allow the simulation of an ecological environment where every exposition cue can be entirely controlled (2, 65–68). For social phobia, VR is slightly inferior to *in vivo* exposure therapy, possibly due to the difficulties in recreating credible social interactions (66) or the uncanny valley hypothesis—briefly, feeling eeriness and aversion toward characters/avatars that closely resemble humans but show "non-human" features (e.g., moving robotically or having "cold" eyes) (80, 81). Moreover, VR is useful to reduce anxiety and pain during medical procedures (e.g., immunization, surgery, and oncological care), thus acting as a powerful distraction (69–72)—the greater the immersive experience, the greater the effects (25).

Beyond the field of psychology, VR improves static and dynamic balance, mobility, gait, stride length, sitting and standing time, fear of movements and risk of falls, aerobic and motor function, muscle tension and strength, and activities of daily life in various populations, healthy or with some disorder (e.g., balance deficit, spinal cord injuries, stroke, PD, and multiple sclerosis) (10, 18, 26–28, 30, 73, 76). Moreover, VR reduces neuropathic pain in spinal cord injuries (27), anxiety, and depressive symptoms in people with PD (76). VR also improves executive functions in case of traumatic brain injury (74) and attention in people with unilateral spatial neglect (USN), a neurological disorder that commonly follows injuries (e.g., stroke) to one brain hemisphere and induces deficit in responding to stimuli placed on one side on the vision field (75). VR also helps reduce musculoskeletal related pain (e.g., chronic neck pain and shoulder impingement syndrome), although often similar or inferior to recommended exercises (77).

It is worth noting that, in both fields of psychology and rehabilitation, VR and AR are used mostly as add-on therapies combined with already established treatments. Indeed, VR and AR seem to enhance the conventional therapies' effects through

TABLE 1 | A summary of the main findings of the systematic reviews about VR and AR.

Field	References	VR/AR	Main findings
Education	Uruthiralingam and Rea, (20)	VR/AR	Improved anatomical education for undergraduate and postgraduate students, residents, dentistry, and nursery students in 75 out of 87 reviewed papers.
	Zhao et al. (22) Kyaw et al. (19)	VR	Improved the test scores compared to other methods (e.g., lectures, textbooks, and dissections) in different anatomical fields (e.g., musculoskeletal, neurologic, and gastroenteric). Longer courses showed larger effect size than short ones. The more the learners could interact with the 3D virtual models, the more the gain in knowledge and in cognitive skills (e.g., history taking, counseling competencies, decision-making, and communication).
	Tang et al. (5)	AR	Improved test scores and higher satisfaction and learning engagement using MagicBook, an AR system that uses webcam or smartphone to recreate 3D interactive models.
	Quintero et al. (21)	AR	Increased the attention, interest and motivation of students, even with disabilities or special educational needs.
Oral and maxillofacial surgery	Joda et al. (4) Farronato et al. (58) Ayoub and Pulijala, (59)	VR/AR	Improved manual dexterity and surgical skills in undergraduate and postgraduate students. Improved the execution of several procedures, including caries and submandibular glands removal and orbital floor reconstruction. The simulations were able to detect students with potential learning challenges and to discriminate between novices and experts.
Surgery	Tang et al. (5) Barsom et al. (60) Wong et al. (61) Tang et al. (62) Meola et al. (63) Fida et al. (64)	VR/AR	Reduced intraoperative times, potential ischemic times, tissue damages in several medical procedures, including laparoscopic tasks, bone reconstruction, lumbar punctures, otorhinolaryngologic and neurosurgical operations. Facilitated and improved pancreatic, hepato-biliary, and urogenital surgery. Surgeons could manipulate the 3D virtual representation to assure to not expose or harm delicate tissues. The AR navigation system allowed to better view the anatomical structures, and reduced mental demand, physical demand, effort, and frustration compared to conventional navigation systems.
Psychology	Freeman et al. (2)	VRET, VR cognitive therapy	Improved specific phobias, social anxiety, PTSD, obsessive-compulsive disorder, generalized anxiety disorder, psychotic disorders (reduced distress and persecutory delusions, and improved social functioning), anorexia nervosa and cravings for substances. The effect sizes were comparable to face-to-face exposure therapy and quite large, and the results persisted for several years after the end of the therapy.
	Chicchi Giglioli et al. (65)	ARET	Improved phobia of small animals and acrophobia.
	Wechsler et al. (66)	VRET and VR cognitive therapy	Improved phobias (especially, specific phobia and agoraphobia) and anxiety more effective than inactive control groups (e.g., waitlist, placebo, or no treatment). Comparable to *in vivo* exposure or cognitive therapies. Slightly inferior for social phobia.
	Segawa et al. (67)	VRET	Mixed results for treating craving of several substances (i.e., nicotine, alcohol, cocaine, and cannabis) or behavior (i.e., gambling and internet gaming). Comparable to CBT in terms of effectiveness and relapse. A combination of VR, exposure, and cognitive therapy could be the best treatment course. Helped in eliciting cravings, thus allowing to comprehend which stimuli can trigger them.
	Fodor et al. (68)	VR and VRET	Reduced anxiety and depression more than control interventions (i.e., waitlist, placebo, relaxation), but similar to other psychological interventions.
	Eijlers et al. (69) Iannicelli et al. (70) Gujjar et al. (71) Chan et al. (72)	VR	Reduced anxiety and pain during medical procedures, including immunization, surgery, burn, dental, and oncological care, and venous access more than usual care (although the reviewed studies did not clearly describe usual care).
	Luo et al. (25)	VR	VR+analgesics for burn care (e.g., dressing change, and physical therapy) reduced unpleasantness, pain, the time spent thinking about pain, anxiety. VR was perceived as fun, even when the level of perceived presence was quite low (3.4 out of 10).
Physiotherapy and rehabilitation	de Amorim et al. (30)	VR	Improved static and dynamic balance, mobility, gait, and reduced sitting and standing time, fear and risk of falls in various elderly samples, healthy or with some disorder (e.g., balance deficit, diabetes mellitus, or PD) more than placebo, standard proprioceptive training, and kinesiotherapy
	Lee et al. (10) de Araújo et al. (18) Iruthayarajah et al. (26) Massetti et al. (28)	VR	Improved balance, stride length, sitting and standing time, when VR was used in rehabilitation programs for spinal cord injuries, limb and overall function in chronic stroke patients, PD, and multiple sclerosis. Improved aerobic and motor function, muscle tension, muscle strength, and activities of daily life alone or in combination with occupational therapy or physiotherapy. Some minor and transient adverse effects (e.g., musculoskeletal pain, fatigue, and dizziness) were reported.
	Ahern et al. (73)	VR	Reduced fear of movement in patients with LBP more than conventional stabilization exercises or physical therapy.

(Continued)

TABLE 1 | Continued

Field	References	VR/AR	Main findings
	Lei et al. (27)	VR	Improved HRQoL, level of confidence in difficult activities that could cause falls, and neuropsychiatric symptoms (i.e., anxiety and depression) more than standard care, conventional therapy, or any other non-VR rehabilitation program for PD.
	Manivannan et al. (74)	VR	Improved executive functions, driving attitude, attention, learning, and problem solving-skills in case of traumatic brain injury, but lack of improvement in employment rate.
	Pedroli et al. (75)	VR	Improved daily life in patients with USN. More useful than classical tests for assessing the severity of USN, since VR had the advantage of testing USN in simulated real-life conditions, e.g., driving in the streets.
Pain	Chi et al. (76)	VR	Reduced neuropathic pain in patients with spinal cord injuries through various VR systems (virtual walking, training, illusion, or hypnosis).
	Gumaa and Rehan Youssef, (77)	VR	Reduced chronic neck pain and shoulder impingement syndrome more than conventional therapy. VR was similar or inferior to exercises in many other conditions, including rheumatoid arthritis, knee arthritis, back pain, and fibromyalgia.
Pathophysiology	Bluett et al. (78)	VR	Improved understanding of the pathophysiology of freezing of gait in PD by reproducing this event in a safe environment (i.e., without the risk of a real fall).

AR, augmented reality; ARET, augmented reality exposure therapy; CBT, cognitive behavioral therapy; HRQoL, health-related quality of life; LBP, low back pain; PD, Parkinson's disease; PTSD, post-traumatic stress disorder; USN, unilateral spatial neglect; VR, virtual reality; VRET, virtual reality exposure therapy.

the intensification of experience induced by gamification and realistic simulations (2, 10, 18, 30, 66).

Lastly, by recreating certain events (e.g., phobias and falls) in a simulated environment, VR and AR could also help understand the causes of psychological and neuromotor disorders and the stimuli that trigger them, allowing practitioners to deliver the therapy that best suits their patients (2, 75, 78).

THE CROSSROADS BETWEEN MTs, VR AND AR

Despite the burgeoning research on VR and AR role in the rehabilitation field, MTs and their combination with these technologies seem to have not received attention. Research has focused primarily on patients experiencing VR and AR before or after physical therapy sessions, with therapists acting as "mere" support (e.g., supervision, safeguarding, and manual assistance) or whenever patients had difficulties in executing a task (82–85). Due to their reported effects, MTs could be combined with VR and AR to improve the management of several clinical conditions, including depression, chronic pain, neuropathic pain, and eating disorders.

Considering that MTs elicit tactile, proprioceptive, and interoceptive sensations, whereas VR and AR send primarily visual and auditory stimuli, these interventions could be complementary. It is true that new technologies are emerging to bring tactile and internal sensations in simulated environments—for example, force feedback systems like Geomagic Touch to simulate tactile sensations and proprioception (86), skin-integrated wireless haptic interfaces to transfer touch (87), and wearable acoustic or vibrotactile transducers for evoking inner body sensations (88), but MTs could be the easiest way to add the sense of touch, proprioception, and interoception to VR and AR (89). On the other hand, VR and AR could be used as add-on therapies to enhance the effects of MTs in the same way they do when added to psychological and rehabilitative treatments (**Figure 1**).

The combination of MTs with VR and AR could define a whole-body intervention that includes both interoceptive and exteroceptive signals, with the potential of improving sensorimotor integration and rebalancing distorted perceptions and body images in patients suffering from eating disorders, autism spectrum disorder (ASD), or other disperceptive conditions (maybe even body identity integrity disorder) (88, 90, 91). Indeed, Suzuki et al. found that, through AR, the online integration of visual, tactile, and internal stimuli (i.e., the heart rhythm) enhances the sense of ownership in the case of rubber hand illusion (RHI) (92).

Therefore, after discussing the usefulness of low-cost head-mounted displays (HMDs), the devices more suitable to introduce VR in the setting of MTs, this section will focus on the potential and reciprocal contributions between VR (in particular), AR, and MTs to improve healthcare.

As a side note, VR and AR could also improve students' training and manual skills. For instance, AR-derived 3D models of the manipulated/mobilized body tissues could enhance the manipulations' efficacy and avoid potential adverse effects. However, the technology required for achieving the high precision in tactile and force reproduction needed to perform efficient training is still lacking at the moment (93).

The Advantages of HMDs in Research and Clinical Fields

A limitation of several VR studies is that the authors used systems such as Nintendo® Wii Fit, PlayStation® 2 EyeToy camera, and Microsoft® Xbox Kinect that, although more engaging than conventional therapy, lack the immersion that should characterize VR—they lack presence (1, 2). Furthermore, they are non-specific systems for rehabilitation as they were designed for other purposes, and therefore, they may show lower therapeutic

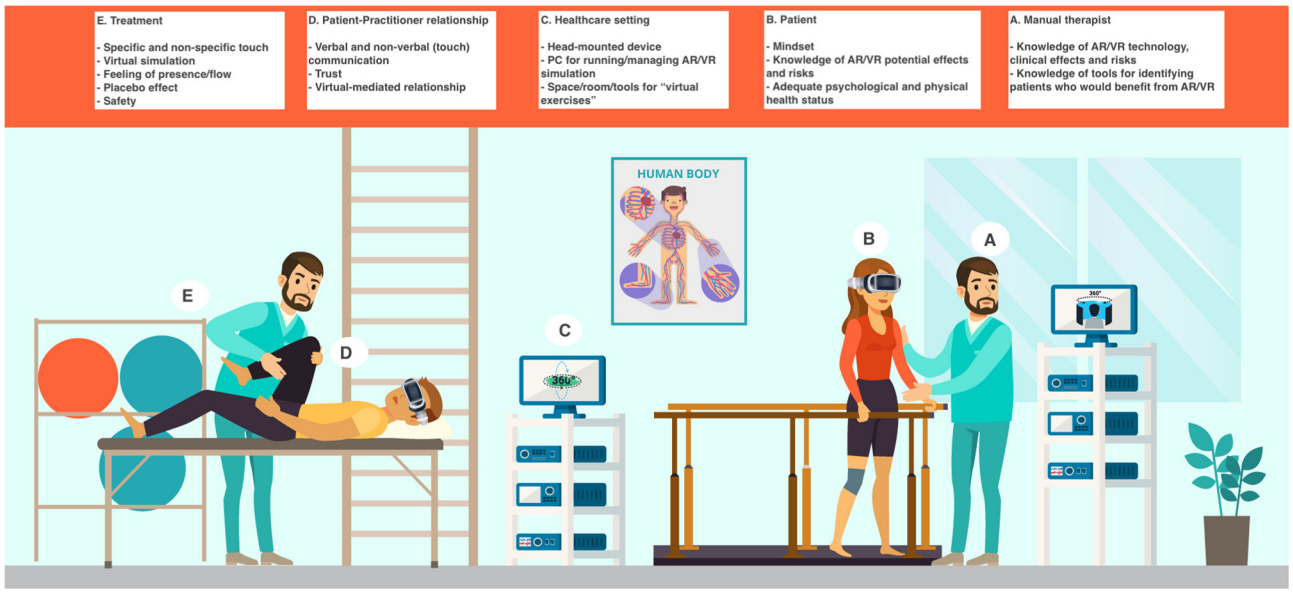

FIGURE 1 | The integration of VR and AR in the MT setting. The MT setting would be enhanced by the addition of VR and AR: however, this implies the therapist and the patient need to pay attention to both old and new therapeutic factors. The factors could be summarized as follows (see the section "The Crossroads between MTs, VR and AR," for further information). **(A)** Manual therapist's features: knowledge of AR and VR technology, clinical effects and risks; knowledge of tools (e.g., questionnaires, biomarkers such as heart rate variability) for identifying patients who would benefit from AR or VR (every patient could respond differently to them and some patients could be at a higher risk of experiencing adverse effects, from cybersickness to depersonalization). **(B)** Patient's features: mindset (i.e., expectation about VR or AR positive effects); knowledge of AR and VR potential effects and risks; adequate psychological and physical health status (based on their psychophysical health, some patients could be at a higher risk of experiencing adverse effects, from cybersickness to depersonalization). **(C)** Healthcare setting: head-mounted device; PC (or other types of hardware) for running/managing AR or VR simulation; space/room/tools for "virtual exercises." **(D)** Patient-practitioner relationship: verbal and non-verbal (touch) communication; trust (it is paramount when the patient is immersed in the virtual environment and, therefore, does not see the "real" therapist); virtual-mediated relationship (in the virtual simulation, there could be an avatar of the therapist and phenomena like the uncanny valley could happen). **(E)** Treatment features: specific (technical) and non-specific (placebo) touch; virtual simulation; feeling of presence/flow (necessary for an optimal AR and VR experience); placebo effect (the patient could feel better just due to the simple fact that an "awesome" technology is being used); safety.

usefulness. Indeed, VR systems explicitly intended for clinical purposes showed more significant effects than non-specific ones and conventional therapy in the rehabilitation of post-stroke motor recovery (11). However, such systems can be costly and need advanced engineering to be realized (88).

The commercialization of low-cost HMDs, which can be associated with personal computers, tablets, and smartphones, partially overcome the lack of immersion (2). Indeed, HMDs could help elicit the feeling of presence through a stereoscopic view of the simulated environment, making the users focus on the virtual experience and avoid external (visual) distractions. HMDs continuously track the position of the user's head to allow a 360° visual navigation of the virtual environment: if turning the head failed to induce a change in the visual image, the users would immediately realize to be in a non-realistic environment and, thus, presence would be impossible (2). HMDs may also include headphones to send auditory stimuli to the users, thus monopolizing both eyes and ears (1, 2). However, visual and auditory stimuli are not enough to create a truly immersive experience, which also needs proprioceptive or haptic stimuli, especially when the simulation aims to target body ownership (1, 2, 88, 90). For this reason, HMDs might be combined with proprioceptive/haptic devices placed on various body parts (1) or real-time motion capture, although the cost for such a set-up could be high (88).

Despite the limitations regarding immersion, HMDs could represent the key for combining VR and AR with MTs: on the one hand, the tactile stimuli of MTs might somehow replace the proprioceptive and interoceptive stimuli needed for immersion; on the other hand, while receiving MTs, patients tend to stand still, e.g., lying on the massage table, and so tracking the body's movements could be unnecessary. Therefore, while receiving treatment, the patients could easily immerse themselves in the VR experience, hence benefitting from interventions. In fact, the therapeutic goal becomes paramount to choose the proper equipment to use: for instance, proprioceptive devices or motion-capture would be necessary if the VR experience had to directly act on body perception, whereas the same devices would be not required if the VR simulation served just as a distractor or relaxing stimulus.

HMDs could also enhance ecological validity in both the research and the clinical setting. In neuroscience, VR has been deemed paramount to introducing ecological validity in the laboratories while maintaining adequate control of experimental stimuli and confounding variables (94). Using VR, researchers may study a range of cognitive processes

in a simulated environment that resembles everyday life—researchers may recreate realistic social interactions, emotional cues, and narrative experiences–, thus eliciting more natural behaviors and physiological reactions and allowing better findings generalization (94, 95). Creating an ecologically valid environment is also paramount in the rehabilitation field: patients could interact with controlled, personalized, and meaningful sensorimotor stimuli, while receiving real-time feedback about the performance through visual, auditory, or kinesthetic means (11, 96, 97).

The portability and accessibility of HMDs could increase the studies' ecological validity and generalization because researchers may study VR directly in the clinical setting or at the patients' homes, thus genuinely bringing VR outside the laboratories and into real life. Indeed, VR helps people perform therapeutic exercises at home with good results in stroke and incomplete spinal cord injury (98–102).

Relying on the Internet and the Cloud, HMDs and associated devices (e.g., smartphones) could send data about the performed exercises directly to the therapists, thus allowing them to supervise their patients better and potentially improving adherence to therapy (103). Even automated daily monitoring by home-based VR systems helps increase patients adherence (98); moreover, it is possible to create a multi-user virtual environment that allows patients and caregivers to interact among themselves to improve rehabilitation outcomes (101, 102).

All these features can also be used to customize the treatment received by the patients. Indeed, technological evolution allows therapists to model therapeutic exercises or tasks for their patients: therapists could record themselves while doing the exercises, save and customize the motions through VR software and, then, construct specific and easily flexible therapeutic plans. On the other side, patients could view the tasks to be performed as many times as they need, detect maladaptive movements (through kinesthetic or visual sensors) and check their performance and progress (97, 98, 103). The correction of maladaptive movements or postures could also be augmented by integrating kinesthetic sensors with output devices placed on various body parts. Whenever the sensors (e.g., accelerometers) detect a maladaptive behavior, the output devices could induce accurate vibrotactile stimuli on the body, prompting the users to adjust their posture or motion (104).

Manual therapists could instruct patients through HMDs as well, showing them how to perform several kinds of self-massage or self-touch that could help maintain the effects of MTs in the long-term. Regarding home-based care, the use of wireless haptic interfaces (87) could even allow therapists to perform MTs remotely (at least, those involving gentle or moderate strokings and pressures).

Although cheaper than other technologies, HMDs are not free: their cost could still be unaffordable for people of low socioeconomic status. Therefore, who should bear the cost of HMDs (or similar devices) for these people, should they need them for improving their health through home-based VR sessions (105)? Indeed, this is a central theme that needs to be faced by the healthcare system if VR and AR are to be introduced in clinical practice.

How MTs Could Enhance VR and AR Experience

MTs may induce local effects, through the activation of mechanobiological pathways that can change the cells' behavior (106), and lead to systemic responses involving the circulatory, immune, endocrine, and nervous systems, and the mental state (6, 7, 9, 107–110). These systemic responses could influence the brain processes and, thus, interact with the VR and AR experience. In particular, MTs could facilitate the feeling of presence by influencing the physiological parameters (e.g., heart and breathing rate) that are typically regarded as markers of flow—the optimal experience of being fully immersed and involved in an activity perceived as immensely rewarding, with a good sense of agency and without self-referential thoughts (111). As flow entails a high degree of presence and concentration, eliciting such an experience could reduce cybersickness, which is negatively correlated to presence (although more rigorous studies are required since presence and cybersickness share common VR features, such as immersion) (3), thus improving VR efficacy.

Indeed, touch activates several neural pathways that project to cerebral areas involved in sensory, affective, and cognitive functions (112). Whereas, the Aβ nervous fibers send information about the sensory quality of touch principally, the Aδ and C fibers mediate affective touch, i.e., touch whose experience is accompanied by hedonic, emotional, and motivational qualities (89, 113). In particular, stimulating C fibers with slow (1–10 cm/s) and gentle (0.3–2.5 mN) strokings or pressures may induce a pleasant feeling and the activation of brain areas involved in interoceptive networks (e.g., insular and cingulate cortex) and emotional regulation (e.g., orbitofrontal cortex) (89, 114–116). The same neural activation occurs in other MTs like Swedish massage and spinal manipulative treatment (117, 118).

Interestingly, in the last few years, several papers showed that OMT may affect brain activity in both healthy adults (57, 119) and patients with chronic LBP (110, 120). OMT influenced regional cerebral blood flow, blood oxygen level dependent response and functional connectivity in many cerebrals areas, including the insula, cingulate cortex, amygdala, striatum, caudate, middle frontal and temporal gyri, cerebellum, and prefrontal cortex (57, 110, 119, 120). As all these areas play paramount roles in reorienting the attention between exogenous and endogenous stimuli, ideating and coordinating movement, monitoring the internal milieu, and regulating emotions, physiological arousal and pain (57, 110, 119, 120), affecting their activity might help people improve their experience in a simulated environment.

MTs may elicit a parasympathetic response, which usually correlates with a state of relaxation (6, 7, 57, 121, 122). MTs could reduce signal molecules tied to the stress response, including adrenocorticotropic hormone (ACTH), cortisol, and vasopressin, and enhance the production of endorphins, endocannabinoids, and oxytocin, hence favoring a more relaxed mind and a better mood (6, 7, 123–126). Touch might also increase trust in other people and prosocial behavior (127–129). These neuroendocrine and psychological effects could facilitate the immersion in the simulated environment, whether realized

through VR or AR, and the flow experience. Although people need to activate stress and sympathetic responses to sustain the metabolic demands and the mental efforts required to accomplish specific VR or AR tasks (e.g., rehabilitation training), Tian et al. found indices of parasympathetic modulation (i.e., higher respiratory depth) in cases of flow (111). A stress response modulated by the parasympathetic tone could favor presence and reduce cybersickness, which is typically characterized by high secretion of hormones such as ACTH and vasopressin (3). Since parasympathetic is related to prosocial behavior, empathy, and a flexible mind (130, 131), MTs could improve the VR and AR efficacy in social phobia.

Currently, there is robust evidence that inflammation may influence the nervous system and cognitive-affective functions (132–135). Therefore, it is not surprising that an inflammatory challenge (typhoid vaccination) compromised spatial memory in a VR task, inducing an IL-6 increase that reduced glucose concentration within the perirhinal and entorhinal cortex and parahippocampal region (136). Since MTs might reduce inflammatory cytokines, including IL-1β, IL-2, IL-6, TNF-α, and INF-γ (123, 124, 137, 138), MTs could improve the performance obtained using simulations, thus augmenting the effect size of VR and AR interventions.

The activation of the interoceptive network and the physiological changes mentioned above, including the possible modifications of heart rate variability (HRV) elicited by the alteration in the autonomic tone (57, 116, 121, 122, 139), could be of great value to VR and AR since a solely exteroceptive illusion seems not enough to significantly reduce clinical pain (140). From recent studies, a more embodied illusion is needed: in particular, since we feel our body "from the inside," VR and AR needs to create a simulation able to modulate the inner body sensations and feelings (e.g., heart rate) (88, 90). Therefore, MTs could help VR and AR create an interoceptive embodiment illusion without the need for complex devices, similarly to Suzuki et al., which showed an improved sense of body ownership with an AR-based integration of visual, tactile, and interoceptive stimuli (92). Moreover, a recent study showed that, after four OMT sessions, regional cerebral blood flow in areas such as the insula and the lentiform nucleus changed in correlation with HRV in patients with chronic LBP (110), thus showing how peripheral stimuli may affect brain activity. However, technological tools would be more precise than MTs in delivering specific stimuli. Besides, more research is required to assess whether MTs could effectively enhance the ownership of a virtual body (141).

How VR and AR Could Improve MTs Effectiveness

VR and AR could help MTs in several ways and especially in treating pain and pain-related disability. Appropriate VR designs are recognized to provide analgesic outcomes (142): they can easily catch the attention of the users, shifting their cognitive resources away from their body to the virtual tasks, effects that can result in pain reduction (143). Considering that just thinking about a movement can trigger pain in some conditions (e.g., complex regional pain syndrome) (144, 145), VR and AR applications could recreate the stimuli that trigger pain in the same way they do with phobias and cravings (2).

A specific simulated environment depicting several types of postures, movements, or situations could help therapists and patients understand better when and how pain occurs. This type of simulation could show postures/movements from both first and third-person perspective: in the former case, appropriate kinesthetic and proprioceptive devices could be paramount to elicit the sense of body ownership efficiently; in the latter case, the observation of another person or avatar would trigger the activation of the mirror neuron system, an essential mediator for successful sensorimotor rehabilitation using VR (146–148).

That same simulated environment could also help decrease the pain-related experience in the same way that interventions such as RHI, mental imagery, and mirror therapy do (149–151). Indeed, VR and AR might revolutionize these and similar interventions by creating highly realistic immersive environments and reproducing a real embodied experience through the induction of visual, auditory, olfactory, tactile, and even interoceptive signals (88, 90).

Through VR and AR, the triggering stimuli can be adapted to patients' needs varying their intensity, duration, repetition, and so on. The simulated stimuli could even surpass reality (e.g., impossible body postures), hence favoring better results with more ease, although this is yet to be tested (2, 66). Indeed, VR and AR reduce pain in phantom limb pain (152) or complex regional pain syndrome (153).

All these effects could make patients more aware of their pain-related experience and improve pain management. For example, patients could better comprehend what events trigger their pain, thus learning how to manage and face them, and what events may reduce pain. On the other hand, therapists could better understand their patients' pain-related experiences. On occasion, pain treatment is problematic because patients fail to reproduce the exact conditions that induce their pain. Therefore, therapists lack a clear understanding of their patients' pain-related experience and the best intervention to perform. This situation is particularly significant when pain is not worsened by physical factors but by psychosocial ones, like stress, negative emotions, and beliefs. Despite evidence demonstrating that psychological and neurobiological factors can significantly influence musculoskeletal pain—pain is more about how the brain elaborates the psychophysical stimuli and responds to them, and that pain is, first and foremost, a subjective feeling (14, 154–156)—too often therapists give patients explanations in primarily biomechanical terms. Consequently, pain and disability persist, HRQoL decreases, and patients' costs to sustain for treatments rise (154, 155, 157–159).

VR and AR could help therapists enhance the effectiveness of pain neuroscience education and other programs aiming to teach the most recent discoveries about the complexity of pain (154, 160). Through virtual simulations, patients could see how the nervous system functions, understand the difference between simple nociception and complex phenomena like central sensitization that play a central role in chronic pain. Since alterations in the brain sensorimotor bodily maps are involved

in chronic pain, VR could help patients actually see those maps. Moreover, therapists might show patients 3D interactive models of body anatomy, for instance, models of the intervertebral disks, thus removing false beliefs about anatomy (e.g., slipped disks) that could perpetrate pain through fear, nocebo effects, or other neural mechanisms (154, 155, 160, 161).

VR and AR applications could help patients overcome the fear of movement through exposition to activities perceived as painful (162, 163). While patients are distracted by VR applications, therapists could also reproduce supposed painful movements and then make patients aware that the movements were executed with little or no pain.

It is worth noting that sometimes pain could arise from traumatic events (e.g., car accidents) the patients fail to correctly remember—the memory was not adequately encoded and, therefore, the event lacks a precise context. A typical example of this situation is PTSD (164). The "blurred" memory could induce an overgeneralization of fear. Since the memory contains just general features of the traumatic event, fear is extended to every situation that shares those general conditions with the traumatic event (e.g., every time the subject gets in a car), increasing disability (164). A recent study found that, in this case, fear is not subject to extinction—the patients are not sure the exposed condition is the traumatic one and, thus, cannot change their behavior. A way to overcome that fear is by enriching the blurred memory, recreating in the therapeutic setting a "controlled" event similar to the traumatic one to skew fear toward this new context and, then, apply exposure therapy (164). VR could be perfect for this purpose and, since fear overgeneralization might sustain chronic pain (165), VR could reduce pain.

VR also has the potential to elicit awe, emotion at the core of experiences such as flow, strong spiritual and mystical feelings, and the "overview effect" (i.e., the sense of the interconnectedness of all life evoked in astronauts by the sight of Earth). Awe-inspiring environments might create a safe space that makes patients relaxed, peaceful, joyful, prosocially active, and ready to have a transformative experience, i.e., changing their behavior (166). This sense of safety and trust induced by VR could strengthen the placebo effect that arises from touch (touch is paramount for the social nature of humans) (89, 167), the therapeutic ritual intrinsic to MTs, and the relationship between therapists and patients, usually viewed as a cornerstone of MTs (168, 169). In the same way, VR could help people overcome the aversion they might have for touch, especially affective touch: indeed, patients who developed an insecure attachment style or experienced traumatic events, as well as patients who have PTSD, anorexia nervosa, ASD, or other conditions involving altered sensations and perceptions, rate affective touch as less pleasant than typical touch or even negative (170–173). Manual therapists might have difficulties in treating these people. A VR environment that induces peace and trust could conceivably elicit the same effects of oxytocin (usually correlated with trust), that is increasing tactile perception and, maybe, pleasantness (174, 175).

Lastly, as already described in the paragraph "3.1 The advantages of HMDs in research and clinical fields," an advantage that VR and AR could give to MTs is the possibility of continuing and monitoring the treatment at the patient's home, thus improving adherence to therapy (103). By remotely connecting through the Internet, therapists could efficiently communicate with their patients, check whether they are performing the given exercises/tasks, and also evaluate how they are proceeding in the therapeutic plan. As therapists may record themselves to better show patients how to perform the therapeutic exercises, so the VR systems could record patients and send therapists their data—this would be particularly useful for those patients who can't reach the therapists' clinic, due to health-related disability or living far away from it.

However, this use of VR entails careful control and protection of patients' personal data to guarantee their privacy, especially if third parties are involved in the applications used by therapists and patients (176).

The Brain, as A Bayesian Organ, Meets VR

The VR's putative modulatory effects on pain and other conditions (e.g., distorted body image) may be achieved since VR might reflect how the brain works (90). If the brain functions as a Bayesian organ that follows the free-energy principle, then the perception of both the inner and outer world arises from the brain—and arguably from the whole organism (14) —internal generative model, which is continuously used for efficiently adapting to the environment (177).

According to this view, the organism does not need to understand what is happening in the world perfectly, nor it could: due to the limited energy and resources (e.g., nutrients and cognitive capacity) available, it would be impossible to pay attention to all the environmental variables, i.e., sensory stimuli. Therefore, based on past sensorimotor activations (past beliefs), the brain creates a surrogate model of reality—the internal generative model—and then makes predictions about the upcoming events (posterior beliefs) by weighting that same model with the sensory evidence (actual information). These predictions must be accurate enough (not the most correct!) to allow the organism to survive and protect its psychophysical integrity. After every experience (and especially during sleep, when the brain is not engaged with the external world), the brain:

- tests its generative model against the sensory information coming from the world;
- tries to fit the sensory information in the generative model;
- if required, updates the generative model (we shall soon see how) to increase its usefulness and accuracy, but always trying to keep the model's complexity and redundancy at a minimum (177).

Since the resources available are limited, the brain needs to make useful predictions while maintaining a surrogate model of reality as simple as possible. This way, both the information free energy (the number of variables accounted for) and the thermodynamic free energy (the metabolic cost to encode and apply the generative model) are minimized [for an in-depth review, see (177)]. From a neural point of view, the brain tries to keep the number of synapses encoding the generative model at a minimum (indeed, during sleep, synaptic pruning occurs) to have simple and efficient neural networks able to respond

to the world promptly and guarantee the organism survival. This process could be considered, briefly, the Bayesian idea of optimization applied to the brain (177).

The Bayesian brain has gained growing attention in the last years. It involves the whole body multisensorial, motor, and interoceptive/affective representation in the brain and its control by a complex neural network—the "body matrix" (88). Indeed, the generative model is an embodied simulation of the potential internal and sensorimotor states of the body. Based on the sensorimotor predictions made by integrating the generative model with the actual sensory information, the body matrix alters the physiological bodily conditions and the interoceptive and exteroceptive sensations through top-down modulation. Then, it redistributes throughout the whole organism the available energy and resources to cope with the upcoming events (88). But the brain has to minimize its free energy, i.e., the occurrence of "surprising" events not accounted for by the generative model. Indeed, the brain uses embodied simulations to represent and predict possible future sensations, actions, and emotions. These sensorimotor expectations may match or mismatch with the actual sensorimotor activity—in the latter scenario, a "surprise" or prediction error arises, which the brain must minimize to regulate the body and respond to it efficiently. As said, the brain could lack energy or not know how to manage the unexpected error (88, 90). Therefore, the brain may: (1) "suppress" prediction errors by superimposing its sensorimotor expectations on the body; (2) update its predictions, also changing the related beliefs about the world. However, it seems that the update of its internal generative model, i.e., learning, needs a great "surprise" and a "destabilized" sense of agency—the subject should fail to gather other information about the current situation or to enact the brain predictions, which means that usually, the brain superimposes "its" reality (88, 177, 178).

VR could facilitate the update of the internal generative model since it seems to function similarly to the brain: indeed, researchers aim to construct VR systems able to create sensory stimuli, detect the subjects' movements or actions and, based on a model of the users' body, try to predict the sensory consequences to give users a plausible and coherent experience, as if they were in the real world (90). If the brain is a Bayesian organ, then the process just described represents just what the brain does. On the other hand, the brain itself could represent a VR generating system that simulates a body and an environment to move around (177).

The more advanced the VR system is—i.e., multimodal devices to recreate every external and internal sensation, and software based on complex machine learning algorithms able to perform the aforementioned processes—the more the simulation is perceived as coherent and embodied. VR users, thus, would feel the virtual body as their own, the brain would generate its internal model based on it, and the sense of agency would become "embodied" in it (88, 90). Again, the simulation does not need to reflect reality, i.e., follow the physical laws of the real world or recreate the actual human body, to induce embodiment: as for presence, what matters is the coherence of the virtual simulation. Whenever the brain perceives coherence between the actions the user performs, the simulated events, and the sensations felt in response, the brain considers the situation as plausible and real, although potentially absurd (for instance, Steptoe et al. showed that it is possible to make people "own" and "control" a tail) (179).

When patients perceive a virtual simulation as coherent, therapists could use VR to elicit specific prediction errors through finely controlled stimuli to violate the internal generative model and facilitate its update. This way, therapists could favor modifying the dysfunctional representations of the body that may be at the root of pain, eating disorders, and other conditions that involve self-perception, including depression. Indeed, the brain uses the embodied simulation to predict sensations, actions, and even emotions (88, 90).

Therefore, complex VR simulations aim to act as cognitive prostheses to change the neurobiological processes that underlie both the perception and the physiological body responses to events. To this end, therapists need systems (hardware and software) that create a scenario that is felt coherent by the patients' brain, despite the awareness that "it is all an illusion," and that is able to elicit specific responses (i.e., prediction errors) useful to reach the desired outcome (e.g., rehabilitation, pain reduction, better body image) (88, 90, 177). The more a VR system can do this, the better it is.

The Limitations to the Integration of MTs With VR and AR

There are several considerations in regards to the integration between MTs and simulated experiences: in particular, they concern the state of research about the relationship between MTs and VR or AR, the characteristics of available VR and AR technologies, the possible negative consequences of their use.

Since literature lacks papers about the integration between MTs and VR or AR, trials that combine these interventions are required, starting from the ones that should assess the feasibility of combining the two approaches and evaluate possible adverse effects. The following trials should assess the effects of VR and AR applied before or after MTs sessions; others should investigate the effects of conducting VR sessions while the patient is receiving MT. Researchers should also evaluate whether VR could help patients change their counterproductive or wrong beliefs about pain and movement. Lastly, there is the need to understand whether manual therapists could use already developed VR and AR applications, or if new and original software is required.

Therapists need valid and reliable devices able to create immersive environments that induce presence/flow and avoid cybersickness. Since presence and cybersickness share a common ground—they are both increased by immersion, research should define which features of the simulation or the technology used could skew the virtual experience toward presence or cybersickness (3, 111, 180). In particular, some VR devices may favor cybersickness due to lack of accuracy in motion tracking or gesture recognition, low or not appropriate visual display frame rate, and even mismatches in conveying to the user different sensory information (especially, mismatches about visual-vestibular cues) (3).

Although useful as explained in "3.1 The advantage of HMDs in research and clinical fields," HMDs might favor cybersickness, in particular, when the body is immobile while the eyes are tracking virtual visual stimuli. This might occur when the patient explores a virtual environment while receiving MT on a massage table (176, 181). In fact, manual stimulation could obstacolate the feeling of presence when it is not mirrored by something that is happening inside the virtual simulation: would it not be strange to feel touched but failing to see who or what is touching? If this were the case, the integration between MTs and VR or AR could be reduced to only specific and restricted interventions, which may require customized software that recreates the exact manual stimulations applied by the therapist. Should such a customized software be required, its cost could be particularly high and, therefore, therapists could have difficulties in acquiring it for their private practice.

According to some authors, HMDs could hinder the immersion in the virtual simulation due to the feeling of wearing HMDs (176). However, depending on the simulation, VR might act as a distractor powerful enough to make users forget about HMDs (as when people are lost in thought). On the other hand, wearing HMDs could help people remember they are experiencing a virtual simulation, that is discriminating between the real and virtual world, thus reducing possible adverse effects of VR (see below) (176).

Researchers could also study which biomarkers can discriminate between presence and cybersickness: for instance, some trials evaluated the use of HRV, which functions as a useful indicator of stress, sympathetic and parasympathetic modulation, all factors that can influence the balance between presence and cybersickness (3). The HRV measuring tools seem to be easily incorporated in the VR equipment and, from the preliminary results, several HRV metrics appear to detect cybersickness (182–184). The evaluation of cybersickness could also be tied to the research of biomarkers revealing the effectiveness of the virtual simulation in updating the brain generative model. Indeed, eliciting prediction errors (surprise) is necessary, but not sufficient for the update to take place: the whole simulation experience needs to be carefully constructed to properly activate the brain networks involved by the body matrix (88). Preliminary results showed some markers (e.g., increased pupil diameter and anterior cingulate cortex activity) might successfully detect the brain update of its beliefs: further proves would help create optimal virtual simulation (88, 185). Therefore, it becomes paramount to see whether MTs could enhance the feeling of presence, favor the update of the generative model and reduce cybersickness through their neuroendocrine effects ("3.2. How MTs could enhance VR experience") or, as mentioned before, hinder presence, worsen the simulated experience and facilitate the negative effects VR and AR could have (see below).

Another possible issue with VR and AR is the uncanny valley phenomenon that could arise, for instance, when VR is used to support and supervise patients at home. The therapist avatar or, more likely, the virtual coach could elicit feelings of aversion if it should look quite-but-not-exactly human (80, 81), thus reducing both motivation and engagement in the VR therapy. The uncanny valley could induce a nocebo effect that would be deleterious in the long-run, especially for those conditions such as chronic pain, whose management needs to reduce any possible source of stress, anxiety, or fear (154, 159, 160). However, in the VR field, the uncanny valley seems to induce fewer avoidance feelings than expected (186), although more research is required to confirm this.

Another limitation is that VR simulations are not usually personalized for specific patients, but represent "generic" scenarios (e.g., events, avatars) to which every patient has to adapt. This limitation could entail a low engagement with the therapy, especially in the long-run and despite relying on specific features such as gamification for increasing motivation. Indeed, even factors such as age, gender, and personality traits may influence the VR experience and its effectiveness (97, 187). On the other hand, a therapy tailored to the patient's needs, preferences, and goals has long been recognized as paramount for the success and efficacy of any treatment plan, in particular, in case of chronic pain (159). Thus, VR software should allow therapists to create or use applications that could be easily customizable to offer calibrated and personalized interventions to their patients. The development of pathology-specific devices and software would help overcome these limitations and define precise treatment protocols, especially if both therapists and patients are actively involved in the development process itself (2, 11, 82). Despite this essential need, such software can be truly expensive to create (88), especially if we think about how every therapist and patient, as complex organisms, can behave differently based on the therapy used and have completely different experiences regarding the "same" symptom (e.g., pain) (14).

The addition of MTs to VR could increase the patients' motivation by improving their body awareness. Therapists can use touch to help patients become more aware of their bodily sensations—touch can elicit both interoceptive and proprioceptive feelings (89, 113) —and their meaning. Especially in case of pathological conditions, people do feel their body but do not know how to make sense of those "chaotic" sensations, thus becoming overwhelmed by them, e.g., people with lower interoceptive awareness show higher insular activation and greater neural processing (i.e., higher metabolic costs) than people with high interoceptive awareness (188). Therapists could then instruct patients to use their bodily feelings to develop better emotional awareness and regulation and guide them during the therapeutic process (189, 190). Consequently, patients could make better use of VR simulations, having been educated about managing the sensations that could emerge from their bodies. Besides, since touch elicits prosocial behavior and therapeutic compliance (127–129), it is conceivable that touch in itself could increase the patients' motivation and adherence to therapy. As interventions applied before a VR or AR session, MTs could overcome the before-mentioned limitations regarding the mismatch between real and simulated experience induced by an "unseen touch." However, all these potential effects of MTs on VR experience are to be critically assessed.

Last but not least, a limitation regarding the use of VR and AR (especially VR) arises from the negative consequences the users could suffer. Patients could have difficulties in "returning to the real world" should the VR sessions be too frequent or take too

much time (176). Motion sickness, nausea, dizziness, vomiting are some of the most common VR adverse effects, which can affect real life (e.g., driving a car) and last even for months for some patients (181). Besides, as VR could change for the better the body image of people, so VR could change it for the worse should the simulation not be carefully designed. By augmenting or intensifying the users' experience through specific stimuli, AR and VR could overload the users' neural and cognitive resources (the brain and the mind could receive too much information), thus increasing stress and inducing a strong "wear and tear" response (176, 191). By having their body swapped with a virtual one, patients could start having negative beliefs about their real body or even experiencing a distorted perception of it (105, 176). Indeed, Kilteni et al. found that even a short exposure to a virtual body illusion changes the corticospinal tracts' excitability, thus inducing cortical reorganization (192). The distorted perception could also affect the sensorimotor control of the real body and spatial navigation. For example, suppose the users experience a virtual body bigger than their own and complete hand-eye coordination tasks: in that case, they could have difficulties in hand-eye coordination once returned to their real body (191).

VR could also induce negative emotions that persist in real life—reliving a fear in a virtual environment could be way more intense than just thinking about it, and indeed immersion/absorption mediates the emotional experience in VR (193)—and cause memory alterations (e.g., did the event happen for real or just in VR?) (176). The same memory reconsolidation mechanism that VR might elicit for reducing fear, and associated pain (164), could negatively alter the patient's memory, especially when the simulation is immersive and realistic (176). Therefore, the patients could experience difficulties in discriminating between reality and virtual simulation, potentially suffering issues of depersonalization—the bodily self is perceived as unreal—or derealization—the external world is perceived as unreal. These problems could occur mainly in those people whose mental health is already fragile or at risk of deterioration (105), as it can be in the case of chronic pain (194). Besides, negative social interactions that the patients could have in VR, for instance, with the therapist's avatar, could lead to altered behavior in real life, thus with the real therapist (105, 176).

All these negative effects on emotion, memory, and behaviors may be increased by body-swapping since different bodies—different embodiments—seem to easily favor different emotions and behaviors that may transfer in real life (105, 176, 195). The virtual simulation could also induce negative effects on the sense of agency. If the virtual body's movements mismatched with the physical body's ones, the subjects could feel reduced control over their real body—this could be one of the aforementioned adverse effects of the integration between MTs and VR or AR. The consequences could be devastating, including depersonalization and feeling as an automaton (the body moves on its own) (105). Since creating a mismatch could be paramount to update the brain internal generative model, it becomes of the utmost importance to understand how to induce that mismatch without harming patients.

Therefore, beyond designing VR and AR technologies able to minimize all the risks mentioned above, it is paramount to help manual therapists understand which patients would benefit from VR and which patients would risk deteriorating their condition (105, 176, 191).

CONCLUSIONS AND FUTURE PERSPECTIVES

The present review discussed the effects of MTs, VR, and AR. These interventions have been applied in several medicine and psychology fields and showed results that could significantly impact healthcare if confirmed by more rigorous trials. The commercialization of low-cost HMDs could allow manual therapists to combine VR and AR with MTs, thus creating an intervention that genuinely affects the whole mind-body unity. Indeed, MTs act primarily through touch, eliciting the tactile, proprioceptive, and interoceptive systems, whereas VR and AR send primarily visual-auditory stimuli and aim to affect the user's body's perception. Both MTs and VR may influence the mind, inspiring calm, joy, trust, and awe. Through remote Internet connection, HMDs would also allow manual therapists to supervise their patients at home and patients to continue their treatment outside the clinic, as it is already successfully happening in the rehabilitation field.

Regarding the effects the integration between MTs and VR or AR might have on balance and gait, both types of interventions have shown positive effects on these conditions, even in the case of pathologies such as PD (10, 55, 56, 82). Therefore, their integration could help improve stability, static and dynamic balance and reduce risk of falls by increasing body awareness through touch and augmenting cognitive functions related to motor skills through simulations. Moreover, as both inflammation and pain are linked to an increased risk of falls (196–198), especially in the elderly, MTs and VR or AR could also positively influence balance due the combination of the anti-inflammatory effects of MTs (6, 7, 123, 124) with the fear and pain modulation effects of VR and AR (2, 142, 143).

However, several limitations exist that must be overcome to fully harness the potential of the integration between MTs and virtual simulations, starting from assessing the feasibility of combining the two interventions. On the one hand, more research is required to see whether MTs could elicit or hinder the feeling of presence or flow during VR and augment the sense of ownership of the virtual body. On the other hand, more research is required to see whether VR and AR could help MTs manage painful conditions and address negative beliefs about movement and pain. There is also the need to evaluate which available VR and AR applications might be adequate to use in the MTs setting. Besides, to define a truly personalized approach, both therapists and patients have to be involved in elaborating VR and AR software and the process of gamification. Lastly, therapists require reliable tools to recognize which patients would benefit from VR and AR since, as any other treatment, they may induce serious adverse effects.

The success of the integration between MTs and VR or AR in everyday clinical practice will also depend on

its practical feasibility. Indeed, although low-cost devices such as HDMs are ever more available (88), the software required for creating personalized applications could result in being particularly expensive for individual therapists without the support of healthcare institutions (4). Moreover, despite its use in rehabilitation and in the psychological field, literature lacks paper, whether controlled trials or systematic reviews, assessing the cost-effectiveness of the integration of VR and AR within the healthcare system (5, 22, 90). In the same way, literature lacks paper evaluating the adoption rate between patients: therefore, as of today, therapists cannot make a precise estimate about how many of their patients would use the potentially expensive and complex VR or AR systems they could buy for improving their practice (142).

All these questions are therefore left for future research, with the hope that healthcare and educational institutions may lead the innovation, both for their patients and the patients of private clinics, thus realizing the clinical usefulness of these interventions—with VR and AR we can make the impossible possible (2, 199).

AUTHOR CONTRIBUTIONS

FC, MA, and MC conceptualized the study. FC and MC drafted the initial manuscript. AG, VM, and AM critically reviewed the manuscript for important intellectual content. FC, MC, and JE revised the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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BRIEF RESEARCH REPORT
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Load Auditory Feedback Boosts Crutch Usage in Subjects With Central Nervous System Lesions: A Pilot Study

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Background: Crutches are the most common walking aids prescribed to improve mobility in subjects with central nervous system (CNS) lesions. To increase adherence to the appropriate level of crutch usage, providing load-related auditory feedback (aFB) may be a useful approach. We sensorized forearm crutches and developed a custom software to provide aFB information to both user and physical therapist (PhT).

Aim: Evaluate aFB effects on load control during gait by a self-controlled case series trial.

Methods: A single experimental session was conducted enrolling 12 CNS lesioned participants. Load on crutch was recorded during 10 Meter Walk Test performed with and without aFB. In both cases, crutch load data, and gait speed were recorded. Usability and satisfaction questionnaires were administered to participants and PhTs involved.

Results: Reliable data were obtained from eight participants. Results showed that compared to the no FB condition, aFB yielded a significant reduction in the mean load on the crutches during gait ($p = 0.001$). The FB did not influence gait speed or fatigue ($p > 0.05$). The experience questionnaire data indicated a positive experience regarding the use of aFB from both participants' and PhTs' perspectives.

Conclusion: aFB significantly improves compliance with crutch use and does not affect gait speed or fatigue by improving the load placed on crutches. The FB is perceived by users as helpful, safe, and easy to learn, and does not interfere with attention or concentration while walking. Furthermore, the PhTs consider the system to be useful, easy to learn and reliable.

Keywords: auditory feedback, crutches, gait, rehabilitation, adherence

INTRODUCTION

Walking is a fundamental human activity (1); when it is affected by illness or injury, people prioritize regaining the ability to walk as a goal of treatment (2). Up to 10% of adults suffer from reduced mobility or balance as a result of conditions, such as a central nervous system (CNS) lesions, which affect balance and gait. In Europe, walking aids are the most commonly prescribed tools to improve balance and mobility in this population (3, 4). Notably, the number of individuals using crutches and assistive devices for mobility is growing rapidly (4).

The main uses of crutches are to better support one's weight (by reducing the magnitude of load on the legs), and to improve balance (by increasing the body's base of support) (5). Patients typically receive training on how to use walking aids during rehabilitation sessions. Clinicians guide the usage of crutches according to patients' functional and recovery states. For example, they ask the user to progressively decrease the load on crutches as they improve motor performance or become more acquainted with a new prosthesis/overground exoskeleton.

Assessing crutch use is critical to ensure the crutches are used properly and to avoid overuse of the upper limbs (4). Clinical assessments focus on the magnitude of support weight and balance control (1). Due to a lack of objective measurements, these assessments performed in daily clinical practice remain subjective and qualitative. The availability of objective, quantitative data on crutch use may improve rehabilitation treatments (5, 6).

Researchers have proposed the introduction of sensors in crutches to monitor several variables, such as upper limb joint forces and torque, the axial load on crutches and their orientation (1, 7, 8). For instance, in (7–11), instrumented crutches were used to objectively monitor the load on the lower limbs of healthy subjects (8, 10, 11) or patients in a rehabilitation framework (7, 9, 12). Other applications include monitoring crutch use during daily life (10) or domestic environments (9), estimating physical activity, performing clinical diagnoses, or monitoring gait training (13).

To improve the ability of individuals to walk with crutches, approaches based on feedback (FB) have been proposed to ensure proper crutch use in individuals with different orthopedic (14) and neurological clinical diseases. Regarding the latter group of individuals, specific tests have been conducted in multiple sclerosis (1) or spinal cord injury (7, 15) subjects. FB is, at present, considered the main approach to guide top-down control mechanisms and to drive recovery, particularly when dealing with external devices (16). FB and traditional physiotherapy complement each other in assisting the patient functional recovery (17). A range of FBs, adapted to user's individual needs and residual functional abilities (18), can be used with the aim to boost neuroplasticity in neurorehabilitation. The FB can be provided in real-time *during* the execution of a task (concurrent FB) or soon *after* (terminal FB). Mainly two types of concurrent FBs are available for clinicians: "biofeedback," that refers to biological signals about which the subject is partially/completely unaware, and "augmented feedback," i.e., a FB given by a device on measures about which the subject is already directly aware (19). In this scenario, different signals can be used to feed FB information, but at present no indication exists for their specific effects on performance (17, 19). Nonetheless, it has been demonstrated that new technologies based on different FB modalities (19), such as visual (20–22), acoustic (23) and/or haptic (24, 25), allow re-education of altered functions (26, 27), and a consensus is forming on the role of FB to guide and improve patient-technological device interactions (16).

The aspects of FB that are important for guiding and improving patient performance include motivation, active participation, and error-driven learning (28). Consequently, patients must be aware of the differences between real-time results and the desired expected performance (28). The possibility of exploiting FB to compare the actual outcomes with expected outcomes in real time may positively affect motivation and self-efficacy, and may motivate participants during training (29).

In this pilot study, we sensorized forearm crutches, one of the most commonly used types of crutches (4). Strain gauges were added at the base of the crutches to monitor crutch-ground axial interaction forces. Moreover, custom software was developed to provide a concurrent auditory FB when prescribed load limits were exceeded during walking.

In this pilot study, we analyzed the capability of CNS-lesioned participants to adhere to a performance target defined for gait rehabilitation by using traditional crutches and sensorized crutches with auditory FB. In particular, the target for the participants was a reduction of the load applied on the crutches during gait. We compared participants' performance with and without the auditory FB information, and we assessed adherence to the walking target in terms of the load placed on crutches, gait speed and related fatigue. The main goal was to determine whether auditory FB information can improve participants' adherence to the imposed target. We also evaluated the participants' experience with the auditory FB and PhTs' perception of the usability of, and satisfaction with the sensorized crutches and the software.

MATERIALS AND METHODS

This pilot study was a self-controlled case series trial. The protocol was written according to the Helsinki declaration and approved by the Independent FSL Ethics Committee (Prot. CE/PROG.741). Written informed consent was obtained from all participants according to the FSL ethical procedures.

Enrolled Participants

A convenience sample of 12 participants admitted to the Neurorehabilitation 1 Department of Fondazione Santa Lucia (Rome, Italy) and to Fondazione Turati (Zagarolo, Italy) from May 2019 until December 2019 was recruited. Data from four participants were excluded due to the presence of noise in the sensors; consequently, the final sample size was equal to eight. The inclusion criteria were (i) subacute or chronic stroke, spinal cord injury (SCI) and multiple sclerosis (MS); (ii) the ability to walk with one or two crutches for at least 10 m; (iii) a FAC (30) score ranging between 3 and 5 for the stroke and MS

participants; (iv) a WISCI (31) level ranging between 9 and 19 for the SCI participants; and (v) the ability to understand verbal instructions. The exclusion criteria were as follows: (i) cognitive or behavioral impairments interfering with the comprehension of instructions; (ii) severe disturbances of the auditory system; (iii) severe concomitant diseases; and (iv) the inability to provide informed consent. The participants' epidemiological, clinical and neurological features are reported in **Table 1**.

Walking Target

All participants were undergoing rehabilitation training at the time of the experiment, with the main goal of improving gait abilities by reducing the load over the aids as much as possible in a safe way. Therefore, the walking rehabilitation objective during the experiment was a reduction in the load applied on the crutches during a walking task at a self-selected comfortable speed.

Auditory Feedback Approach

To provide participants with the auditory FB, instrumented crutches with a peak detection algorithm were employed, as detailed in section Wireless Instrumented Crutches. The general approach to monitor the load and generate sounds accordingly was as follows:

1. Three threshold values were defined from the data collected during a baseline evaluation: the lowest threshold $Th_{\min}$ only discriminated the stance and swing phases, while the other two thresholds, Th and Th_{MAX}, indicated excessive load values. For this reason, the three thresholds were set as the 40th, 82nd, and 97th percentiles of the load distribution.
2. Different sounds were triggered when these thresholds were exceeded: the crutches produced no sound when the load was below $Th_{\min}$ (stance phase) and between $Th_{\min}$ and Th (participant applies correct loads), a low-pitched tone when the load was between Th and Th_{MAX} and a high-pitched tone when the load exceeded Th_{MAX}.

Experimental Design

Wireless Instrumented Crutches

A pair of instrumented crutches capable of measuring the real-time axial forces, with a sensitivity of 0.005 V/N in the range of 0–600 N (7, 10) was used in all the trials (simultaneously or individually). Each instrumented crutch (**Figure 1A**) was equipped with one strain gauge full bridge (nominal resistance: 120Ω); a data acquisition board composed of a microcontroller (Arduino Nano) for data acquisition, an AD converter (10 bit resolution) for strain gauge bridge conditioning, an inertial unit (LSM9DS1) for detecting the impact with the ground, and a Bluetooth module (ESD200) for wireless data transmission; and a battery power supply. The electronic board was attached to each crutch by using a removable box and connected to the strain gauges through a detachable flat cable. Force data were acquired at 50 Hz and sent in real time to a client PC by using a custom virtual instrument (VI) developed in LabVIEW™ (National Instruments). The LabView VI was used for data processing and visualization.

Experimental Session

Data were collected during a single experimental session. Each session included the following phases:

i) During the baseline evaluation, the participants were asked to comfortably walk at their self-selected velocity with one or two crutches, according to their training protocol, along a 10 m path for the 10 Meter Walk Test (10MWT) (32); the test performance and the load on the crutches were recorded. For the 10MWT a clear straight pathway of 20 m in length over solid flooring was required. Clear marks at the start and end point of 20 m walkway were applied, as well as two more marks at 5 and 15 m to identify the central 10 m path to be timed by PhT with a stopwatch. Excluding from measurement acceleration and deceleration, that occur outside of the timed portion, allows to only assess steady-state walking speed. During test execution, the patient was instructed to start on the 0 m mark, walk at her/his own comfortable walking speed and stop when reaching the farthest mark (32). Based on the load data, the load thresholds Th and Th_{MAX} were set to be used during the subsequent testing phases. No verbal instructions from PhTs were provided.

ii) For the familiarization phase (10 min), the participants were asked to walk both with auditory FB and PhT verbal instructions and with PhT verbal instructions only without FB. These instructions aimed to promote a more physiological gait pattern with a little load as possible on the crutch (es). During familiarization, as well as in the testing phase, the participants received different auditory FB related to the load, as detailed in section Auditory Feedback Approach. The participants rested for 5 min before continuing to the next phase.

iii) During the testing phase, the participants walked with the sensorized crutches three times with FB and three times without FB (noFB condition) in a randomized order, and 10MWT performance was recorded. A PhT was present for safety reasons, but no verbal instructions were provided in either condition, with or without FB. At the end of each of the six runs, the BORG scale (33) was administered to the participants.

iv) During the experience assessment, user-related data were acquired by a specific questionnaire developed on the basis of previously validated data (34, 35). The PhTs' perspectives about the system (FB software and crutches) were evaluated with the System Usability Scale (34) and the Quebec User Evaluation of Satisfaction with assistive technology 2.0 (35).

Data Extraction and Analysis

A peak detection algorithm was used to identify the maximum value of a signal selected by the experimenter (namely, control variable, CV) in real time during each gait cycle. The available CVs include the axial force on a single (right or left) crutch or the mean value calculated between the left and right axial forces. The peak detection algorithm identifies the peak of each gait cycle F_{peak} by computing and analyzing the first derivative d of the CV. A state machine approach was used as described in **Figure 1B**.

TABLE 1 | Epidemiological, clinical, neurological data, and experimental conditions for each participants (P1–P8).

	P1	P2	P3	P4	P5	P6	P7	P8
Epidemiological, clinical and neurological data								
Age	23	52	21	45	64	51	39	45
Gender	M	M	M	F	M	M	F	M
Weight [kg]	51	81	63	60	84	75	70	80
CNS lesion	Traumatic SCI (C5 AIS D)	Traumatic SCI (C4 SCI AIS)	Traumatic SCI (C5 AIS D)	SM	SM	Stroke	Stroke	Traumatic SCI (L4 AIS D)
Days since lesion	119	113	143	5458	1806	104	92	365
Experimental condition								
Routine aids	Walker	Walker/AFO	Human assistance	2 crutches	2 crtuches/AFO	Walker	Walker	2 crtuches/AFO
Number of crutches	2	1	1	2	2	1	1	2
Crutch pattern	4	2	2	2	4	2	2	4
Crutch (es) with FB	1	1	1	2	1	1	1	1

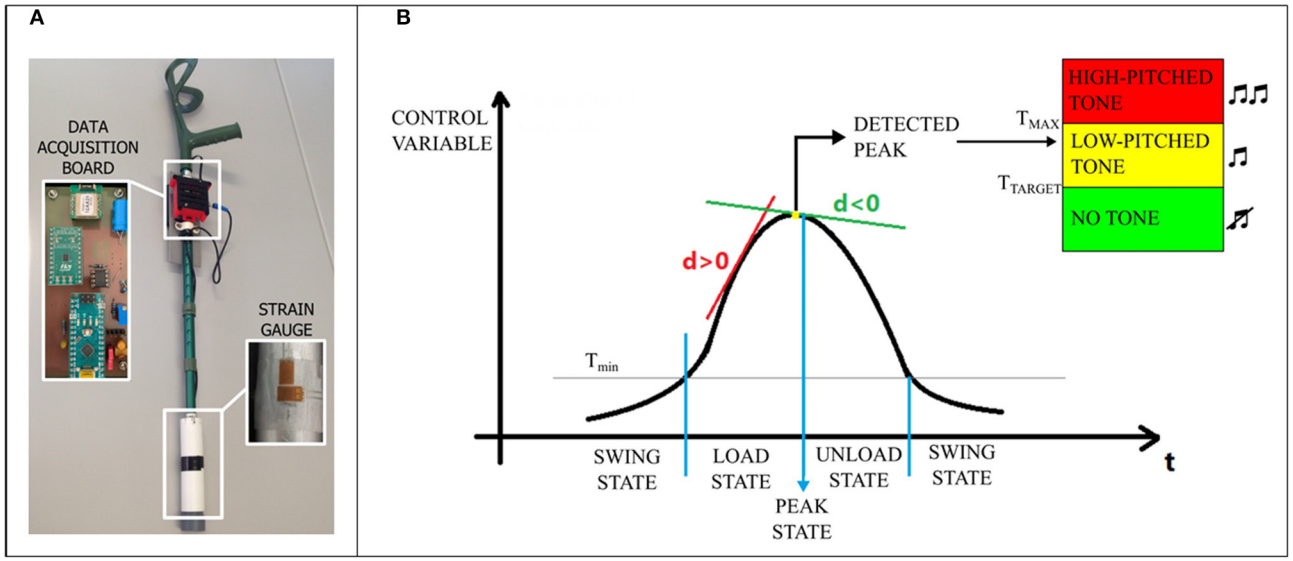

FIGURE 1 | Instrumented crutch **(A)** and peak detection algorithm description **(B)**.

Four different states were defined: (i) the SWING state, (ii) the LOAD state, (iii) the PEAK state, and (iv) the UNLOAD state. The SWING state was activated when the CV decreased below the minimum threshold $Th_{\min}$ (experimentally set as the 40th percentile of the distribution of the CV). When the SWING state was activated a new stride was segmented. When the CV exceeded $Th_{\min}$, the LOAD state was activated ($d > 0$). The PEAK state was activated when d changed its sign, and the peak was identified as the current value of the CV. Then, the UNLOAD state was activated ($d < 0$). When the signal decreased below $Th_{\min}$, the peak search was reset, and a new peak search started.

When the PEAK state was activated, the algorithm compared the CV with two other thresholds, Th and Th_{MAX} (experimentally set as the 82nd and 97th percentile of the distribution of the CV, respectively), and generated a single-tone sound whose frequency f was set based on the following rules:

- $f = 0$ Hz (no tone) if $F_{peak} < Th$;
- $f = 440$ Hz (low-pitched tone) if $Th \leq F_{peak} < Th_{MAX}$;
- $f = 880$ Hz (high-pitched tone) if $F_{peak} \geq Th_{MAX}$.

Th and Th_{MAX} were considered limits for the participants, who were asked to walk without generating sounds.

The following variables were extracted by averaging the values from three runs for each FB condition:

i) For the load data, we calculated the following metrics: $\overline{F}$ - mean peak load on crutch (es), i.e. the average of the peak values identified in a walking path; $\overline{F}_{\%}$ - percentage of variation of $\overline{F}$ with respect to the target threshold (Th); N_{TOT} - number of crutch contacts on the ground (i.e., number of load peak values); and N_{Th} - percentage of peak values lower than Th.

TABLE 2 | List of items included in the *ad-hoc* feedback questionnaire.

	***Ad-hoc* feedback questionnaire**
1	The auditory feedback was helpful during the training
2	The auditory feedback distracted me during the training (R)
3	The auditory feedback helped me to feel safe
4	The auditory feedback helped me to walk
5	The auditory feedback helped me to reach the goal planned by the PhT
6	Thanks to the auditory feedback, I was able to execute the instructions given by the physiotherapist more easily
7	If I had the opportunity to receive a feedback during daily life, I would be able to walk better
8	I think that the familiarization phase was enough to get me to handle the use of the crutches with the auditory feedback
9	When I walk with the crutches, I can focus on the necessary movements to walk

ii) To determine gait speed, the 10MWT (m/s) was administered. The total time taken to walk in the central 10 m path was recorded and the speed was consequently calculated.
iii) To determine fatigue, the Borg scale for fatigue was administered.
iv) For the experience data, an *ad hoc* FB questionnaire composed of 9 items was administered. It was developed to assess 4 factors (**Table 2**): *utility/usability* (items 1, 4, 5, 6, 7), *safety* (item 3), *attention* (items 2, 9), and *learnability* (item 8). The participants used a 7-point Likert scale (36), ranging from 1 ("*I strongly disagree*") to 7 ("*I strongly agree*"), to respond to each item. The wording of item 2 (*attention*) was reversed, which means that its meaning was opposite to the construct of interest (37).

The System Usability Scale (SUS) was administered to the PhTs to evaluate *usability*, whereas the Quebec User Evaluation of Satisfaction with assistive technology 2.0 (QUEST 2.0) was used to assess *satisfaction* with the system. The SUS is a 10-item questionnaire rated on a Likert scale from 1 to 5, particularly used for the assessment of usability, perceived ease of use, and complexity. It was designed to evaluate a wide variety of products and services, including hardware, software, mobile devices, and websites (34). QUEST 2.0 is a 12-item standardized assessment tool with five response options. It is the most widely used questionnaire to evaluate satisfaction with assistive technologies. It provides direct data on user interactions with technology and is used to determine how useful and acceptable a technology is perceived in various settings. QUEST 2.0 has limited applicability with prototypes, so in our case, not all the items were used. The questionnaire consists of two parts: the first part is for the rating of the device's characteristics (dimensions, weight, adjustments, safety, durability, simplicity of use, comfort, and effectiveness), whereas the second part evaluates the services with five items. We only assessed the first part since no services were provided (38). After the rating procedure, a list with the satisfaction characteristics was presented to the user, and he or she was asked to choose the three most important ones (35).

Statistical Analysis

Statistical tests were performed by using SPSS software (Statistical Package for the Social Sciences–Chicago, IL, USA). Differences between the FB and noFB conditions were assessed with the paired *t*-test for the parametric variables (load data, 10MWT) and by the Wilcoxon test for the non-parametric variables (Borg data). Statistical significance was indicated when $p < 0.05$.

RESULTS

The data for six males and two females (age: 42.5 ± 14.6 years, mean time from lesion: 2.74 ± 4.99 years) were analyzed. The participants were assigned identifiers from P1 to P8. The aids used by the participants for routine gait are reported in **Table 1**, as well as the details of the experimental conditions, such as the FB source, number of crutches used and crutch gait pattern during testing. Indeed, there are multiple ways to walk with crutches, depending on the specific injury or disability. The points of contact or contact patterns indicate the basic structure of gait with crutches, as they reflect the number of times the crutches leave the ground and land within one gait cycle in the direction of walking (4).

Load Data

For all participants, the mean load on the crutches $\overline{F}$ was significantly smaller by ∼0.9 kg ($p = 0.001$) in the auditory FB condition than in the noFB condition (FB $\overline{F}$: 7.9 ± 6.03 kg; noFB $\overline{F}$: 8.8 ± 6.06 kg) (**Figure 2A**).

Interestingly, a different behavior was observed in terms of the FB effects related to $\overline{F}_{\%}$ for the participants. P1, P3, and P6 were able to load the crutches with loads smaller than the selected target for both the FB and noFB conditions, even when $\overline{F}$ was lower with FB. In contrast, P5 and P8 did not exhibit loads below the threshold for either the FB or noFB condition, although the load on the crutches was lower in the FB condition. For P2, P4, and P7, the presence of the FB reduced only $\overline{F}_{\%}$. Across the participants, $\overline{F}_{\%}$ was significantly smaller by ∼15% ($p = 0.002$) with FB than without FB (FB $\overline{F}_{\%}$: −6.9 ± 19.64%; noFB $\overline{F}_{\%}$: 8.5 ± 17.75%) (**Figure 2A**). In detail, three participants (P1, P3, and P6) exhibited low $\overline{F}_{\%}$ values for both conditions, and two participants (P5 and P8) had low values that were not smaller than *Th*.

Auditory FB did not influence the participants in terms of N_{TOT} ($p > 0.05$). Indeed, no differences were present in the comparison FB vs. noFB (FB: 13.6± 3.66 peaks; noFB: 13.3 ± 3.22 peaks). Even though no differences in N_{TOT} between the FB and noFB conditions were observed, for all participants, N_{Th} (i.e., correct load) was higher with FB (**Figure 2A**). This finding was particularly evident for P2, P4, and P7, who were able to maintain $\overline{F}_{\%}$ only with FB. The percentage of peaks under the selected threshold N_{Th} with FB was 19.7% higher than that under the noFB condition ($p = 0.003$) (FB N_{Th}: 61.5 ± 25.5%; noFB N_{Th}: 41.8 ± 26.07).

Gait Speed Data

No significant differences were observed in the comparison of the FB vs. noFB conditions for gait speed ($p > 0.05$ – FB 10MWT: 0.38 ± 0.18 m/s; noFB 10MWT: 0.39 ± 0.17 m/s) or

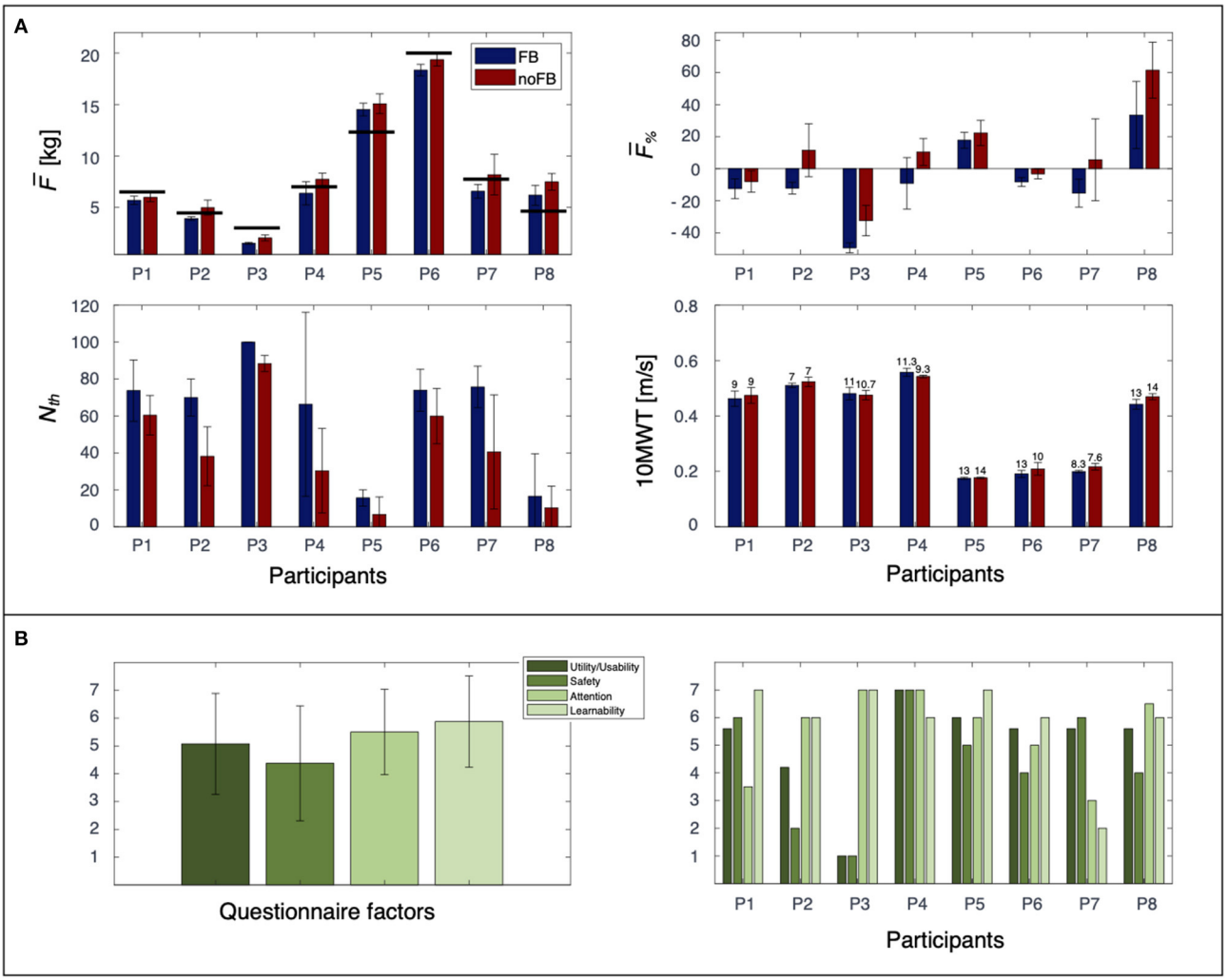

FIGURE 2 | Load and 10MWT data for P1–P8 are reported in **(A)**. Error bars indicate standard deviation. The target threshold *Th* for each participant is represented by black horizontal lines in the $\overline{F}$ graph and by the zero value in the $\overline{F}_{\%}$ graph. BORG values, averaged over three runs, are reported on top of the bars in the 10MWT graph. Overall experience with the auditory FB for each factor is reported in **(B)** as mean across participants (left) and separately for each participant (right).

the Borg score ($p > 0.05$ – FB Borg: 10.7 ± 2.2; noFB Borg: 10.2 ± 2.46) (**Figure 2A**).

Experience Data

Overall, the participants responded positively regarding the use of the crutches with the auditory FB (**Figure 2B**). In fact, the mean score for all items was higher than 4, which is the intermediate score of the questionnaire. In detail, the participants perceived the auditory FB as useful (*utility/usability* score: 5.07 ± 1.81) and easy to *learn* (*learnability score:* 5.87 ± 1.64), with no impact on concentration while walking (*attention* score: 5.5 ± 1.53). *Safety* had a lower score (4.37 ± 2.06), suggesting that auditory FB might not have had a high impact on participants' perceived safety when they used the crutches.

Interestingly, although the general response was positive according to the questionnaire, different behaviors were observed from the individual participants (**Figure 2B**). In detail, the factor distribution showed large variability in the way participants perceived auditory FB. P4 and P5 gave high scores for all the factors in line with good load reduction in the FB condition. P3 gave very high scores for *attention* and *learnability*, while the *utility/usability*, and *safety* scores were low. As shown in **Figure 2A**, P3 had a value of 100% of peaks under the selected threshold: he never heard the auditory FB during the experimental session, which may have prevented him from being able to properly evaluate its utility and safety. P2 and P7 presented an opposite trend in questionnaire answers (P2 gave high scores for *attention* and *learnability* and low scores for *utility/usability* and *safety; P7* gave high scores for *utility/usability* and *safety* and low scores for *attention* and *learnability*), although they both showed the same behavior during gait (reduced the load the on crutches under the selected threshold only in the FB condition).

Regarding the PhT point of view, the SUS score was 87.5 (± 13.2) out of 100, indicating that PhTs perceived the system as useful, easy-to-learn and reliable. Furthermore, the QUEST 2.0 results indicated that PhTs were satisfied with the use of the system (4.38 ± 0.37 out of 5), and the three most important *satisfaction* items were weight, ease-of-use and effectiveness.

DISCUSSION

The significant load reduction in the FB testing condition demonstrates the usefulness of the peak load auditory FB during walking with crutches. Forearm crutch-assisted gait is frequently used in clinical settings for rehabilitation in individuals with CNS lesions (28, 39, 40). The amount of body weight that should be loaded on the crutch (es) depends on the pathology and the recovery phase that the participant is in (41, 42). At the time of the experiment, all participants were receiving rehabilitation with the goal of reducing the load on the aids as much as possible to improve their ability to walk independently. The crutches developed for this research are a type of wearable rehabilitation technology, and these technologies have been receiving increasing interest and offer advantages over traditional rehabilitation services (43, 44), such as lower costs, a wider range of applications, remote monitoring and greater comfort (29).

In this pilot study, we performed a single experimental session using a concurrent auditory FB and did not assess crutch usage longitudinally, and we asked participants to walk with instrumented aids at their self-selected comfortable speed. According to Agresta et al. (45), concurrent (auditory or visual) FB is one of the most effective, and it has been demonstrated that it produces the best short-term results (18). In line with these evidences, even without dedicated training for the use of the FB, all participants reduced the mean load on the crutches more when auditory FB was present. Furthermore, even though the number of times the crutches contacted the ground did not vary between conditions, the mean value of the number of correct peaks (i.e., peaks with a value below the selected threshold) was significantly higher when the participants received auditory FB. Moreover, 10MWT gait speed and fatigue perception did not vary between trials. These results suggest that the presence of the auditory FB did not affect gait speed or the number of times the crutches contacted the ground. Overall, these results appear particularly encouraging since, even in the absence of dedicated training, a single-use session still allows an immediate significant variation in the mean load on the crutches during gait. It is then expected that specific prolonged training could potentially further enhance load control.

This finding is confirmed by the subjective responses of the participants, which despite heterogeneity, were generally positive. One of our main concerns was that the FB could overload participants' attention by interfering with their ability to handle the load on the crutches. Instead, auditory FB did not interfere with the participants' attention while walking, and it was perceived as useful. Additionally, the PhTs showed a high level of satisfaction and a positive attitude toward the system, as it was perceived as useful and easy to use. These data indicated positive responses regarding the use of the auditory FB with the sensorized crutch system in the rehabilitation environment from both the participants and PhTs. Furthermore, these data suggest that PhTs trust the system and that it meets their planned rehabilitation objectives for CNS patients, such as improving the support of weight and balance. This is in line with the clinical professionals' needs for rehabilitation systems, which should be easy to use (18, 46) and applicable in the everyday clinical practice to improve the functional recovery process (14, 24).

In this work, we analyzed CNS-lesioned participants' adherence to crutch use during gait. Good adherence implies that the patients and physicians collaborated well to improve patient health (47). It has been demonstrated in CNS lesions that PhT-participant interactions are important for the success of rehabilitation. Physical, verbal, and technical exchanges between the PhT and participant highly influence the outcome, suggesting the importance of collaborative work in the rehabilitation framework (48). Moreover, increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments (49).

Limitations of the Study

This study was planned as a pilot one: the sample size ($N = 8$) was relatively small, thus reducing the statistical power of the study. Nevertheless, significant differences were observed in the comparison of the FB vs. noFB load data, and as suggested by Friston (50), significant results based on a small sample may indicate a larger FB influence than the equivalent results with a large sample. Future investigations should include a larger number of participants to confirm these preliminary findings. The possibility of recruiting a larger number of participants is potentially useful to identify which disease could mostly benefit from the use of the auditory FB during gait rehabilitation. In addition by analyzing the time elapsed from the occurrence of the CNS lesion and the progression of the ongoing rehabilitation phases, it could be possible to clarify, within a patient-specific rehabilitation project, the optimal time to introduce the use of this system and to favor the load control during gait. This study was a self-controlled case series with a single experimental session. Therefore, a devoted training period and follow-up examination were absent. It may be interesting to include more training sessions with auditory FB in the rehabilitation context, considering the significant improvement observed with a single session, as well as the positive experience reported by both subjects and PhTs. Despite these limitations, our results indicate that sensorized crutches with auditory FB may positively affect participants' adherence to gait objectives.

CONCLUSIONS

These preliminary data suggest that for individuals with CNS lesions, auditory FB significantly improves adherence to instructions to reduce the load on sensorized crutch (es) without affecting gait speed or leading to fatigue. In addition, the participants' experience with FB was positive, and the PhTs' level of satisfaction with the system was substantially high. These

positive responses could potentially facilitate collaborations between participants and PhTs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Indipendente Fondazione Santa Lucia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FT, MLo, NLT, IP, AB, MLa, SP, VS, and MMo contributed to the conception and design of the work. MMa, MLo, and FT contributed to the recruitment of participants. MLa, SP, and MG developed the crutches and the software for the auditory feedback. FT, MLo, NLT, IP, and AB performed experimental sessions. FT, MLo, NLT, FB, AB, and IP worked on data collection, analysis, and interpretation. FT, MLo, NLT, FB, AB, IP, and SP wrote the manuscript and MLa, MG, MMa, VS, and MMo revised it. For this paper the engineering, medical and rehabilitation spheres were combined with the participation of two rehabilitation partners (Fondazione Santa Lucia and Fondazione Turati) and two engineering partners (Campus Bio-Medico University of Rome and University of Brescia). All authors approved the final version of the manuscript.

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CASE REPORT
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Case Report: Acute Onset Fear of Falling and Treatment With "Cognitive Physical Therapy"

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Fear of falling (FoF) is prevalent in older adults, especially those with previous falls, and typically starts insidiously. We present a 78-year-old woman with an abrupt onset FoF and no history of falls, balance problems, vertigo, oscillopsia, psychiatric or psychological issues to account for this. These cognitive changes led to a behavioural alteration of her gait that became slow and wide-based, with her gaze fixed on the floor. She began a tailored program of "Cognitive Physical Therapy (CPT)" combining cognitive behavioural therapy (CBT) and physical rehabilitation. 1 month later her 6 m walk time and steps were reduced by a 25 and 35%, respectively, and the stride length increased by 34%, with further improvement 2 months later. We postulate that the abrupt onset of symptoms triggered a central shift toward postural hypervigilance and anxiety, suppression of anticipatory (feed forward) postural adjustments (APA) leading to FoF. CPT improved objective gait parameters related to FoF and reduced postural anxiety suggesting that early diagnosis and prompt treatment may avoid chronic symptoms and social isolation.

Keywords: fear of falling, falls, postural anxiety, cognitive behavioural therapy, cognitive physical therapy

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INTRODUCTION

Fear of falling (FoF) is an abnormal psychological or cognitive response to one's perception of stability, usually developing insidiously. It has a high prevalence, especially in community-dwelling older adults (1), and often leads to behavioural changes in walking patterns. Whilst a cause is not always obvious, the debilitating fear leads to a vicious cycle of avoidance of physical activity (2) and progressive physical disability (1), which in itself may be a precursor to actual falls. Sufferers of FoF may also modify their gait in detrimental ways, including a slower gait and a reduced stride length, which can further increase their risk of falling (3). Limited data exists regarding the neural pathways involved in FoF, and studies have instead focussed on the biomechanical or environmental multifactorial nature of the condition.

Several treatment interventions have been trialled in patients with FoF with varying success. These include integrated exposure therapy (4), cognitive behavioural therapy (CBT) (5) and exercise training (6). However, most interventions have focussed on either the biomechanical manifestations that underpin poor balance (strength, range of motion, endurance, balance skills), or primarily on the psychological fear responses that often lead to task avoidance strategies (7).

Here we present the case of a 78-year-old woman with an abrupt onset FoF that improved through targeted cognitive physical therapies. We discuss the interaction between brain mechanisms and cognitive function in FoF and describe an effective intervention to tackle this condition.

CASE DESCRIPTION

A 78-year-old Caucasian woman presented at age 74 with a sudden sensation of imbalance whilst walking down a sloping road and feeling herself being propelled forwards. She immediately held onto a passer-by to keep her balance. Since then, she has suffered a persistent sensation of imbalance and a constant fear of falling if unsupported, which led her to the immediate avoidance of daily life activities such as walking unaided, despite no physical impediment. Before this episode, the patient led an active life, without any limitations to her daily activities. She had no history of falls, balance problems, vertigo, oscillopsia, or hearing loss, either reported at consultation or on her medical records. She reported no sensory symptoms and had no relevant neurological history of note. She had been taking alendronate, vitamin D, atorvastatin, levothyroxine, ramapril and indapamide for several years with no recent change to the doses. There was no prior history or record of any psychiatric or psychological issues or mental illness to account for the balance disorder. She lives with her husband and reported good family relationships and strong social support networks. She scored 1 on the Clinical Frailty Scale, equivalent to "very fit" (8) for her age. On examination her gait was slow and wide-based, and her gaze remained fixed on the floor (**Supplementary File 1**). Ankle reflexes were absent bilaterally, but the remainder of the neurological examination was normal. She had normal corrected visual acuities, no spontaneous or gaze-evoked nystagmus, normal positional (Dix-Hallpike) manoeuvres, normal vestibulo-ocular reflexes, and intact proprioception proximally and distally. An MRI of her head and cervical and thoracic spine and routine nerve conduction studies were normal. Somatosensory evoked potentials were performed due to absent ankle reflexes, which initially demonstrated delayed responses of both legs. Nevertheless, repeat testing revealed these to be of normal latency and symmetrical. Routine blood tests and standard serological tests for neuropathy were normal (including B12, folate, calcium, magnesium, bone profile, serum protein electrophoresis, HIV, syphilis, and Hepatitis B & C). Corrected visual acuity was normal. Vestibular function test including caloric test, vHIT, videonystagmography were also normal. She was diagnosed with primary FoF and began a tailored program of what we term "cognitive physical therapy," combining cognitive behavioural therapy (CBT) techniques and physical rehabilitation (see below).

METHODS

Assessment of Gait

Initial formal gait assessment was performed 8 months after symptom onset, then at 1 month and 3 months after initial assessment. The patient was assessed on her time to completion, number of steps taken and average stride length during a 6 m walk. This was compared with our (unpublished) database of healthy age-matched controls.

Assessment of Mood and FoF

Measures of psychological variables and fear of falling were assessed using validated questionnaires. The Hospital Anxiety and Depression Scale (HADS), State and Trait Anxiety Inventory (STAI) and International Fall Efficacy Scale (FES-I) provided subjective measures of her anxiety and fear of falling. When answering the FES-I questionnaire, she provided answers for both aided (single walking aid) and unaided situations. Questionnaires were completed at initial assessment 8 months after symptom onset and 1 month later.

The Hospital Anxiety and Depression Scale

The HADS assesses anxiety (HADS-A) and depression (HADS-D) separately. Participants are asked to rate how they have felt in the last week (9).

The State and Trait Anxiety Inventory

The STAI consists of two subscales: the State Anxiety Scale (S-Anxiety) measuring the participant's current state of anxiety and the Trait Anxiety Scale (T-Anxiety) which measures the participant's anxiety feelings in general (10).

The International Falls Efficacy Scale

The short FES-I is a questionnaire that assesses participants' perception of their fall-related self-efficacy. Participants rank their concern about the possibility of falling in different scenarios (11).

Existing Therapeutic Strategies

Traditional therapies for FoF are based around physical therapy, including muscle strengthening and increasing muscle flexibility or graded balance skills training (12) that are primarily aimed at avoidance of falls by reducing the impairments underlying the motor aspects of task performance such as reaction times or muscle strength (13).

FoF tends to increase with age, along with biomechanical sequalae such as weakness, joint and muscle changes, and alterations in balance performance. It is perhaps not surprising that traditional interventions reported in the literature are aimed at improving these requisites for performance of a motor behaviour as they have been shown to be related to falling risk (14, 15). Physical training is key to addressing risk of falls, and should be included when treating this group of patients, however, the impact of psychological sequalae in fear of falling has not been well-addressed in traditional physiotherapy approaches for falls (16).

Several authors have proposed the inclusion of task specific activity training within a multidimensional approach to fall prevention and rehabilitation, however this is typically described as a series of daily activity skills training—such as transfers, sit to stand or stair climbing. This may fall short of addressing the fear of falling within the context of the fear-inducing activity or location (17).

Cognitive Behavioural Therapy (CBT) is a psychotherapeutic intervention that targets maladaptive beliefs and re-direct behaviours toward positive strategies such as regular and safe exercise (18). FoF however may additionally generate maladaptive behaviours that alter posture and gait patterns (3, 19), that could themselves induce worsening balance and perpetuate FoF. Isolated CBT would not necessarily address these objective postural impairments.

Cognitive Physical Therapy

The patient was offered a combination of "falls-oriented physical therapy" with aspects of CBT to provide a more holistic approach to treatment. Considering the patient's access to the health centre, the treatment programme consisted of three 30 min in-person sessions of "non-sedentary" therapy focussed on diverting attention on voluntary motor gait control through use of auditory cuing, and cognitive distractors during walking (that are used in functional gait disorders). The patient was encouraged to take longer strides in time to a self-generated beat or finger click, whilst using relaxation and realistic thinking strategies to explore, understand, and manage her underlying FoF-related anxiety. We focused on rationalisation of perceived postural instability to avoid "catastrophisation." The patient was encouraged to practise the strategies learned during each session at home, first as a formal exercise session and later as part of her normal walking. Follow-up in person sessions occurred once every 4 weeks over a 3-month period and were delivered by a research audiologist trained in vestibular rehabilitation and CBT. The rehabilitation program and its delivery was based on evidence from systematic and meta-analysis reviews both CBT for fear of falling (5, 18) and vestibular rehabilitation for treatment of balance disorders (20), although there is no consensus for optimum frequency or treatment duration. The patient was not prescribed any additional pharmacological therapy.

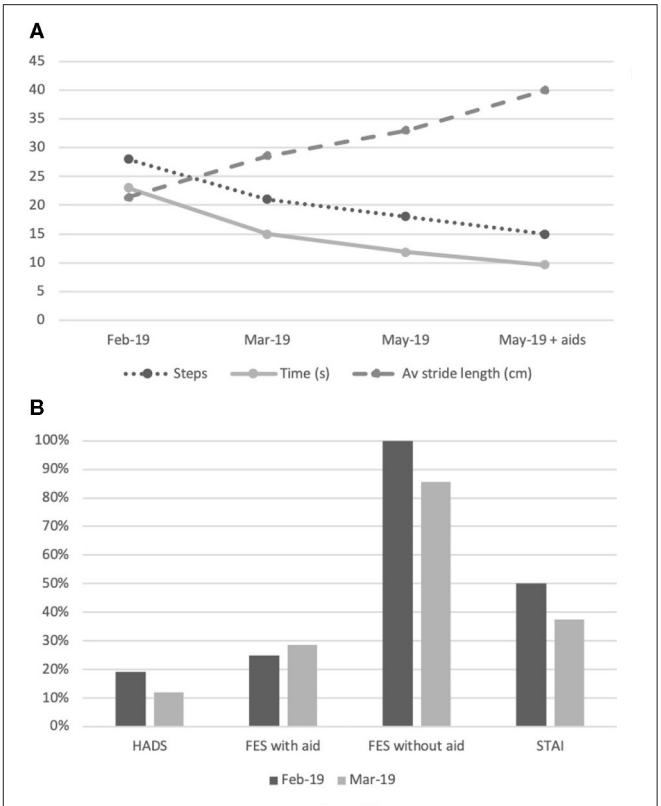

FIGURE 1 | Summary of gait assessments and subjective measurements. **(A)** Changes in step count, time (seconds) and average stride length (cm) for a 6-metre walk. Data obtained at three time points: February 2019, March 2019, and May 2019. Further data provided in May 2019 for 6 m walk aided with a walking stick; **(B)** Subjective measures of anxiety and fear of falling with HADS, FES-I and STAI as a proportion of maximum possible scores at two time points: February 2019 and March 2019.

RESULTS

Gait Parameter Improvements

Formal gait assessment was performed 8 months after symptom onset; during a 6 m walk she took 28 steps in 23 s, with an average stride length of 21.4 cm (**Figure 1A**). Healthy controls of comparable age complete a 6 m walk with 10.4 steps in 6.9 s, with an average stride length of 57.7 cm ($n = 15$, unpublished data from out unit). During this session she was given advice on improving her gait and was instructed to adopt a rhythmic walk by marking the beat with her hands, and finger-clicks. Her progress was reviewed 1 month later when her 6 m walk time and steps were reduced by a 25 and 35%, respectively and the stride length increased by 34% (**Figure 1A**). She reported being able to walk longer distances unassisted, however, was still mostly reliant on her three-wheel walker. Qualitatively, her walk was more confident and less "shuffling." During this second session she was advised to increase her stride length and walking speed and it was suggested that she replace the three-wheel walker with a single walking stick. Reassessment 2 months later again revealed a time reduction on the 6 m walk to 11.8 s, reduction in number of steps to 18, and increased stride length of 33 cm (**Figure 1A**; **Supplementary File 2**).

Self-reported Measures

On initial assessment her total HADS score was 8, scoring 2 on HADS-A and 6 on HADS-D. Her STAI score was 40 and her FES was 7 with a walking aid and 28 unaided. This demonstrates low-grade anxiety, (which reduced even further in later evaluations), but a significant FoF when asked about her balance perception without the use of the walking aid.

On assessment 1 month later her HADS score was 5, scoring 1 on HADS-A and 4 on HADS-D. Her STAI score was 30 and her FES was 8 with a walking aid and 24 unaided. Despite the improvement in her gait and subjectively on her confidence, the reduction of her FoF when unaided was only marginal (14%, **Figure 1B**). Nevertheless, she reported subjective functional improvements with greater confidence when walking inside and also in the garden. After the second treatment session she was no longer using the three-wheeler walking aid for long distances and was completing shorter distances unaided. She was now performing tasks that she had previously avoided, a manifestation of improved balance confidence.

CONCLUSION AND DISCUSSION

Whilst FoF is a common disorder in the elderly, it is likely to be under-recognised given the perceptual nature of the syndrome, lack of confirmatory tests and reluctance to seek medical help due to fear of stigmatisation (21). This case represents an unusually abrupt onset in an otherwise elderly healthy non-faller. The patient improved with a tailored "Cognitive Physical Therapy (CPT)" programme, embedding FoF within a cognitive neuroscience framework. CPT may have a role across a range of perceptual disturbances of gait and motor control in the elderly.

Causes of FoF are multifactorial and include prior falls, although this is not a prerequisite for developing FoF (22). Data from several case-control studies with FoF as an outcome measure identified other risk factors such as female gender, old age, dizziness, health status, depression, anxiety, poor mobility and poor self-perceived well-being (1, 11, 23–25). Traditional conceptualizations of FoF are based on fear avoidance, suggesting a cycle of FoF and subsequent avoidance of activity leading to muscle atrophy, worsening balance and gait and therefore falls (26). Hadjistavropoulos et al. adapted this model to incorporate multiple factors that are relevant in fear of falling including an individual's appraisal of their own ability to maintain balance which is affected by factors such as their self-assessed health status, fall risk factors and a history of previous falls (27). This more robust model does not however account for the acute onset of fear of falling–and subsequent improvement with CPT—that was apparent in our patient.

The acute onset of FoF demonstrated here suggests an abrupt shift in perceptual processing of self-stability. We have postulated that FoF may represent a heightened and permanent state of postural anxiety due to an internal awareness of altered balance function in elderly individuals, as evidenced by a negative correlation between the perception of stability and age (28). Interestingly, our patient demonstrated low-grade anxiety when assessed with HADS and STAI but significant FoF when assessed with FES-I. This suggests that her anxiety was directly related to falls and not symptomatic of a more generalised anxiety disorder. It also highlights the need for both objective and *subjective* measurements of FoF to ascertain the extent of the problem, construct a treatment protocol, and accurately track recovery.

Individuals with FoF may manifest heightened postural anxiety–irrespective of impaired balance function–through an awareness of the potential consequences of falling (e.g., fractures and facial injuries). Castro et al. investigated healthy subjects and demonstrated that whilst perception of instability is congruent with body sway across the ages, in older subjects a reduction in sway was not accompanied by a reduction in subjective measures of anxiety or instability (28). Thus, postural anxiety persists in the elderly in the absence of a postural threat. Considering the present case, the patient exhibited an immediate shift to a fearful response when exposed to a loss of stability, which translated for her into a significant increase in postural threat. The stimulus, which triggered the patient's symptoms, was equivalent for her in perceived magnitude to an actual fall, thus generating a central shift toward postural hypervigilance and anxiety and leading to persistent FoF. Such a shift to cortical-based control of posture appears to involve abnormal frontoparietal interactions (29). This is further supported by evidence implicating the prefrontal cortex in fear conditioning and extinction (30), decision confidence (31) and executive behaviour planning (32). Holtzer et al., assessed activation and efficiency of the prefrontal cortex in older participants with and without FoF during single-task and dual-task walking. They demonstrated greater activity in the prefrontal cortex when switching from single-task to dual-task walking in the FoF group. Since FoF subjects showed slower gait velocity, this finding suggests inefficient activation of the prefrontal cortex during dual-task walking. This inefficiency appears to be specific for attention-demanding locomotion as it was not present when completing isolated cognitive tasks (33). Thus, we postulate that inefficient prefrontal cortex activity may underpin the development of FoF in our patient (**Figure 2**). Such altered activity may in turn relate to an acute increase in postural anxiety.

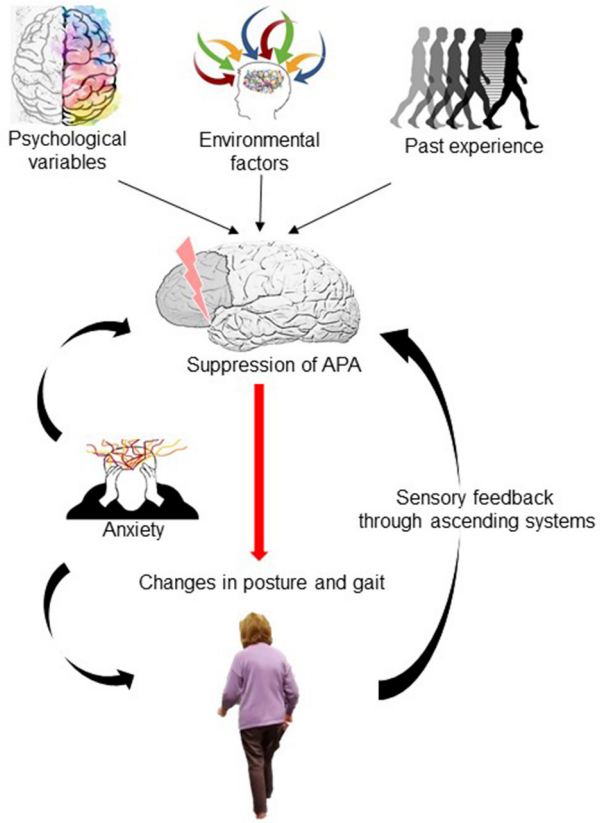

FIGURE 2 | Diagrammatic schema for gait impairment in Fear of Falling. Past experiences (previous falls or near-falls) combine with psychological variables (state anxiety, bodily hypervigilance) and environmental factors (uneven or sloping surfaces) to alter prefrontal cortex activation leading to a suppression of anticipatory postural adjustment (APA) activity. This occurs in an attempt to increase balance performance and safety by reducing the size, speed and amplitude of such postural adjustments. This however becomes a less successful movement strategy, increasing risk of falls through stiffening of posture, and leads to heightened perception of falls risk through ascending sensory feedback, further cementing the suppression of APA. Postural anxiety increases postural stiffening and contributes to APA suppression.

Although fear responses have a primary psychological construct, FoF leads to measurable changes in balance behaviour and function. Adkin et al. (34) showed suppression in anticipatory postural adjustments (APA) activity in healthy normal individuals by changing the height of the task or the proximity to the edge of a raised platform (34). Naugle and colleagues (35) demonstrated direct effects on APA activity in gait initiation following exposure to positive or negatively arousing images, proposing direct modulation of motor circuitry via dopaminergic neurones via the basal ganglia (Naugle et al.). Suppression of APA activity, putatively mediated through prefrontal cortex top-down influences–may represent an attempt to increase balance performance and safety by reducing the size, speed and amplitude of such postural adjustments (**Figure 2**). Paradoxically, this becomes a less successful movement strategy, actually increasing risk of falls. This may account for the need for the treatment intervention to integrate task-based practise using graded environmental exposure/desensitisation, with cognitive coping strategies (including distraction/external cuing/coaching).

Gait assessment at presentation in our patient showed a reduced stride length, an increase in number of steps and time taken to complete a 6 m walk when compared with healthy controls. Such changes in gait correlate with anxiety in community-dwelling older adults (36). We demonstrated an improvement in all objective measures of gait with CPT, that were a behavioural consequence of the FoF. Perceptual measures of FoF were however less amenable to treatment over a short 1-month period, indicating perhaps the requirement for longer-term treatment. Moreover, FoF is a complex neuropsychological construct and perceptual or emotional variables may be more resistant to therapeutic interventions despite objective reduction in maladaptive gait strategies, and improvements in everyday function.

Traditional treatments for FoF focus on the use of physical therapy *or* CBT. Balance training, strength and resistance training and tai chi, have been used to treat FoF and have shown mild to moderate improvement in dynamic control and sensory integration (37). Specific and focussed guidelines to avoid falls in older people with a high fall risk have been developed by NICE and the Centres for Disease Control and Prevention, however, these are mainly focussed on home adaptations and muscular strengthening training, targeting fall avoidance specifically, but not FoF. Recommendations include the curtailment of possibly hazardous activities (13) in patients at risk of falls. Considering that our patient had restricted her movement to avoid falls due to a *perceived* but not objective fall risk, this recommendation may in fact be detrimental to recovery in patients with FoF with low falls risk.

The Strategies for Increasing Independence Confidence and Energy (STRIDE) study demonstrated a reduction in FoF with CBT delivered by healthcare assistants compared to usual care alone (referral to community exercise and home exercise) in the control group. However, they did not report a reduction in anxiety as measured by the HADS following CBT (5). Similarly, randomised controlled trials of cognitive intervention together with physical training reduces FoF and increases activity in healthy older adults with low levels of FoF (38). CBT-based multicomponent interventions for FoF are supported by meta-analysis data (39). Whether such benefits are also achievable in patients with higher burden of FoF has not been formally evaluated but our case suggests this may be possible. If we theorise that FoF is secondary to changes in the prefrontal cortex, then management programmes that specifically target prefrontal cortex efficiency, for example dual-task walking (33) should be incorporated into FoF interventions.

Limitations

We acknowledge that this is a single case study and therefore the individualised therapy may not be generalisable to other elderly patients who present with FoF. Furthermore, there is no consensus regarding the optimum frequency and duration of physical and/or cognitive therapies for FoF, although we based our programme on evidence from systematic reviews and meta-analyses and were additionally guided by the time constraints and patient's geographical distance to the treatment centre.

In summary, whilst FoF often has an insidious onset, it may present abruptly in susceptible individuals and lead to postural anxiety and a shift to cortically-based postural control. CPT was helpful in improving objective gait parameters and reducing postural anxiety, perhaps by preventing (frontal lobe) cortical suppression of balance performance, in turn downregulating abnormal postural feedback to reduce postural anxiety.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Material preparation, data collection and analysis were performed by PC, SV, and DK. All authors contributed to the study conception and design, commented on versions of the manuscript, read, and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.707840/full#supplementary-material

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ORIGINAL RESEARCH
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Effects of Galvanic Vestibular Stimulation on Visual Verticality and Standing Posture Differ Based on the Polarity of the Stimulation and Hemispheric Lesion Side in Patients With Stroke

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Introduction: There is growing evidence supporting the relationship of vertical misperception and poor balance control with asymmetrical standing posture in patients with stroke. Although the vestibular system has been shown to be responsible for vertical misperception and balance disorders, the effect of galvanic vestibular stimulation (GVS) on both vertical misperception and postural asymmetry after stroke remains elusive. The aim of this study was to investigate the effects of GVS on visual verticality and postural asymmetry after stroke and to clarify whether the effects differ depending on the polarity of the stimulation and hemispheric lesion side.

Methods: We measured the subjective visual vertical (SVV) and body weight distribution on each foot in an upright stance in 24 patients with a hemispheric stroke (10 with a left hemisphere lesion and 14 with a right hemisphere lesion) and nine age-matched healthy controls. During the measurements, bipolar GVS (1.5 mA) was applied over the bilateral mastoid processes in three stimulation conditions: contralesional-anodal and ipsilesional-cathodal vestibular stimulation, ipsilesional-anodal and contralesional-cathodal vestibular stimulation, and no stimulation. To examine whether GVS modulates visual verticality and standing posture, SVV and weight-bearing in the three conditions were analyzed.

Results: During no stimulation, the SVV deviated to the contralesional side in patients with a right hemisphere lesion, while more weight-bearing was observed on the ipsilesional limb than on the contralesional limb in both patient groups than in the controls. The SVV was modulated by reversing the polarity of GVS in all the groups when the cathodal stimulus side was either ipsilateral or contralateral to the lesion while the ipsilesional-cathodal vestibular stimulation reduced weight-bearing asymmetry in only the patients with a right hemisphere lesion.

Conclusions: These findings demonstrate that the effects of GVS on the SVV and standing posture differ depending on the polarity of GVS and the hemispheric lesion side. Patients with a right hemisphere lesion have difficulty maintaining their preferred standing posture under visual verticality modulation evoked by GVS. The application of GVS may clarify whether the vestibular system has neural redundancy after stroke to suppress any effects of the stimulation, including modulation of the visual verticality, on balance.

Keywords: cerebrovascular disorder, hemiparesis, postural balance, subjective visual vertical, vestibular control

INTRODUCTION

Postural control to maintain upright posture is impaired in stroke survivors (1). The standing posture of patients with hemiparetic stroke is characterized by more weight-bearing on the ipsilesional limb than on the contralesional limb and by postural instability (2, 3). There is growing evidence that deviation of the subjective vertical is related to asymmetrical standing posture (4, 5), poor balance control (6), and poor recovery of balance in patients with stroke (7). Particularly, in patients with a right hemisphere lesion, poor recovery of the deviation of the subjective visual vertical (SVV), poor postural control, and the presence of visuospatial neglect were closely related to each other (8–11). Based on lesional and imaging studies in patients with peripheral vestibular lesions or stroke, it has been proposed that a dysfunction of the vestibular system can cause misperception of the SVV and postural disorders (12). However, whether manipulation of the vestibular system can change the misperception of the visual vertical and asymmetrical postural control after stroke is unclear.

Galvanic vestibular stimulation (GVS) can increase or decrease the firing rate of vestibular afferents by reversing the polarity; the cathodal galvanic stimulation results in excitation, and the anodal galvanic stimulation results in inhibition of the vestibular afferents through the spike trigger zone of primary afferents (13). GVS has been an easily applicable tool in clinical and therapeutic investigations over the last decade (14). However, only a few studies (15, 16) have investigated the effects of GVS on verticality after stroke, reporting that contralesional-cathodal vestibular stimulation reduced the pathological deviation of the SVV in patients with a right hemisphere stroke who have visuospatial neglect. Although one study observed that cold caloric vestibular stimulation reduced postural asymmetry when patients stood spontaneously (17), no study has clarified the effects of GVS on their preferred weight-bearing asymmetry. Bilateral bipolar GVS, delivered with a cathodal electrode on the mastoid process behind one ear and an anodal electrode on the other ear, produces mediolateral postural sway in healthy subjects (18), which can appear as the sum of the vestibular organs responses (19). Therefore, the potential effects of bipolar GVS on both visual verticality and asymmetrical standing posture in patients with stroke remain elusive. In addition, it is unclear if these potential effects differ depending on the polarity of the stimulation and hemispheric lesion side.

The aim of this study was to investigate the effects of bipolar GVS on visual vertical perception and asymmetrical standing posture after stroke and to clarify whether the effects differ depending on the polarity of the stimulation and hemispheric lesion side.

MATERIALS AND METHODS

Participants

Patients admitted to Tokyo Bay Rehabilitation Hospital, Narashino, Japan, were included in this study if they developed a new single cerebral stroke lesion, understood verbal instructions, and were able to stand independently without the use of any orthosis or aids at the time of the study. Patients were excluded if they had a history of stroke, other neurological diseases, or orthopedic impairments affecting an upright stance. Twenty-four patients, of whom 14 had a right hemisphere stroke lesion and 10 had a left hemisphere stroke lesion, participated in this study. All the patients underwent a conventional rehabilitation program of physical therapy, occupational therapy, and speech therapy if needed. The brains of the patients were scanned using computed tomography or magnetic resonance imaging. The locations of lesions were classified using the Talairach and Tournoux atlas (20). Nine age-matched healthy individuals without any neurological or orthopedic impairments that could affect an upright stance were recruited as controls. The characteristics of the patients are shown in **Table 1** and summarized in **Table 2**. The purpose and procedures of the study were explained to the participants, and they provided their written informed consent. The study protocol was reviewed and approved by the local ethics committee.

Clinical Assessment

We performed neurological examinations before the SVV and standing posture assessment. The following impairments were evaluated: hemiparesis using the summed motor item scores of the Stroke Impairment Assessment Set (SIAS) for the hip, knee, and ankle joint (range of each joint score: 0–5, where 0 indicates no muscle contraction, and 5 indicates limb movement that is as fast as the non-paretic limb) (21, 22), proprioception of the great toe using the position sensation score of the lower limb sensory item of the SIAS (range: 0–3, where 0 indicates no sense of movement on the great toe, and 3 indicates small changes in the position of the great toe that can be perceived as exactly like that of the non-paretic limb), and visuospatial perception using the visuospatial score of the SIAS (range: 0–3, where 0 indicates more than 15 cm deviation from the mid-point when bisecting a 50-cm line, and 3 indicates <2 cm deviation from the mid-point).

TABLE 1 | Characteristics of the patients with stroke.

Patient	Age/Sex	Handedness	Etiology	Lesion		Time from lesion (days)	Stroke Impairment Assessment Set		
				Location	Side		Motor score	Sensory score	Visuospatial score
1	67/m	R	H	Th	R	83	10	3	3
2	72/m	R	I	F/Rc/P/C/T	R	141	0	0	2
3	55/m	R	I	F/Rc/P/C/S/Ic/T	R	157	4	0	1
4	78/f	R	I	C	R	104	7	2	3
5	64/m	R	I	C/F/S	R	97	12	3	2
6	61/m	R	I	C/F/S/T/Rc	R	144	4	2	3
7	74/m	R	H	Th	R	104	12	3	3
8	66/m	R	H	C/Th	R	148	9	2	3
9	65/m	R	I	Ic/C/F	R	99	15	3	3
10	79/m	R	I	C	R	57	10	3	2
11	47/m	R	H	C/S/Ic	R	141	8	1	3
12	70/f	R	I	F/T	R	123	15	3	3
13	70/m	R	I	C	R	76	8	3	3
14	55/m	R	I	C/S	R	40	9	3	3
15	64/m	R	I	C/S	L	113	12	3	3
16	76/m	R	I	F/P	L	163	1	2	n/a
17	54/m	R	H	C/S/Ic	L	80	3	1	3
18	39/m	R	I	F	L	48	15	3	3
19	64/f	R	I	F/T	L	46	15	2	3
20	69/m	R	I	F	L	33	15	3	3
21	64/f	R	H	C/S	L	72	11	3	3
22	64/f	R	H	C/S	L	92	11	3	3
23	42/m	L	H	F/C/S	L	56	12	3	3
24	66/m	L	H	C/S/Ic	L	65	7	3	3

m, male; f, female; R, right; L, left; H, hemorrhagic; I, ischemic; Th, thalamus; F, frontal cortex; Rc, Rolando's cortex; P, parietal cortex; C, corona radiata; T, temporal cortex; S, striatum; Ic, internal capsule; n/a, not available.

Assessment of SVV Perception

The SVV was measured with participants seated on a chair in front of a monitor covered with a cylinder (diameter, 25 cm; height, 25 cm) to eliminate any visual reference cues. The participants could look at the monitor through the cylinder using binoculars. A white line (7×0.5 cm) was projected onto the black background of the monitor in a pseudo-random oblique position. An examiner rotated the line around its center until the participants perceived it as vertical. The rotation angle formed by the subjective vertical and gravitational vertical lines was measured. The direction to the ipsilesional side (for the controls, the right side, i.e., clockwise rotation, was used) was set as positive. The mean SVV value of eight trials in each session was calculated and used for further analysis.

Assessment of Standing Posture

To evaluate the standing posture of the participants, bodyweight distribution was measured by two rectangular force platforms (G-7100; Anima; Tokyo, Japan) placed side by side. The participants stood barefoot with each foot placed on one of the two platforms (heels separated by 9 cm, toe out at 30°), arms relaxed and hanging freely along the body, and eyes opened, looking straight ahead at a fixed target. The participants were instructed to stand for 30 s during a recording of a trial. For three trial recordings, with short resting intervals between the trials, no feedback or information was given to the participants. Postural asymmetry was evaluated using the weight-bearing ratio (WBR), expressed as the percentage of the total body weight loading the ipsilesional side (for the controls, the right side was used). The mean WBR of the three trials in each session was used for further analysis. More than 50% of WBR indicates more weight-bearing on the ipsilesional limb than on the contralesional limb (for the controls, more than 50% on the right side than on the left side).

Galvanic Vestibular Stimulation

Direct current was delivered to a pair of self-adhesive electrodes (35 mm in diameter) made of Ag/AgCl placed over the bilateral mastoid processes using an electrical stimulator (SEN-3301; Nihon Kohden; Tokyo, Japan). The participants received bipolar GVS in three conditions: contralesional-anodal and ipsilesional-cathodal vestibular stimulation (ipsiVS), ipsilesional-anodal and contralesional-cathodal vestibular stimulation (contraVS), and no stimulation. The abbreviations were determined based on the side of the excitation. The participants first performed the tasks

TABLE 2 | Summary of the characteristics of the controls and patients with stroke.

Variables	Controls ($n = 9$)	Stroke		*P*
		Left hemisphere lesion ($n = 10$)	Right hemisphere lesion ($n = 14$)	
Age, years, mean (SD)	60.6 (5.7)	60.2 (11.7)	65.9 (9.1)	0.249*
Sex, male/female, *n*	4/5	7/3	12/2	0.116†
Handedness, right/left, *n*	8/1	8/2	14/0	0.244†
Etiology, hemorrhagic/ischemic, *n*	–	5/5	4/10	0.402†
Time from stroke onset, days, mean (SD)	–	76.8 (38.4)	108.1 (36.0)	0.052‡
Stroke Impairment Assessment Set				
Motor score (range: 0–15), median (IQR)	–	11.5 (8)	9 (5)	0.345§
Sensory score (range: 0–3), median (IQR)	–	3 (1)	3 (1)	0.456§
Visuospatial score (range: 0–3), median (IQR)	–	3 (0)	3 (0)	0.273§

SD, standard deviation; IQR, interquartile range.
**Comparisons using a one-way analysis of variance (ANOVA).*
† Comparisons using the Fisher's exact test.
‡A comparison using the two-sample t-test.
§A comparison using the Wilcoxon rank sum test.

for the SVV and WBR measurements, with electrodes in place without the stimulation. They then performed the tasks again with bipolar GVS. They were blinded to the type of stimulation being delivered. The intensity of the current was gradually increased from zero to 1.5 mA. During the tasks, all participants received 1.5 mA constant bipolar GVS. During the SVV task, a vestibular stimulation was applied in eight trials in a session. During the standing posture task, a vestibular stimulation for 30 s was applied in a trial. The standing posture trial was repeated a total of three times in a session. The SVV task and the standing posture task on the same stimulation were performed in the same day. The time interval between the ipsiVS and the contraVS was 1–3 days. The controls received vestibular stimulation with the same procedures as that of the patients with stroke [left-anodal and right-cathodal vestibular stimulation (rtVS), right-anodal and left-cathodal vestibular stimulation (ltVS), and no stimulation]. For the readability of the names of stimulation conditions, only the cathodal stimulus side has been presented from here.

Statistical Analysis

The normality of the data was examined using the Kolmogorov-Smirnov test. The Bartlett test was performed to examine the equality of variances between the groups. Comparisons of the clinical backgrounds of patients with a left hemisphere lesion and those with a right hemisphere lesion were performed using the Fisher's exact test, the two-sample *t*-test, or the Wilcoxon rank sum test according to the type of variable. The comparisons of the SVV or WBR during no stimulation between the controls and the patients with stroke were performed using a one-way analysis of variance (ANOVA) or the Kruskal-Wallis test according to the normality and equality of variances of the data. The comparisons of the SVV or WBR among the types of bipolar GVS within each group were performed using a one-way ANOVA with repeated measures. The Greenhouse-Geisser correction was used if sphericity was not met. *Post-hoc* pairwise comparison tests were performed using Bonferroni's method. To measure the absolute effect size of bipolar GVS within each group, Cohen's *d*-value between the two stimulation conditions (ipsiVS and contraVS for the patients with stroke; rtVS and ltVS for the controls) was calculated. Classification of the effect size was based on the Cohen's criteria (23). All tests were performed using MATLAB R2020a (Mathworks, Natick, MA, USA) or R version 3.5.3 (2019-03-11) (The R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). A $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the Controls and the Patients With Stroke

The demographics and clinical details of the patients are shown in **Table 1** and summarized in **Table 2**. There were no significant differences in age, sex, and handedness between the groups (all $p > 0.05$). Mean (SD) time from stroke onset in the patients with a right hemisphere lesion was 108.1 (36.0) days and tended to be longer than that in the patients with a left hemisphere lesion (mean [SD], 76.8 [38.4] days; $p = 0.052$). No significant differences in the severity of the motor impairments ($p = 0.345$) and sensory function ($p = 0.456$) of the lower limbs and visuospatial function ($p = 0.273$) were found between patients with a left hemisphere lesion and those with a right hemisphere lesion.

Visual Verticality and Weight-Bearing Without Stimulation in Three Groups

Between-group comparisons of the SVV and WBR during no stimulation are shown in **Table 3**. The SVV was more significantly deviated ($p = 0.048$) to the contralesional side in the patients with a right hemisphere lesion (mean [SD], -1.0° [2.5°]) than in the controls (0.7° [1.0°]), suggesting that the patients with a right hemisphere lesion misperceived the gravitational vertical toward the contralesional side. There was no significant difference in the SVV between the patients

TABLE 3 | Visual verticality and weight-bearing without stimulation in three groups.

Variables	Controls ($n = 9$)	Stroke		*P*	*P*
		Left hemisphere lesion ($n = 10$)	Right hemisphere lesion ($n = 14$)	ANOVA	*Post-hoc*
Subjective visual vertical, degree, mean (SD)	0.7 (1.0)	−0.5 (1.5)	−1.0 (2.5)	0.047	C vs. L: 0.208 C vs. R: 0.048 L vs. R: 0.999
Weight-bearing ratio, %, mean (SD)	46.1 (5.6)	58.0 (8.7)	59.6 (12.2)	0.007	C vs. L: 0.038 C vs. R: 0.009 L vs. R: 0.999

SD, standard deviation; C, controls; L, left hemisphere lesion; R, right hemisphere lesion.

with a left hemisphere lesion (−0.5° [1.5°]) and the controls ($p = 0.208$). Contrarily, asymmetry in weight-bearing was found in the patients with a right hemisphere (mean [SD], 59.6% [12.2%]) and a left hemisphere lesion (58.0% [8.7%]) compared with that found in the controls (46.1% [5.6%]) ($p = 0.009$ and $p = 0.038$, respectively); weight-bearing was more on the ipsilesional (non-paretic) limb than on the contralesional limb. There was no difference in weight-bearing between the patients with a right hemisphere lesion and those with a left hemisphere lesion ($p = 0.999$).

Effects of Bipolar Galvanic Vestibular Stimulation on the Visual Verticality in Three Groups

To examine the within-group differences of bipolar GVS effects on visual verticality, the SVV was compared among the types of stimulation in each group (**Figure 1**). There were significant differences in the SVV among the types of stimulation in all the groups: controls [$F_{(2, 16)} = 12.49$, $p < 0.001$], patients with a left hemisphere lesion [$F_{(2, 18)} = 10.48$, $p < 0.001$], and patients with a right hemisphere lesion [$F_{(2, 26)} = 6.92$, $p = 0.014$]. *Post-hoc* analyses revealed that the SVV during the rtVS was more significantly deviated to the left side compared to the SVV during no stimulation and the ltVS in the controls ($p = 0.008$ and $p = 0.018$, respectively) (**Figure 1**; left). Similarly, the SVV more significantly deviated to the contralesional side during the ipsiVS than during the contraVS in patients with both left hemisphere lesion or right hemisphere lesion ($p = 0.008$ and $p = 0.048$, respectively) (**Figure 1**; middle and right). The effect size was large in the controls (Cohen's $d = 1.23$) and in the patients with a left hemisphere lesion (Cohen's $d = 1.28$). In addition, the effect size was almost large in the patients with a right hemisphere lesion (Cohen's $d = 0.74$).

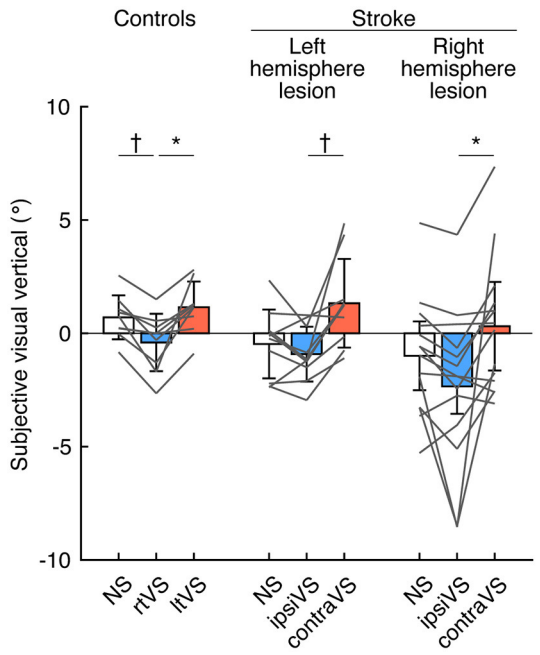

FIGURE 1 | Effects of bipolar galvanic vestibular stimulation on the visual verticality in the controls, patients with a left hemisphere lesion, and patients with a right hemisphere lesion. Each color bar indicates the mean of the subjective visual vertical (SVV) during each type of bipolar galvanic vestibular stimulation (GVS). Positive values indicate rotations to the right side (for the controls) and the ipsilesional side (for the patients with stroke). Each error bar indicates a standard deviation. Each gray line indicates changes in the SVV during each type of bipolar GVS in each participant. NS, no stimulation; rtVS, left-anodal and right-cathodal vestibular stimulation; ltVS, right-anodal and left-cathodal vestibular stimulation; ipsiVS, contralesional-anodal and ipsilesional-cathodal vestibular stimulation; contraVS, ipsilesional-anodal and contralesional-cathodal vestibular stimulation. $^{*}p < 0.05$; $^{\dagger}p < 0.01$.

Effects of Bipolar Galvanic Vestibular Stimulation on Weight-Bearing in Three Groups

To examine the within-group differences of bipolar GVS effects on standing posture, the WBR was compared among the types of stimulation in each group (**Figure 2**). There were no differences in weight-bearing among the types of stimulation in the controls [$F_{(2, 16)} = 1.96$, $p = 0.173$] and the patients with a left hemisphere lesion [$F_{(2, 18)} = 1.55$, $p = 0.245$] (**Figure 2**; left and middle). The effect size was small in the controls (Cohen's $d = 0.32$) and in the patients with a left hemisphere lesion (Cohen's $d = 0.41$). However, there was a significant difference in weight-bearing in the patients with a right hemisphere lesion [$F_{(2, 26)} = 6.36$, $p = 0.005$]; the ipsiVS significantly reduced the asymmetry in weight-bearing compared with that by no stimulation and the contraVS

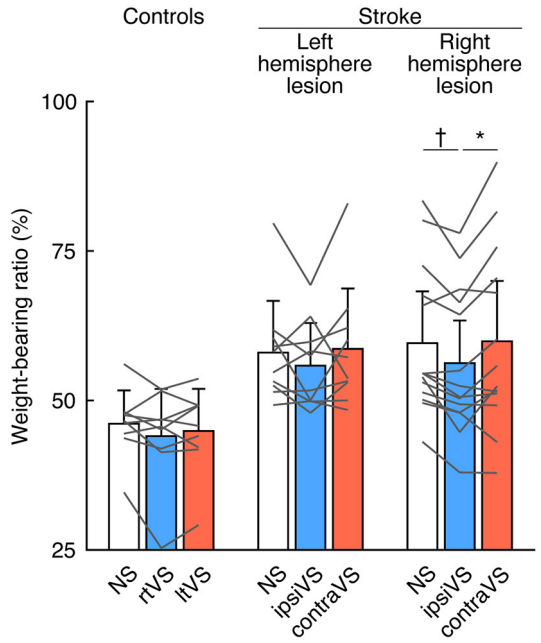

FIGURE 2 | Effects of bipolar galvanic vestibular stimulation on weight-bearing in the controls, patients with a left hemisphere lesion, and patients with a right hemisphere lesion. Each color bar indicates the mean weight-bearing ratio (WBR) during each type of bipolar galvanic vestibular stimulation (GVS). More than 50% of WBR indicates more weight-bearing on the right side (for the controls) and the ipsilesional side (for the patients with stroke). Each error bar indicates a standard deviation. Each gray line indicates changes in the WBR during each type of bipolar GVS in each participant. NS, no stimulation; rtVS, left-anodal and right-cathodal vestibular stimulation; ltVS, right-anodal and left-cathodal vestibular stimulation; ipsiVS, contralesional-anodal and ipsilesional-cathodal vestibular stimulation; contraVS, ipsilesional-anodal and contralesional-cathodal vestibular stimulation. $^{*}p < 0.05$; $^{\dagger}p < 0.01$.

($p = 0.007$ and $p = 0.039$, respectively) (**Figure 2**; right). The effect size was almost large in the patients with a right hemisphere lesion (Cohen's $d = 0.77$).

DISCUSSION

We examined the effects of bipolar GVS on both visual verticality and standing posture in patients with hemispheric stroke, and whether the effects differ depending on the polarity of the stimulation and hemispheric lesion side. We obtained the following results: (i) modulation of the visual verticality by reversing the polarity of the stimulation in all the groups when the cathodal stimulus side was either ipsilateral or contralateral to the lesion and (ii) a shift of weight-bearing from the ipsilesional limb to the contralesional limb; reduction of weight-bearing asymmetry during the ipsilesional-cathodal vestibular stimulation compared to no stimulation and the contralesional-cathodal vestibular stimulation in the patients with a right hemisphere stroke only. The effects of bipolar GVS on visual verticality were consistent among the groups; however, the effects of bipolar GVS on standing posture were dependent on the stimulus side and hemispheric lesion side. Therefore, we conclude that the effects of bipolar GVS on visual verticality and standing posture differ depending on the polarity and hemispheric lesion side.

In general, the SVV is measured when testing the static otolith function. The SVV often deviates toward the contralesional side in patients with an acute right hemisphere stroke [mean deviation, −5.2° (15); −8.8° (24); −2.2° (10)], which is closely associated with visuospatial neglect, presenting contribution of the higher visuospatial cognition function to the SVV perception. In the present study, contralesional deviation of the SVV during no stimulation in the patients with a right hemisphere lesion was relatively small (mean [SD], −1.0° [2.5°]) (**Table 3**) compared to that in previous studies (10, 15, 24), and most of the patients showed few symptoms of visuospatial neglect on the line bisection test (**Tables 1**, **2**). The patients included in the present study needed to stand independently without any support. This inclusion criterion induced a sampling bias of patients who had a longer time from stroke onset at the time of the study. None of the patients had an acute stroke, and the time from lesion tended to be longer in the patients with a right hemisphere lesion than in the patients with a left hemisphere lesion. Misperception of SVV often decreases within weeks from the onset of stroke (25).

Contralesional-cathodal vestibular stimulation can reduce the pathological deviation of the SVV in patients with a right hemisphere stroke who have visuospatial neglect (15, 16). In the present study, although there was a trend toward a decrease in SVV deviation with contralesional-cathodal stimulation compared to no stimulation in the patients with a right hemisphere lesion, the differences did not reach statistical significance (**Figure 1**). This finding may be attributed to the fact described above that the patients in the present study had few symptoms of visuospatial neglect, and thus the deviation of SVV without stimulation was small. Interestingly, the effects of bipolar GVS on SVV when reversing the polarity of the stimulation were similar in all groups: controls, the patients with a left hemisphere lesion, and the patients with a right hemisphere lesion (**Figure 1**). The application of bipolar GVS was highly likely to result in deviation of the visual vertical away from the cathodal stimulus side (toward the anodal stimulus side), as previously reported in healthy participants (26). The common finding observed in all groups indicated high susceptibility to vestibular stimulation for the perception of the visual vertical regardless of the presence of hemispheric strokes, suggesting a direct link and/or overlap of the neural substrates for processing the visual vertical and mediating a vestibular signal by the stimulation. A functional magnetic resonance imaging (fMRI) study has shown that the bilateral temporo-occipital and parieto-occipital cortical networks associated with cerebellar and brainstem areas were involved in the perception of the visual vertical (27), which was consistent with neuroanatomical studies in patients with stroke (28–30). Recently, some areas in this network have been shown to be involved in vestibular information processing (31).

GVS was used to measure short-latency balance responses in patients with middle cerebral artery stroke standing with their eyes closed (32). Imbalance in activities of the bilateral vestibular afferents evoked by GVS produces a sensation

of head movement and compensatory vestibulo-ocular and vestibulospinal reflexes (19). In the present study, vestibular stimulation lasted for 30 s, and the patients were required to stand with their eyes open for the stimulation period. Since sensory reweighting involves control of a stable stance in various environments (33), the procedures in the present study allowed us to investigate the ability to adjust balance control against imbalance in the bilateral vestibular afferents using other sensory modalities, including visual inputs. In contrast to the findings on modulation of visual verticality, where the effect of reversing the polarity of bipolar GVS on SVV was similar in all the groups, asymmetry in the standing posture was significantly reduced in only the patients with a right hemisphere lesion (**Figure 2**), even though the weight-bearing asymmetry during no stimulation did not differ between patients with lesions in opposite hemispheric sides (**Table 3**). These findings reveal that it is difficult for patients with right brain damage to maintain their preferred standing posture under modulation of visual verticality evoked by bipolar GVS, unlike patients with left brain damage or healthy controls. As it has been reported that patients with peripheral vestibular dysfunction showed dramatically inability to appropriately suppress the influence of visual and proprioceptive inputs (34), the vestibular function to appropriately suppress other sensory inputs might deteriorate after right brain damage. The difference in postural responses between the lesion sides suggests that the right hemisphere is likely to have a dominant role in the vestibular inhibitory control of the influence of visual verticality on standing posture, which is consistent with the dominance of the non-dominant hemisphere for vestibular function (35). For clinical measurements, the application of bipolar GVS can clarify whether the vestibular system has neural redundancy after stroke to suppress any effects of the stimulation, including modulation of the visual verticality, on balance. The response of the standing posture to bipolar GVS in the present study was similar to that observed in the previous study using caloric vestibular stimulation, showing that cold caloric vestibular stimulation on the contralesional side reduced postural asymmetry in patients with stroke, predominantly in those with right hemisphere lesions (17), although the mechanism of caloric vestibular stimulation differs from that of GVS. For the clinical use of vestibular stimulation, GVS intensity and duration would be easier to control than caloric vestibular stimulation, reducing adverse effects.

Regarding the stimulus side, a previous study (32) did not observe any polarity-dependent effects of GVS on sway response when patients with middle cerebral artery stroke stood with their two limbs equally loaded and their eyes closed. Contrary to their study (32), we observed polarity-dependent effects on standing posture in patients with a right hemisphere stroke. The ipsilesional-cathodal vestibular stimulation, but not the contralesional-cathodal vestibular stimulation, reduced weight-bearing asymmetry (**Figure 2**). Since patients always sway away from the cathodal side (32), and the weight-bearing on the ipsilesional limb during no stimulation can decrease to achieve an equilibrium with weight-bearing on the bilateral limbs (**Table 3**), the relationship between the direction of sway evoked by ipsilesional-cathodal vestibular stimulation and the biased distribution of weight-bearing on the two limbs during no stimulation may be important in understanding the stronger effects observed during the ipsilesional-cathodal vestibular stimulation compared to that observed during the contralesional-cathodal vestibular stimulation. The responses of the standing posture to the stimuli were probably related to the responses of the hemispheres to the stimuli, as vestibular information processing requires multisensory signal integration occurring at structures from the vestibular nuclei to the cortices via thalamic relay (36–46) and middle cerebral artery stroke may result in disruption of the cortico-bulbar projection involving the vestibular control of balance (32). By analyzing fMRI in healthy individuals receiving GVS, more pronounced activation patterns were found in the right hemisphere irrespective of the stimulus side (46, 47). In addition, there were different activation patterns between the hemispheres when GVS with reversed polarity was applied; the right-cathodal vestibular stimulation (the ipsilesional-cathodal vestibular stimulation in the patients with a right hemisphere lesion) induced increased neural activity compared to no stimulation in the cortices involving vestibular processing in only the right hemisphere, whereas the left-cathodal vestibular stimulation (the contralesional-cathodal vestibular stimulation in the patients with a right hemisphere lesion) led to increased neural activity in these areas bilaterally (46, 47). These patterns were considered to arise from two determinants: first, the dominance of the right hemisphere for vestibular processing and second, the stimulated side with the stronger activation ipsilateral to the stimulation (35). In the present study, the two determinants might be responsible for the polarity-dependent effects of bipolar GVS on weight-bearing asymmetry in the patients with a right hemisphere lesion because the right-cathodal vestibular stimulation (the ipsilesional-cathodal vestibular stimulation in the patients with a right hemisphere lesion) can affect vestibular information processing occurring dominantly in the right hemisphere more than in the left-cathodal vestibular stimulation (the contralesional-cathodal vestibular stimulation in the patients with a right hemisphere lesion).

Neuromodulation evoked by vestibular stimulation is essential to understand the responses of visual verticality and standing posture in patients with stroke. Signals evoked by the stimulation are transmitted through the vestibular afferents to the vestibular nuclei. The vestibular nuclei send projections to the cerebellum and are critically involved in the vestibulo-ocular reflex or the vestibulocollic and vestibulospinal reflexes. Furthermore, the vestibular nuclei integrate vestibular, cerebellar, visual, and somatosensory signals (44) and project to the thalamic nuclei associated with other modalities where vestibular information processing is considered to occur as well (48). The parieto-insular vestibular cortex receives its main thalamic input in non-human primates (41) and has neuronal responses to multi-modal stimulation (37, 38), while the human homolog of the parieto-insular vestibular cortex comprises multiple areas (45) and its location is still inconclusive. Results of human imaging studies pointed to a distributed cortical network revealed by GVS, including regions in the parietal,

frontal, temporal, and insular cortices (36, 46, 47). In the present study, bipolar GVS signals mediated by vestibular pathways modulated visual verticality in all participants (**Figure 1**), while the signals modulated standing posture in only the patients with a right hemisphere lesion (**Figure 2**). Therefore, the right hemispheric stroke (**Table 1**) is likely to directly or indirectly interrupt bipolar GVS signal integration with other modalities occurring at the multi-level vestibular network to maintain stable stance under modulation of visual verticality. We emphasize that bipolar GVS can clarify the function of the vestibular network in patients with stroke to suppress and integrate unexpected neuromodulation evoked by it, which cannot be uncovered by just identifying the lesion location or observing the neurological symptoms.

There are some limitations of the present study. First, we did not test whether our sample size of 33 participants was sufficient to answer the study questions. Instead, we calculated the absolute effect size between the two stimulation conditions in each group (see Materials and Methods). The effect size on SVV was almost large in the patients with a right hemisphere lesion and was large in the patients with a left hemisphere lesion and in the controls. In contrast, the effect size on standing posture was almost large in only the patients with a right hemisphere lesion; it was small in the patients with a left hemisphere lesion and in the controls. These findings support our conclusions irrespective of the sample size. Second, we did not examine the effects of bipolar GVS on SVV and standing posture in relation to brain lesions, although information regarding the stroke area is provided in **Table 1**. A further study with detailed imaging analyses of a large number of samples will clarify the neural correlates of visual vertical, postural balance, and vestibular function. Third, we did not assess the semicircular canal function and the otolith function in detail. GVS has an influence on these functions, therefore, we cannot exclude the possibility that the conditions of these functions affected our findings. Finally, we focused on the effects of bipolar GVS on only the visual verticality and weight-bearing. It is worth noting that previous studies have reported that egocentric vertical perception (the longitudinal body axis), but not the allocentric vertical perception (SVV), is related to weight-bearing asymmetry after adjusting for motor and sensory functions (4, 5). Furthermore, compared to the deviation of the visual vertical, the deviation of the postural vertical was more closely related to postural disorders (49). Further studies are required to explore the effects of GVS on egocentric vertical and the relationship between egocentric/allocentric vertical and weight-bearing asymmetry. This study could not address the causal relationship between verticality and standing posture. However, we can state that there is a dissociation of responses of the SVV and weight-bearing to bipolar GVS based on the polarity of the stimulation and hemispheric lesion side. This might be a key to understanding the neural mechanisms underlying balance disorders after stroke.

CONCLUSIONS

We demonstrated that manipulation of the vestibular system using bipolar GVS has an influence on visual vertical perception and standing posture depending on the polarity of the stimulation and hemispheric lesion side. The response of the standing posture under the modulation of visual verticality may represent an intrinsic characteristic of patients with right brain damage who have reduced neural redundancy in the vestibular inhibitory system. This will improve the understanding of the neural mechanisms that underlie balance disorders after stroke and the development of effective therapy and rehabilitation in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Tokyo Bay Rehabilitation Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TT designed the research, performed experiments, and analyzed data. TT, KK, and YO discussed the results. TT and YO wrote the paper. All authors contributed to the article and approved the submitted version.

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Trunk Muscle Activation Patterns During Standing Turns in Patients With Stroke: An Electromyographic Analysis

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Recent evidence indicates that turning difficulty may correlate with trunk control; however, surface electromyography has not been used to explore trunk muscle activity during turning after stroke. This study investigated trunk muscle activation patterns during standing turns in healthy controls (HCs) and patients with stroke with turning difficulty (TD) and no TD (NTD). The participants with stroke were divided into two groups according to the 180° turning duration and number of steps to determine the presence of TD. The activation patterns of the bilateral external oblique and erector spinae muscles of all the participants were recorded during 90° standing turns. A total of 14 HCs, 14 patients with TD, and 14 patients with NTD were recruited. The duration and number of steps in the turning of the TD group were greater than those of the HCs, independent of the turning direction. However, the NTD group had a significantly longer turning duration than did the HC group only toward the paretic side. Their performance was similar when turning toward the non-paretic side; this result is consistent with electromyographic findings. Both TD and NTD groups demonstrated increased amplitudes of trunk muscles compared with the HC groups. Their trunk muscles failed to maintain consistent amplitudes during the entire movement of standing turns in the direction that they required more time or steps to turn toward (i.e., turning in either direction for the TD group and turning toward the paretic side for the NTD group). Patients with stroke had augmented activation of trunk muscles during turning. When patients with TD turned toward either direction and when patients with NTD turned toward the paretic side, the flexible adaptations and selective actions of trunk muscles observed in the HCs were absent. Such distinct activation patterns during turning may contribute to poor turning performance and elevate the risk of falling. Our findings provide insights into the contribution and importance of trunk muscles during turning and the association with TD after stroke. These findings may help guide the development of more effective rehabilitation therapies that target specific muscles for those with TD.

Keywords: stroke, turning, electromyography, trunk muscles, muscle activation patterns

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INTRODUCTION

More than 40% of walking involves turning in daily life (1); however, turning frequently results in falls for patients with stroke (2). Patients with stroke require more time and additional steps (3) to turn in place (4, 5) or while walking (3, 6) compared with healthy adults, indicating that these patients experience difficulty in turning after stroke. Recent evidence indicates that the turning difficulty (TD) may be correlated with trunk control capacity (7, 8).

Lamontagne and colleagues employed motion analysis and observed that eye, head, and trunk rotations during walking turns in patients with subacute stroke were en bloc, and the patients did not exhibit intersegmental coordination (9). The simultaneous rotation of body segments may indicate axial or trunk instability during turning. By employing the Functional Assessment for Control of Trunk, Kobayashi and colleagues found that the time and number of steps required during 360° turning in place were strongly associated with trunk control (7). Similarly, Liang and colleagues reported that the duration of 180° walking turns was significantly associated with trunk control, as determined using the Trunk Impairment Scale (TIS) (8). In addition, our previous study indicated that turning toward the paretic side was associated with trunk flexion and rotation, trunk flexor strength, dynamic sitting balance, and trunk movement coordination (10). These findings highlight the importance of trunk function in turning performance and suggest that trunk instability contributes to the TD in individuals with stroke.

Compared with healthy adults, patients with stroke exhibited trunk muscle weakness including in the flexors, extensors, rotators, and lateral flexors of the trunk (11). Magnetic resonance imaging (12) and computer tomography (13) studies have revealed that the cross-sectional areas of trunk muscles were smaller after stroke than in healthy adults, indicating trunk paralysis. Weakness and spasticity are main motor impairments after stroke. Muscle weakness is primarily a result of damage to motor cortices and their descending corticospinal tract while medial reticulospinal tract hyperexcitability appears to be the most likely mechanism related to spasticity (14). In addition to trunk paralysis, trunk muscle spasticity, as well as limited trunk flexibility and abnormal position sense can further affect trunk function and motor control, as indicated by the dynamic balance subtest and the trunk rotation movement measure of the TIS (15).

The trunk contains the proximal and axial parts of the body, and its main function is to keep the body upright and maintain stability when performing static or dynamic activities. However, electromyography findings revealed that the trunk muscles of patients with stroke had slower onset latency and lower muscle amplitudes while standing and raising their arms (16). In addition, lower symmetric indexes in the internal oblique and rectus abdominal muscles during trunk flexion and in the erector spine muscles during trunk extension were observed (17), indicating trunk impairment after stroke. Furthermore, deficits in trunk muscles were significantly associated with balance problems, gait dysfunction, mobility impairment, dependency in the activities of daily living, and increased risk of falls (18). Although poor electromyographic performance of the trunk may be correlated with TD in patients with stroke, this correlation has not yet been investigated. Therefore, the current study evaluated the trunk muscle activation pattern during standing turns in healthy adults and patients with stroke with and without TD.

MATERIALS AND METHODS

Participants

This prospective, cross-sectional study recruited patients with chronic stroke from the outpatient clinic of the department of physical and rehabilitation medicine of a regional hospital in New Taipei City, Taiwan, from June to November 2020. The study followed Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The inclusion criteria were as follows: (1) survivors of a single and unilateral stroke with hemiparesis experienced for at least 6 months prior to participation in the study, (2) ability to walk independently over a distance of 10 m without requiring walking aids or orthoses, and (3) ability to provide informed consent and follow instructions. The exclusion criteria were (1) having an additional musculoskeletal condition or comorbid disability that could affect the assessment or (2) experiencing cognitive problems that were defined as having a Mini-Mental State Examination (MMSE) score of <24 or aphasia that could prevent patients from following instructions. Patients who received medical treatment and underwent rehabilitation were considered to have stable stroke conditions throughout the course of the study. Healthy controls (HCs) were recruited from the local community as the control group and were excluded if they had any neurological or musculoskeletal condition that could affect normal balance or the assessment procedure. All eligible participants provided written informed consent prior to participation in the study. This study was approved by the Institutional Review Board of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (Reference No. 08-XD-051) and registered on clinical.trials.gov (NCT04668573).

Data Collection

Demographic data were recorded, namely age, sex, height, weight, and body mass index. Information regarding the poststroke duration, paretic side, lesion type, history of falls in the previous year, assistance devices, and rehabilitation frequency of patients with stroke was obtained, and their physical characteristics such as general cognitive function, lower-limb motor function, and functional mobility were evaluated. Subsequently, the 180° walking-turn performance of the patients with stroke was assessed, which were used to divide them into two groups according to the suggestion of Thigpen et al. (19). Finally, the activation pattern of the trunk muscles of the participants was evaluated during 90° standing turns. Taking one step to complete a 90° turn was chosen because one step made the beginning and end of turning easier to define and the patients with stroke experienced difficulty in completing a turn with a greater angle in one step, such as a 180° turn. All assessments were individually completed within 1 h by a well-trained research assistant.

Measurements

General Cognitive Function

General cognitive function was evaluated using the MMSE (20), which assesses orientation to time and place, word registration, attention, calculation, recent word recall, language, and visual construction. Cognitive impairment was defined as an MMSE score of $\leq$24 points.

Lower-Limb Motor Function

Lower-limb motor function was defined according to the seven Brunnstrom classification stages: (1) flaccidity, (2) appearance of spasticity, (3) increased spasticity, (4) decreased spasticity, (5) complex movement combinations, (6) spasticity disappearance, and (7) return of normal function (21).

Functional Mobility

Functional mobility was assessed as balance, mobility, and walking function.

Functional Reach Test

Balance was assessed using the functional reach test (22). The participants stood close to the wall with their feet and shoulder width apart and non-paretic arms raised to 90° flexion. They reached as far forward as possible while maintaining their balance. A longer distance (cm) represented better balance.

Timed Up and Go Test

Mobility was examined using the timed up and go test (TUG) (23). The participants were instructed to stand up from a chair, walk 3 m, turn around, walk back to the chair, and sit down. The time (s) required to complete the task was recorded. Longer time was representative of a lower level of mobility.

Ten-Meter Walk Test

Walking function was measured using the 10-m walk test (24). The participants were asked to walk straight along a 14-m walkway at their fastest walking pace. The initial and final 2 m of the walkway were used for acceleration and deceleration. Only the time spent in the middle 10 m was recorded, and walking velocity (m/s) was calculated by dividing the walking distance by walking time. A faster walking velocity indicated better walking function.

Turning Performance

The participants were instructed to perform the TUG for the 180° walking-turn task. They were asked to rise from a chair, walk straight for 3 m, exceed a line, turn around (180°), walk back to the chair, and return to a seated position at a self-selected speed. The participants performed the task in each direction only once before one practice trial. We noted the direction in which the participants chose to turn and asked them to repeat the procedure in the opposite direction.

Turning performance was measured using APDM Opal wireless sensors and Mobility Lab software (APDM, Portland, OR, USA). The Opal is a lightweight (22 g) inertial sensor with a battery life of 16 h and 8 GB of storage. Three Opal inertial sensors were firmly attached to the participants by using elastic Velcro bands, with one on the middle lower back (5th lumbar vertebra process) and one on the top of each foot. Data were recorded at 128 Hz, stored in the internal memory of the Opal sensor, and uploaded later to a laptop computer. The duration (s) and number of steps (n) of the 180° turns were recorded. The horizontal rotational rate of the lumbar sensor was employed with a minimum of 45° accompanied with at least one right and one left foot stepping to detect turns (25, 26). The patients with stroke who required more than 3 s or five steps to complete a 180° walking turn were seen as poor turning performance and were included into the TD stroke group (19), whereas the remaining patients were seen as better turning performance and were included into the no TD (NTD) stroke group.

Muscle Activation Patterns

Surface electromyography (EMG) data were obtained using a TeleMyo Mini DTS System (Noraxon USA, Inc., USA), with a sampling rate of 1,500 Hz. The skin was shaved and cleaned with alcohol swabs before applying disposable and self-adhesive Ag/AgCl snap surface electrodes (Noraxon USA, Inc., USA) for recording EMG data. The electrodes were positioned with an interelectrode distance of 2 cm. Due to technological restrictions, surface EMG signals were collected bilaterally (right and left) from the following trunk muscles and locations: external oblique (EO), ∼15 cm lateral to the umbilicus, and erector spinae (ES), ∼1 cm lateral to the L5 spinous process (27) (**Figure 1**). These muscles were chosen because they participate in the movement of trunk rotation (28). Because generating the maximal voluntary isometric contraction values in prone, supine, or side lying positions is difficult for patients with stroke (29, 30), normalization was performed using percentage reference voluntary contraction (RVCs). The RVCs of the trunk muscles for all the participants were tested in a sitting position on a bench with their legs bent and feet strapped down with a belt (31). One of the researchers provided a matching resistance to the participants during the maximal exertions to restrain their movement. To measure the RVC in the EO, the participants attempted to flex the upper trunk in the sagittal plane while their sternal notch was manually braced by the researcher. To measure the RVC in the ES, the participants attempted to extend the upper trunk in the sagittal plane, whereas their first thoracic vertebra spinous process was manually braced by the researcher. Each task was performed three times, and the resistance was applied for 6 s.

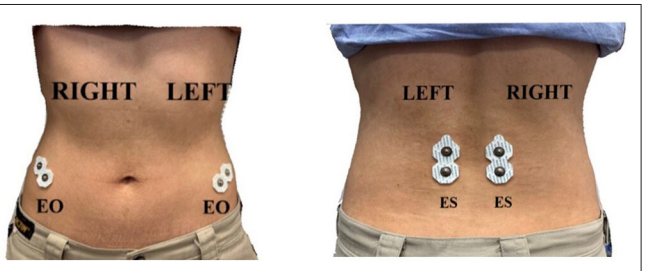

FIGURE 1 | Placement of surface EMG electrodes. EO, external oblique muscle; ES, erector spinae.

The participants were asked to stand with feet and shoulder width apart and arms at their sides and then to take one step to complete a standing 90° turn (standing and then turning to face the target) toward the paretic and non-paretic sides at a self-selected pace, corresponding to non-dominant and dominant sides, respectively, in HCs, in a counterbalanced order among participants. The dominant side of the HCs was determined by the side of the writing hand. Prior to testing, the researcher demonstrated the procedure to the participants. All the participants performed a practice trial to familiarize themselves with the test before three actual trials. The participants wore their regular footwear during testing. The EMG data of the four trunk muscles were recorded during turning and then averaged. We placed two accelerometers in bilateral shoe heels, the position corresponding to the calcaneus tuberosities, to determine the beginning and end of turning. Signals from trunk EMG and the accelerometer were simultaneously input into the software package for processing through a PC interface receiver (MyoResearch XP master, version 1.07.01, Noraxon USA, Inc., USA). All EMG data were bandpass filtered (10–500 Hz), full-wave rectified, and smoothed every 50 ms by using the root mean square. Muscle activity was normalized by RVC and is presented as the percent RVC.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences, version 19.0 (SPSS, Chicago, IL, USA). The statistical significance level was set at $p < 0.05$. Due to non-normally distributed data examined by the Shapiro–Wilk test, non-parametric tests were applied in the study. Data are presented as the number (percentage) and median (interquartile range). The Mann–Whitney U test or the Kruskal–Wallis test for continuous variables and the chi-squared test for categorical variables were applied to compare demographic data among the groups. The duration and number of steps in all turning tasks among the groups (TD stroke, NTD stroke, and HC) were analyzed using the Kruskal–Wallis test with *post-hoc* Mann–Whitney U test for between-group comparisons and the Wilcoxon signed-rank test for turning direction comparisons within groups. The Kruskal–Wallis test with *post-hoc* Mann–Whitney U test and the Friedman test with *post-hoc* Wilcoxon signed-rank test were used to compare the amplitude of trunk muscles between the groups and within the groups, respectively. In addition, we pooled all EMG data into SigmaPlot software (version 10.0, Systat Software Inc, San Jose City, CA, USA), which allowed us to create schematics that provided a visual comparison of changes in trunk muscle amplitudes over time during standing turns.

RESULTS

A total of 42 participants (14 HCs, 14 TD stroke, and 14 NTD stroke patients) were recruited (**Table 1**). No difference was observed among the groups in the demographic characteristics except for sex ($X^2 = 7.000$, $p = 0.03$). The number of male patients with stroke was significantly higher than that of male HCs. The TD and NTD groups had similar ratios of paretic (P) side and lesion type, poststroke duration, cognitive function, lower-limb motor function, functional mobility, history of falls, use of assistance devices, and rehabilitation frequency.

Turning Duration and Steps

The TD stroke group exhibited a significantly longer duration and more number of steps than did the NTD stroke and HC groups when turning toward either side. The NTD group had a significantly longer turning duration toward the P side than did the HC group; however, the performance of the NTD group was similar to that of the HC group when turning toward the other side (**Table 2**). In terms of the turning direction, the TD stroke and HC groups exhibited similar turning performance toward either side, whereas the NTD stroke group used significantly more steps turning toward the P side than toward the non-paretic (NP) side ($p = 0.036$).

Muscle Activation Patterns in the Process of Turning Mobility

The muscle activation patterns of the groups during turning toward P and NP sides were compared visually by means of line graphs (**Figure 2**). The HC group exhibited stable and consistent contractions with an amplitude of approximately 20% RVC among the four trunk muscles throughout the entire movement of standing turns regardless of the turning direction. The amplitude in the ES of the turning side was increased in the beginning of turns but returned to the baseline after the midpoint. However, the TD group demonstrated gradually increased amplitudes in all the trunk muscles throughout the entire movement of standing turns, especially for bilateral ES muscles. The amplitude increased from 20 to 80% RVC of bilateral ES. A similar pattern was observed in the NTD group with the amplitude increasing from 20 to 60% RVC when turning toward the P side. The ES of the turning side was increased and then decreased afterward in the NTD stroke group when turning toward the NP side.

Muscle Activation Patterns When Turning Toward the Paretic Side

The results of between-group analysis indicated significantly different muscle amplitudes in EO-P muscles [X_F^2 (2) = 6.731, $p = 0.035$] among the groups, with a higher amplitude in the TD group than in the HC group ($p = 0.006$). A significant difference was noted in ES-NP [X_F^2 (2) = 7.893, $p = 0.019$] muscle activity among the groups, with a higher amplitude in the TD ($p = 0.004$) and NTD ($p = 0.041$) groups than in the HC group. Significant differences in ES-P [X_F^2 (2) = 10.435, $p = 0.005$] muscle amplitudes were observed among the groups, with a higher amplitude in the TD group than in the HC group ($p = 0.001$). However, the amplitude of EO-NP among the groups was similar.

The findings of within-group analysis indicated that both the TD [X_F^2 (3) = 11.571, $p = 0.009$] and NTD [X_F^2 (3) = 13.886, $p = 0.003$] groups had significantly different levels of muscle amplitudes among the trunk muscles, whereas the HC group had similar levels of amplitude among the trunk muscles. Further analysis demonstrated that the TD group had a higher amplitude

TABLE 1 | Demographic and physical characteristics of participants with stroke and healthy controls.

	TD stroke ($n = 14$)	NTD stroke ($n = 14$)	Healthy controls ($n = 14$)	*p* value
Sex (male, n, %)	10 (71%)	10 (71%)	4 (29%)	**0.030**
Age (years)	55 (50–68)	55 (53–67)	62 (60–65)	0.275
Height (cm)	170 (158–174)	167 (159–174)	160 (157–170)	0.205
Weight (kg)	73 (65–81)	52 (68–76)	60 (53–76)	0.202
Body mass index (kg/m^2)	26.0 (22.8–29.4)	23.5 (19.8–25.3)	24.3 (20.9–26.4)	0.400
Paretic side (left, n, %)	8 (57%)	8 (57%)		1.000
Post-stroke duration (month)	34 (14–140)	54 (26–109)		0.401
Lesion type (infarction, n, %)	4 (29%)	7 (50%)		0.440
Mini-mental state examination score (/30)	28 (25–29)	27 (25–28)		0.401
Brunnstrom stage-Leg (/6)	4 (4–4)	4 (3–5)		0.734
Functional reach test (cm)	18.0 (9.0–20.5)	18.0 (16.0–24.8)		0.306
Timed up and go test (s)	25.6 (17.3–36.7)	24.4 (16.1–24.8)		0.635
10-meter walk test (m/s)	0.6 (0.3–0.7)	0.6 (0.4–0.8)		0.667
History of falls (n, %)	11 (79%)	7 (50%)		0.236
Use of assistant devices (n, %)	12 (86%)	8 (57%)		0.209
Rehabilitation (hours per week)	3.5 (2.0–6.0)	3.5 (2.0–6.0)		0.839

Values are presented as the number (percentage) and median (interquartile range, IQR). TD , turning difficulty; NTD , no turning difficulty. Significant difference was set as $p < 0.05$ and highlighted in bold.

TABLE 2 | Duration (s) and number of steps (n) for stroke participants with and without turning difficulty and healthy controls during 90° standing turns.

	TD stroke	NTD stroke	HC	X^2	*p* value	*post-hoc* analysis	p^1	p^2	p^3
Turning toward paretic side									
Duration (s)	3.2 (2.9–3.4)	2.4 (2.0–2.7)	2.0 (1.8–2.2)	19.008	**<0.001**	TD > NTD > HC	**<0.001**	**0.001**	**0.014**
Number of steps (n)	4.5 (4.0–5.4)	3.0 (2.9–4.0)	3.8 (3.0–4.5)	14.695	**0.001**	TD > NTD	0.116	**0.017**	0.114
Turning toward non-paretic side									
Duration (s)	3.0 (2.7–3.6)	2.0 (1.7–2.7)	1.9 (1.8–2.1)	7.315	**0.026**	TD > NTD = HC	**<0.001**	**0.002**	0.667
Number of steps (n)	5.0 (3.5–5.5)	2.9 (2.0–3.6)	3.5 (3.0–4.0)	12.820	**0.002**	TD> NTD = HC	**0.009**	**0.001**	0.164

Values are presented as median and interquartile range (IQR). Significant difference was set as $p < 0.05$ and highlighted in bold.
HC , healthy controls; TD , turning difficulty; NTD , no turning difficulty.
p^1 = p value for difference between TD stroke and HC groups.
p^2 = p value for difference between TD and NTD stroke groups.
p^3 = p value for difference between NTD stroke and HC groups.

in ES-P than in EO-NP ($p = 0.005$) and EO-P ($p = 0.019$) muscles, whereas the NTD group had a higher amplitude in ES-P and ES-NP compared with EO-NP ($p = 0.022$ and $p = 0.005$, respectively) and EO-P ($p = 0.004$ and $p = 0.006$) muscles (**Figure 3**).

Muscle Activation Patterns When Turning Toward the Non-paretic Side

The results of between-group analysis revealed significantly different muscle amplitudes in EO-P muscles [X_F^2 (2) = 6.297, $p = 0.043$] among the groups, with a higher amplitude in the TD group ($p = 0.041$) and the NTD group ($p = 0.023$) than in the HC group. A significant difference in ES-NP [X_F^2 (2) = 6.073, $p = 0.043$] muscle activity was observed among the groups, with a higher amplitude in the TD than in the HC group ($p = 0.013$). Significant differences in ES-P [X_F^2 (2) = 12.201, $p = 0.002$] muscle amplitudes were observed among the groups, with a higher amplitude in the TD ($p = 0.002$) and NTD ($p = 0.002$) groups than in the HC group. However, the amplitudes for EO-NP among the groups were similar.

In within-group analysis, only the TD group [X_F^2 (3) = 10.200, $p = 0.017$] had significantly different levels of muscle amplitudes among the trunk muscles, with a higher amplitude in ES-P than in EO-P muscles ($p = 0.016$). The NTD and HC groups had similar levels of amplitude in trunk muscles (**Figure 3**).

DISCUSSION

This study investigated trunk muscle activation patterns during standing turns in healthy adults and patients with stroke with and without TD. The results indicated that the TD group exhibited a longer duration and required more steps to turn than did the HC group, independent of the turning direction. However, the NTD group exhibited a significantly longer turning duration toward

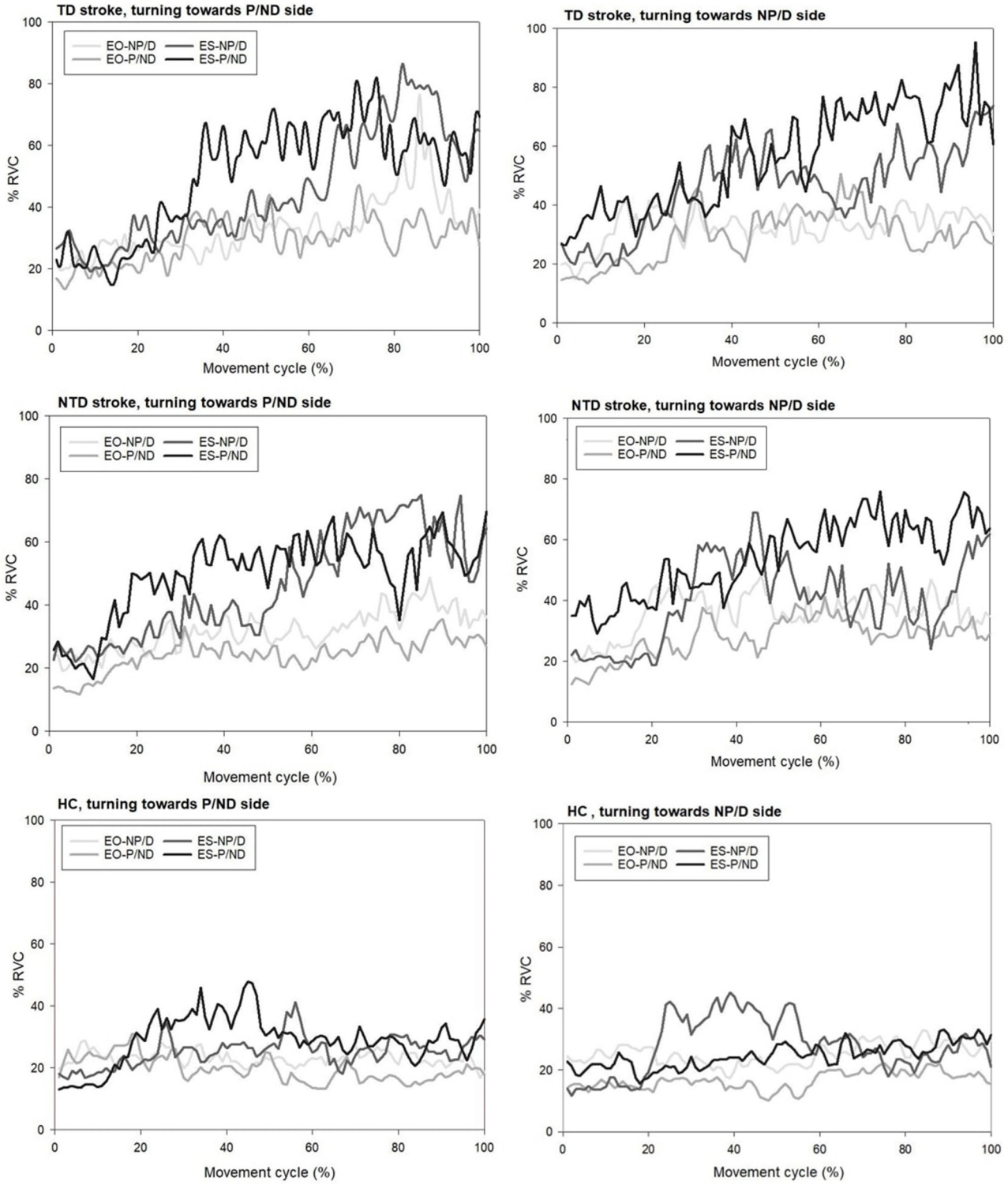

FIGURE 2 | Representative plots of trunk muscle amplitudes for participants with stroke with and without turning difficulty and healthy controls when performing standing 90° turn tasks toward both sides. EO, external oblique muscle; ES, erector spinae; TD, turning difficulty; NTD, no turning difficulty; P, paretic side; NP, non-paretic side.

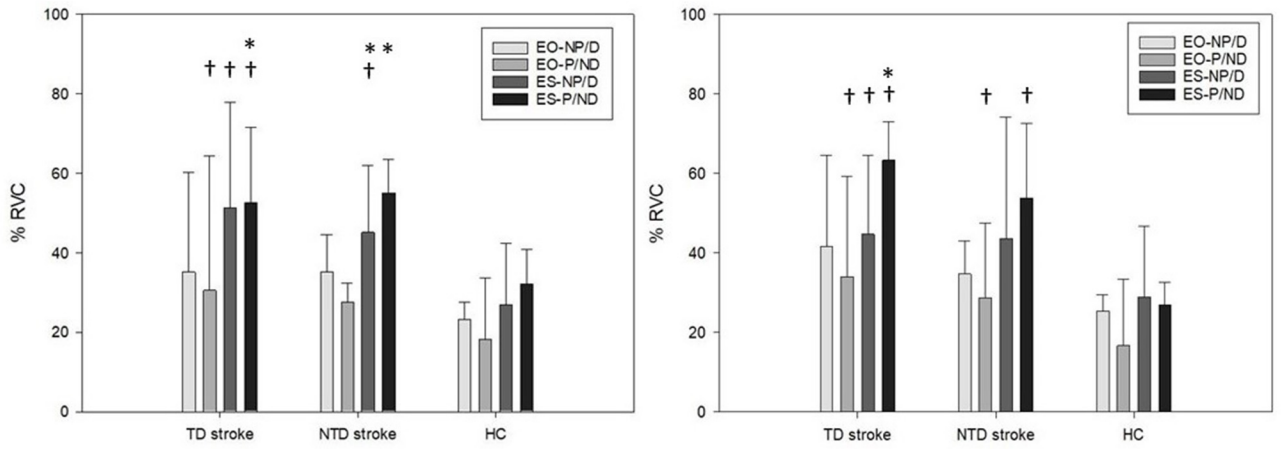

FIGURE 3 | Bilateral external oblique and erector spinae muscles amplitudes (% RVC) for stroke participants with and without turning difficulties and healthy controls during 90° standing turns toward paretic (left) and non-paretic sides (right). EO, external oblique muscle; ES, erector spinae; TD, turning difficulty; NTD, no turning difficulty; P, paretic side; NP, non-paretic side; HC, healthy control. *represents a significant difference compared with EO. †represents a significant difference compared with HCs.

the paretic side than did the HC group but their performance was similar when turning toward the non-paretic side. We observed that turning performance poststroke was related to trunk control capacity, as indicated by EMG findings. Both TD and NTD groups demonstrated an increased amplitude of trunk muscles compared with the HC group, and they failed to maintain consistent amplitudes among the four trunk muscles during the entire movement of standing turns in the direction that they required more time or steps to turn toward (i.e., turning in either direction for the TD group and turning to the paretic side for the NTD group). The results demonstrated the role of trunk control in standing turns, suggesting that trunk control capacity contributes to function recovery in turning after stroke.

In the healthy adults, the ES muscles of the turning side had a burst activity at 20–50% of the movement cycle, and then, a weak tonic activation of trunk muscles was maintained throughout the subsequent period during standing turns. The contralateral ES and bilateral EO muscles consistently demonstrated tonic contractions with amplitudes of ∼20% RVC throughout the entire movement of standing turns regardless of the turning direction. Previous studies have reported that both the phasic and tonic periods of lumbar trunk muscle activity are required, and the activation of ES muscles is coordinated with the beginning stance of the contralateral leg (32, 33). The function of such anticipatory trunk muscle activity during functional tasks is to conserve trunk stability and to boost an inward tendency of body tilt toward the travel direction (32, 33). Limited studies have examined the role of trunk flexors in standing turns relative to trunk extensors; however, bilateral trunk flexors were observed to exhibit steady co-contraction with no burst activity preceding or during turning while pushing a cart (34). This finding suggests that bilateral trunk flexors steadily and cooperatively contract as anticipatory activation for the maintenance of core stability in response to turning by increasing trunk stiffness around the longitudinal axis (34).

We observed that patients with stroke demonstrated gradually increased amplitudes in all the trunk muscles throughout the entire movement of standing turns. The difference in the amplitude of the ES muscles between baseline and peak values even reached three to four times. Bilateral trunk flexors successfully co-contracted with weak tonic activation throughout the entire task, although the activation of paretic trunk flexors in the patients with stroke was greater than that in the HCs. After a stroke, the contractility of the trunk muscle is impaired and associated with balance ability and fall risk (35). We speculated that the augmented muscular activity establishes the core stability, which is a poststroke adaptation for balance maintenance and fall prevention because of higher challenges in dynamic balance during turns.

Such increased trunk muscle activity may compensate for the insufficient muscular recruitment of the lower extremities. The inner and outer legs normally play different roles during turns compared with linear walking. The inner leg must stabilize the posture, whereas the outer leg provides propulsion and swing to realign the body in the new direction (36). In our previous study, individuals with stroke had insufficient muscle activation in the tibialis anterior and biceps femoris of the paretic inner leg (36). Therefore, patients with stroke may increase the amplitude of trunk muscles to increase stiffness for greater trunk stability while turning toward the paretic side to compensate for poorer medial–lateral stability of the paretic leg working as the inner leg. Moreover, patients with stroke failed to selectively flex the hip and knee joints of the paretic outer leg and presented poor ground clearance while turning toward the non-paretic side (37). Patients with stroke compensate for the poor motor control of lower limbs by recruiting trunk muscles, such as a larger trunk rotation might be a compensation for limited hip flexion, or trunk leaning toward the paretic side for a pelvic drop at the swing leg (38). Although patients with stroke can perform standing turns, such malfunctioning movement patterns may

result in the wastage of energy and inefficient performance (as was seen in the longer duration and greater numbers of steps relative to age-matched healthy adults). Future research should examine the kinematic characteristics of the trunk in standing turns after stroke.

Although muscles in the trunk and lower limb were impaired after stroke, their performance and EMG activity appeared to differ during turning tasks. The level of muscle activation was lower in the paretic lower limb (30) and higher in trunk muscles. A possible explanation is the distinct recovery process of neuromuscular pathways between muscles in the trunk and limbs. A recent transcranial magnetic stimulation study reported the role of the compensatory activation of uncrossed pathways from the non-paretic hemisphere in the recovery of trunk function (39). Other studies have suggested that the ipsilateral pathways of the non-paretic hemisphere would not be helpful in the motor recovery of the upper extremity (40). Trunk muscle performance is usually considered to be less affected after stroke than the performance of the upper and lower extremities and perhaps could contribute to the maintenance of whole-body balance under demanding equilibrium conditions during standing turns.

Our study goes beyond previous research with its comparison of patients with stroke and healthy adults and its analysis of turning performance and trunk muscle activation patterns in patients with stroke with and without TD. Most previous studies have reported a longer duration and greater numbers of step to complete a turn for patients with stroke (3–5, 41), and the performance was similar whether turning toward the paretic or non-paretic side (7, 42, 43). However, these results were observed only in the TD group in the current study; the NTD group turned differently according to the direction. They spent a longer duration than did the HC group when turning toward the paretic side, but their performance was similar to that of the HC group when turning toward the non-paretic side. This direction-specific difference was supported by our EMG findings. The NTD group demonstrated co-activation among the four trunk muscles while turning toward the non-paretic side, which was similar to the activation pattern observed in the HCs. However, more muscle activation of bilateral trunk extensors than trunk flexors was observed while turning toward the paretic side; this was similar to the activation pattern seen in the TD group. The compensation of trunk extensors may be used to provide a supportive function for the paretic leg to maintain balance. Such compensation could contribute to the quicker time and fewer steps to turn, but it may elevate the risk of falling. In a previous study, most falls among patients with stroke were reported to occur during turning to the paretic side (44). Our previous study also indicated that patients with stroke experienced greater difficulty turning toward the paretic side due to having a longer duration and reduced center of gravity displacement (10). We suggest that therapeutic rehabilitation programs include turning training for patients with stroke with and without TD, and turning toward both sides should be practiced. Investigating the direction-specific risk of falls during turning would also be useful with further subgroup analysis based on patients with stroke with or without TD.

A study reported a non-linear U-shaped relationship between the walking speed and fall rate (45). Such a relationship seems to also be present in turning tasks. Patients with stroke with slower turns with multiple steps may simply be walking more carefully to prevent falling. Patients with stroke with inadequate duration and numbers of steps in turning may not have sufficient balance control to successfully complete a turn. Therefore, in addition to turn duration and steps, muscular components during standing turns toward either direction should be considered in stroke rehabilitation to improve turning performance and prevent falls.

Previous studies have indicated that the motor control of the lower limb, balance ability, and cognitive function could contribute to turning performance after stroke (7, 42, 46). We did not observe significant differences in general cognitive function or functional mobility lower-limb motor function between the TD and NTD groups. Successful turning may require more motor recovery of trunk control than expected. Our findings highlight the role of trunk control in turning and neuromuscular strategies in stroke patients with and without TD.

This study has limitations. Only patients with chronic stroke who were able to walk a distance of 10 m without walking aids or orthoses were recruited. Caution should be taken when generalizing the results and conclusions. Moreover, due to technological restrictions, we examined only the activation patterns of four principal trunk muscles that identify the function of the lower back during standing turns. More trunk muscles should be included to comprehensively understand neuromuscular control in the trunk during turning. In addition, the increased trunk muscle activity observed in this study represents the greater muscle contraction, but could not exclude the possibility of hypertonic interference. Although our stroke patients had relatively decreased spasticity for paretic leg (median stage 4 in Brunnstrom classification) and may have similar observation in trunk, trunk muscle tone was not measured in the current study and future research can take this into consideration. The classification criteria based on suggestion of Thigpen et al. may not perfectly identify patients with TD from NTD because the development of the criteria was derived from the turning performance of the elderly. However, there are currently no other criteria for differentiating stroke patients with and without TD, and thus additional work is required to find more precise cut-off points. Finally, we chose a standing turn of 90° as the target task. To provide the whole picture regarding the role of trunk control in the directional change while walking, varied turning tasks including different turn angles or different circumstances could be considered in future studies.

CONCLUSIONS

The main function of the trunk is to keep the body upright and maintain stability during static or dynamic activities. Turning is a challenging task for patients with stroke because of the requirement for side-dependent modulation of the legs and demanding trunk control to maintain balance. To the best of our knowledge, this is the first study to compare the activation patterns of the trunk flexors and extensors between healthy adults

and patients with stroke with and without TD during standing turns. We observed augmented activation of trunk muscles in patients with stroke relative to HCs. When the TD group turned toward either direction and when the NTD group turned toward the paretic side, the flexible adaptations and selective actions of trunk muscles seen in HCs were absent. Such distinct activation patterns between patients and age-matched controls during standing turns could contribute to poor turning performance and may elevate the risk of falling in patients with stroke. The results provide insights into the contribution and importance of the trunk muscles during turning and the association with TD after stroke, which may help guide the development of more effective rehabilitation therapies that target specific muscles for those with TD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (Reference No. 08-XD-051). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SCL was a major contributor in study design. PJL and VJYC have done the data collection. IHC and SCL analyzed and interpreted data. IHC, PJL, and SCL have done the manuscript writing. All authors read and approved the final manuscript.

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Walking With Horizontal Head Turns Is Impaired in Persons With Early-Stage Multiple Sclerosis Showing Normal Locomotion

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Background: Turning the head while walking (an action often required during daily living) is particularly challenging to maintain balance. It can therefore potentially reveal subtle impairments in early-stage people with multiple sclerosis who still show normal locomotion (NW-PwMS). This would help in identifying those subjects who can benefit from early preventive exercise aimed at slowing the MS-related functional decline.

Objectives: To analyze if the assessment of walking with horizontal head turns (WHHT) through inertial sensors can discriminate between healthy subjects (HS) and NW-PwMS and between NW-PwMS subgroups. To assess if the discriminant ability of the instrumented WHHT is higher compared to clinical scores. To assess the concurrent validity of the sensor-based metrics.

Methods: In this multicenter study, 40 HS and 59 NW-PwMS [Expanded Disability Status Scale (EDSS) $\leq$2.5, disease duration $\leq$5 years] were tested. Participants executed Item-6 of the Fullerton Advanced Balance scale-short (FAB-s) wearing three inertial sensors on the trunk and ankles. The item required to horizontally turn the head at a beat of the metronome (100 bpm) while walking. Signals of the sensors were processed to compute spatiotemporal, regularity, symmetry, dynamic stability, and trunk sway metrics descriptive of WHHT.

Results: Mediolateral regularity, anteroposterior symmetry, and mediolateral stability were reduced in NW-PwMS vs. HS ($p \leq 0.001$), and showed moderate discriminant ability (area under the receiver operator characteristic curve [AUC]: 0.71–0.73). AP symmetry and ML stability were reduced ($p \leq 0.026$) in EDSS: 2–2.5 vs. EDSS: 0–1.5 subgroup (AUC: 0.69–0.70). The number of NW-PwMS showing at least one abnormal instrumented metric (68%) was larger ($p \leq 0.002$) than the number of participants showing abnormal FAB-s-Item6 (32%) and FAB-s clinical scores (39%). EDSS: 2–2.5 subgroup included more individuals showing abnormal instrumented metrics (86%) compared to EDSS: 0–1.5 subgroup (57%). The instrumented metrics significantly correlated with FAB-s-Item6 and FAB-s scores (|Spearman's r_s| $\geq$ 0.37, $p < 0.001$), thus demonstrating their concurrent validity.

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Conclusion: The instrumented assessment of WHHT provided valid objective metrics that discriminated, with higher sensitivity than clinical scores, between HS and NW-PwMS and between EDSS subgroups. The method is a promising tool to complement clinical evaluation, and reveal subclinical impairments in persons who can benefit from early preventive rehabilitative interventions.

Keywords: multiple sclerosis, wearable inertial sensors, instrumented assessment, dynamic balance, rehabilitation outcome assessment

INTRODUCTION

The head is a natural reference frame for movement since it contains the visual and vestibular systems indispensable to correctly detect self-motion in space (1). Since head stabilization during movement is of paramount importance to optimize the functioning of these sensory systems, head oscillations during natural walking are kept minimal (around 2°) (2). On the other hand, common daily-life actions, such as crossing a street or talking with a friend during a stroll, require walking with larger horizontal head rotations.

Moving the head during locomotion naturally challenges the balance control system since it requires the accurate integration of vestibular, visual, and proprioceptive information to modulate the vestibulo-ocular and vestibulospinal reflexes responsible for gaze stabilization/redirection and dynamic balance maintenance (3, 4). Consequently, walking with horizontal head turns (WHHT) is particularly difficult for individuals showing vestibular dysfunction (4, 5), and/or deficits in sensory processing and integration commonly present in people with multiple sclerosis (PwMS) (6, 7). Previous studies on PwMS with moderate-to-severe mobility impairment showed that WHHT was abnormal in 80% of participants (8) and represented the most difficult item of the Dynamic Gait Index (DGI) (9). Importantly, WHHT, as measured by the Fullerton Advanced Balance scale-short version (10), resulted to be the most impaired item (together with turning 360°) also in early-stage PwMS (11). Recently, Cattaneo et al. (12) found that WHHT is more impaired in PwMS compared to stroke survivors and people with Parkinson's disease, complementing previous results showing more severe static and dynamic balance deficits in PwMS (7, 13, 14).

Considering its high impact on dynamic balance maintenance, turning the head while standing or walking is included in several rehabilitation programs (6, 15–17) and clinical assessment scales, such as the DGI (9), the MiniBESTest (18), and the Fullerton Advanced Balance scale (19) and its short version (10). Although widely used, these evaluation tools may suffer from ceiling effect, limited sensitivity, and poor details in assessing different aspects of a task (20). These limitations may be partly overcome by wearable inertial measurement units (IMUs) which allow easy objective assessments of a motor task outside dedicated labs (20). Previous studies on PwMS have shown that IMU-based assessments may provide additional information about *how* a task is performed (21) through indexes more responsive to subtle impairments (22), disease progression (20, 23), and rehabilitation effects (24).

While most literature refers to natural walking and Timed Up and Go (TUG) test (20), no studies exist about the instrumented assessment of WHHT in early-stage non-disabled PwMS. Given the complexity of this task in terms of load on the sensorimotor system and considering that the sensory symptoms represent the first clinical manifestation of MS in 43% of patients (25), it can be hypothesized that the instrumented assessment of WHHT could detect subclinical motor impairments even in the early stages of MS when natural walking (i.e., walking with no imposed head rotations) is still normal. This would be of paramount importance to follow the course of these impairments and to identify, from the very early stages of the disease, those individuals who could benefit from preventive rehabilitation exercises, potentially useful to slow the MS-related functional decline, as recently indicated (26).

This multicenter cross-sectional study aims at analyzing the discriminant ability and the concurrent validity of an IMU-based assessment of WHHT in early-stage PwMS with normal natural walking (NW-PwMS). We hypothesized that the instrumented assessment of WHHT (i) can discriminate between healthy subjects and NW-PwMS, and between NW-PwMS subgroups, (ii) its discriminant ability is higher compared to clinical scales, and (iii) provides valid indexes to complement clinical assessments of WHHT and dynamic balance in early-stage PwMS.

METHODS

Participants

A total of 82 consecutive PwMS [age, mean ± SD (range): 39.5 ± 10.6 (20–64) years; % females: 65.9%] were enrolled from three clinical Italian centers in Milan, Turin, and Genoa. Inclusion criteria were: age ≥ 18 years, MS diagnosis based on McDonald criteria (27), disease duration ≤ 5 years, and Expanded Disability Status Scale (EDSS) (28) ≤ 2.5. Exclusion criteria were: increase ≥ 1 in EDSS score over the last 3 months, diagnosis of major depression, severe joint and/or bone disorders interfering with balance and gait (based upon clinical judgment), and cardiovascular or other concomitant neurological diseases.

A total of 40 healthy subjects (HS) without any musculoskeletal or neurological disorders (age: 39.0 ± 10.9 years, 28 females) were also recruited. All the participants signed a written informed consent to the study that was approved by the local ethical committee of each center (approval numbers,

Milan: 21/2017/CE_FdG/FC/SA; Turin: AslVC.CRRF.17.03; Genoa: 026/2018).

Selection of Normal-Walking PwMS

People with multiple sclerosis were assessed with the Timed 25-foot Walk test (T25FWT) and with an IMU-based instrumented gait test.

The T25FWT measures the time taken to walk at maximum speed along a 7.62-m linear course (29). Participants presenting T25FWT scores above the normative cut-off [5.2 s (29)] were excluded from the subsequent analyses. The cut-off value of 5.2 s was chosen as it was the maximum T25FWT score [median (range): 3.7 (2.8–5.2) s] found by Phan-Ba et al. (29) in a sample of 104 healthy subjects with an age range (18–60 years) and sex distribution (% females: 63.5%) similar to those of the PwMS here recruited.

The remaining participants were required to walk a 15-m straight corridor at their maximum speed wearing three IMUs (MTw, Xsens, The Netherlands) above lateral malleoli and on the lower back. The latter position was chosen as it is the most widely used during gait tests, as described in the review by Vienne-Jumeau et al. (20). Signals of IMUs related to the middle five strides were processed (30) to compute three parameters commonly impaired in early-stage PwMS: cadence, stance time, and double-support time (23, 31). Since the present sample of forty HS did not execute the above test, the data of each patient were compared to the normative ranges collected from another group of 21 healthy volunteers (NORM) recruited in our previous studies. The NORM sample had age and sex distribution (age: 36.4 ± 8.8 years, % females: 66.7%) comparable to those of the PwMS here analyzed, and performed the straight-line walking test wearing the same sensors of the PwMS and following the same protocol. In particular, both groups were required to walk for 15 m at their maximum speed. PwMS showing at least one instrumented parameter outside the normative ranges were excluded, while the other ones were labeled as normal-walking PwMS (NW-PwMS) and underwent subsequent analyses.

Clinical Assessment

In addition to the T25FWT and the 15-m instrumented test, the following clinical assessments were administered to NW-PwMS: the 12-item Multiple Sclerosis Walking Scale (MSWS-12) and the Fullerton Advanced Balance-short Scale (FAB-s). FAB-s was administered also to HS.

The MSWS-12 is a patient-reported questionnaire on walking ability. The questions focused on the self-perceived impact of MS on 12 daily-life locomotor activities in the last 2 weeks. The transformed total score is between 0 and 100, with higher scores indicating higher perceived walking difficulties (32, 33). The FAB-s measures dynamic balance during 6 tasks of daily living. Each item is rated on a 5-point (0–4) ordinal scale, with higher scores indicating better performances. Scores < 23 are considered abnormal (10).

Instrumented Assessment—WHHT

Healthy subjects (HS) and NW-PwMS were equipped with three wireless IMUs (MTw, Xsens, The Netherlands) secured on both shanks (above lateral malleoli) and the sternum. The position of the latter IMU was chosen to better describe sway and possible instability of the upper trunk that, based on our clinical experience, seem to occur more frequently during locomotor tasks particularly demanding in terms of dynamic balance [e.g., TUG test (34), walking while turning the head (13), walking around/over obstacles (13), stairway walking (14)], than during straight-line walking. IMU-derived accelerations and angular velocities were recorded at 75 Hz. Participants performed Item 6 of FAB-s (i.e., walk with horizontal head turns) following published instructions (19). In particular, a metronome was set to 100 bpm. Participants practiced horizontal head turns of 30° at the rhythm of the metronome while standing in place. When they felt ready, they walked along a 9-m straight path while turning their head from side to side at the metronome beat.

Trunk anteroposterior (AP), mediolateral (ML), and vertical (VT) accelerations were reoriented to a horizontal-vertical coordinate system (35). Heel-strike and foot-off instants were identified (30), and data related to the middle five strides [10 steps as indicated by the FAB instructions (19)] were used to compute 12 metrics organized in gait domains as described in **Table 1**.

The same parameters were computed also from the instrumented gait test executed during the screening procedure, although the position of the trunk sensor was different (low back). This was done (i) to make sure that the NW-PwMS actually walked normally, not only in terms of spatiotemporal aspects, and (ii) to allow comparisons with previous literature that have analyzed straight-line gait of early-stage PwMS using a sensor on the low back (36–39). Data processing was performed using MATLAB R2017b (The MathWorks, MA, USA).

Statistics

Non-parametric statistics were used since data were not normally distributed (Shapiro–Wilk's test < 0.05). HS and NW-PwMS were compared using the chi-squared test (χ^2) for sex, and the Mann–Whitney *U*-test for all the other clinical and instrumented features. Bonferroni–Holm (BH) correction for multiple comparisons was applied. The discriminant ability of each parameter was assessed by computing the area under the receiver operating characteristic curve (AUC). Only those parameters showing a statistically significant difference between HS and NW-PwMS were further analyzed. This subset of metrics was compared among HS, NW-PwMS with EDSS: 0–1.5, and NW-PwMS with EDSS: 2–2.5 using Kruskal–Wallis (KW), and Bonferroni–Holm *post-hoc* tests. The number of NW-PwMS showing abnormal values of the selected instrumented metrics was compared with the number of participants showing abnormal clinical scores using the chi-squared test. A parameter was considered abnormal if it was above the 95th (or below the 5th) percentile of HS values, depending on if its increase (or decrease) was indicative of poorer performances.

Concurrent validity of the instrumented metrics was assessed through Spearman's correlation coefficient (r_s) with FAB-s, FAB-s-Item6, and MSWS-12 scores. The same method was

TABLE 1 | Description of the instrumented metrics.

Domain	Metric	Description
Spatiotemporal	Gait Speed (m/s)	The ratio between the pathway's length and the time taken to walk it.
	Cadence (stride/min)	Computed as $60/T_{stride}$, where T_{stride} is the stride duration (i.e., the time interval between two consecutive heel-strikes of the same foot).
	Stance duration (%)	Time interval between the instants of heel-strike and toe-off of the same foot, expressed as a percentage of T_{stride}
	Double-Support Duration (%)	Time interval between the instants of heel-strike of one foot and the toe-off of the contralateral foot, expressed as a percentage of T_{stride}
Regularity	AP and ML Stride Regularity (-)	The second peak of the normalized autocorrelation function computed from the trunk AP and ML acceleration components (40). Increasing values, from 0 to 1, indicate higher stride regularity.
Symmetry	AP and ML improved Harmonic Ratio (iHR) (%)	The trunk AP and ML acceleration signals were decomposed into harmonics using a discrete Fourier transform. Hence, iHR was computed as the percentage ratio between the sum of the powers of the first 10 in-phase harmonics to the sum of the powers of the first 20 (in-phase and out-of-phase) harmonics (41). Increasing values, from 0 to 100%, indicate more symmetrical gait.
Dynamic Stability	AP and ML short-term Lyapunov exponent (sLyE) (-)	sLyE reflects the ability of the locomotor system to manage small perturbations naturally occurring during walking, such as external mechanical disturbances or internal control errors (42). Trunk AP and ML acceleration signals related to five consecutive strides in the central part of the pathway were re-sampled to 5 × 100 frames to maintain equal data length across subjects. sLyE is estimated from each acceleration segment following Rosenstein method (43). In summary an m-dimensional state-space ($m = 5$) was reconstructed from each acceleration component and its delayed copies (delay $T = 10$ samples). The values of m and T parameters were estimated using published algorithms (44). The mean divergence curve (D) of the acceleration trajectories in the state-space was computed, and sLyE was calculated as the slope of the log(D) between 0 and 0.5 stride (1 step). Increasing values of sLyE (i.e., faster trajectory divergence) indicate a lower ability of the motor system to cope with small perturbations, thus reflecting lower dynamic stability.
Trunk Sway	AP and ML Normalized Trunk Acceleration (-)	SD of trunk AP and ML acceleration normalized with respect to the SD of the acceleration modulus. Increased values of this parameter indicate larger trunk sway, independently from gait speed (45).

AP, anteroposterior; ML, mediolateral.

used to evaluate the correlation among instrumented features. Statistical analyses were performed using STATISTICA (Statsoft, OK, USA).

RESULTS

Sample Description

From the recruited sample of PwMS ($n = 82$), 22 were excluded because they showed T25FWT scores above the normative cut-off and/or because they presented at least one temporal aspect of instrumented natural walking outside the normative range. One participant was excluded since his/her instrumented data were corrupted. The remaining 59 participants (72%) were considered as normal-walking PwMS (NW-PwMS). The sample size (40 HS and 59 NW-PwMS) was considered adequate based on previous results on healthy subjects and early-stage PwMS (11) showing a mean between-group difference in the FAB-s Item 6 score of 0.6 ± 0.9 points (effect size: 0.66). These data indicated that 39 subjects per group were necessary to obtain a difference between groups with $\alpha = 0.05$ and Power $(1\text{-}\beta) = 0.80$.

As shown in **Table 2**, NW-PwMS included 37 participants with EDSS: 0–1.5 and 22 with EDSS: 2–2.5, all diagnosed with relapsing-remitting MS. All NW-PwMS showed T25FWT scores below the normative cutoff value (<5.2 s) (29). All the instrumented metrics describing natural walking were comparable between NW-PwMS and normative data, and between EDSS subgroups (**Table 3**). Twenty-nine (49%) NW-PwMS reported that MS had an impact on their walking ability, which was minimal ($0 < \text{MSWS-12} \leq 25$) in 18 (30%) and mild ($25 < \text{MSWS-12} \leq 50$) in 11 (19%) participants (46). As shown in **Table 2**, FAB-s and FAB-s-Item6 scores were higher in HS compared to EDSS: 0–1.5 ($p_{BH} \leq 0.041$) and EDSS: 2–2.5 ($p_{BH} \leq 0.016$) subgroups. Clinical scores were comparable between EDSS subgroups (**Table 2**).

Instrumented WHHT: HS vs. NW-PwMS

As reported in **Table 4**, spatiotemporal parameters and trunk sway during WHHT were comparable between NW-PwMS and HS and showed poor discriminant ability ($0.52 \leq \text{AUC} \leq 0.58$). ML stride regularity and AP gait symmetry (AP iHR) were lower in NW-PwMS compared to HS. ML dynamic stability was reduced (higher ML sLyE) in NW-PwMS compared to HS. These three metrics showed moderate discriminant ability ($\text{AUC} \geq 0.71$) and were therefore considered for the subsequent analyses.

The number of NW-PwMS showing abnormal values was 25 (42%) for ML stride regularity, 18 (31%) for AP iHR, and 22 (37%) for ML sLyE (**Figure 1**).

Instrumented WHHT: HS vs. EDSS: 0–1.5 vs. EDSS: 2–2.5

Significant differences between HS and EDSS subgroups were found ($p_{KW} < 0.001$). ML regularity, AP symmetry, and ML dynamic stability were higher in HS compared to EDSS: 0–1.5 ($p_{BH} \leq 0.027$) and EDSS: 2–2.5 ($p_{BH} \leq 0.034$) subgroups (**Figure 1**). ML regularity was comparable between EDSS subgroups ($p_{BH} = 0.490$). EDSS: 0–1.5 subgroup showed higher

TABLE 2 | Demographic and clinical characteristics of healthy subjects and normal-walking people with MS.

	HS ($N = 40$)	NW-PwMS ($N = 59$)	*p*-value	EDSS: 0–1.5 ($N = 37$)	EDSS: 2–2.5 ($N = 22$)	*p*-value
Age (years)	37.5 (24.5; 57)	37 (25; 53)	0.895	35 (25; 55)	40.5 (26; 55)	0.384
Sex (female/male)	28/12	41/18	0.957	25/12	16/6	0.677
Disease duration (years)	-	2 (0; 5)	-	2 (0; 5)	2.5 (0; 5)	0.589
EDSS (0–10)	-	1.5 (0; 2.5)	-	1 (0; 1.5)	2 (2; 2.5)	<0.001
T25FWT (seconds)	-	3.8 (3.2; 5.0)	-	3.8 (3.2; 5.0)	3.8 (3.2; 4.9)	0.857
MSWS-12 (0–100)	-	0 (0; 41.7)	-	0 (0; 41.7)	7.3 (0; 41.7)	0.105
FAB-s (0–24)	24 (23; 24)	23 (19; 24)	<0.001	23 (19; 24)	22 (19; 24)	0.185
FAB-s item 6 (0–4)	4 (4; 4)	4 (2; 4)	<0.001	4 (2; 4)	4 (2; 4)	0.276

Values are median (5th; 95th percentiles) or number. HS, healthy subjects; NW-PwMS, normal-walking people with MS; EDSS, Expanded Disability Status Scale; T25FWT, Timed 25-foot Walk Test; MSWS-12, 12-item Multiple Sclerosis Walking Scale; FAB-s, Fullerton Advanced Balance scale—short version. p-value: results of the chi-squared test for sex and Mann–Whitney U-test for all the other variables.

TABLE 3 | Instrumented metrics describing fast straight-line walking in normal-walking people with MS (NW-PwMS) and healthy subjects previously tested (NORM).

	NORM ($N = 21$)	NW-PwMS ($N = 59$)	*p*-value	EDSS: 0–1.5 ($N = 37$)	EDSS: 2–2.5 ($N = 22$)	*p*-value
	Median (5th–95th percentile)	*Median (5th–95th percentile)*		*Median (5th–95th percentile)*	*Median (5th–95th percentile)*	
Spatiotemporal domain						
Gait speed (m/s)	1.8 (1.4–2.2)	1.7 (1.4–2.0)	0.158	1.7 (1.4–2.0)	1.7 (1.4–1.9)	0.090
Cadence (stride/min)	65.7 (59.0–76.8)	64.9 (59.0–76.9)	0.530	64.9 (59.0–79.6)	64.4 (59.8–70.2)	0.351
Stance duration (%)	53.9 (51.4–57.6)	53.6 (51.2–57.4)	0.460	54.1 (51.2–57.4)	53.3 (51.3–56.5)	0.600
Double support duration (%)	3.3 (0.8–6.6)	3.3 (0.9–6.4)	0.281	3.0 (0.9–6.5)	3.6 (1.1–5.5)	0.567
Regularity domain						
AP stride regularity (-)	0.81 (0.60–0.94)	0.80 (0.50–0.94)	0.588	0.80 (0.51–0.96)	0.82 (0.50–0.92)	0.678
ML stride regularity (-)	0.82 (0.66–0.93)	0.81 (0.56–0.94)	0.694	0.82 (0.56–0.96)	0.80 (0.59–0.94)	0.259
Symmetry domain						
AP iHR (%)	84.0 (74.5–91.0)	84.7 (69.3–93.2)	0.634	85.0 (69.3–93.7)	84.3 (75.2–91.7)	0.562
ML iHR (%)	90.0 (75.6–91.9)	85.7 (69.0–96.0)	0.170	85.4 (55.9–96.1)	86.7 (71.6–94.1)	0.900
Local dynamic stability domain						
AP sLyE (-)	0.75 (0.38–1.40)	0.81 (0.33–1.42)	0.814	0.82 (0.33–1.47)	0.72 (0.35–1.15)	0.562
ML sLyE (-)	0.88 (0.49–1.70)	0.91 (0.33–1.40)	0.706	0.95 (0.26–1.48)	0.81 (0.42–1.17)	0.672
Trunk sway domain						
AP normalized acceleration (-)	0.48 (0.41–0.57)	0.47 (0.34–0.60)	0.548	0.46 (0.33–0.60)	0.49 (0.41–0.55)	0.170
ML normalized acceleration (-)	0.52 (0.38–0.62)	0.54 (0.38–0.82)	0.235	0.56 (0.33–0.86)	0.51 (0.43–0.70)	0.100

AP, anteroposterior; ML, mediolateral; iHR, improved harmonic ratio; sLyE, short-term Lyapunov exponent. p-value: results of the Mann–Whitney U-tests with Bonferroni–Holm correction for multiple comparisons.

AP symmetry ($p_{BH} = 0.019$) and ML dynamic stability (i.e., lower ML sLyE) ($p_{BH} = 0.026$) than EDSS: 2–2.5 subgroup (**Figure 1**). The discriminant ability was moderate [AUC mean (95% CI) AP symmetry: 0.70 (0.56–0.84); ML sLyE: 0.69 (0.55–0.84)].

The number of participants showing abnormal values of ML regularity was comparable between EDSS subgroups [EDSS: 0–1.5: 16/37 (43%); EDSS: 2–2.5: 9/22 (41%); $p_{\chi 2} = 0.861$]. A larger number of EDSS: 2–2.5 vs. EDSS: 0–1.5 NW-PwMS showed abnormal scores of ML dynamic stability [12/22 (55%) vs. 10/37 (27%); $p_{\chi 2} = 0.035$] and AP symmetry [12/22 (55%) vs. 6/37 (16%); $p_{\chi 2} = 0.002$].

Instrumented WHHT vs. Clinical Scales

Figure 2A reports the percentages of NW-PwMS showing abnormal instrumented metrics (ML regularity, AP symmetry, and ML dynamic stability) and abnormal FAB-s scores (<23) and FAB-s-Item6 subscores (<4). Forty NW-PwMS (68%) showed at least one abnormal instrumented metric. This percentage was larger than those representing individuals with abnormal FAB-s-Item6 subscore [19/59 (32%), $p_{\chi 2} < 0.001$] and FAB-s score [23/59 (39%), $p_{\chi 2} = 0.002$].

The number of individuals presenting at least one abnormal instrumented metric was larger ($p_{\chi 2} = 0.019$) in EDSS:

TABLE 4 | Instrumented metrics describing walking with horizontal head turns in healthy subjects and normal-walking people with MS.

	HS ($N = 40$)	NW-PwMS ($N = 59$)	*p*-value	AUC
	Median (5th; 95th percentile)	*Median (5th; 95th percentile)*		*Mean (95% CI)*
Spatiotemporal domain				
Gait Speed (m/s)	0.93 (0.66; 1.22)	0.89 (0.54; 1.20)	0.199	0.57 (0.46; 0.69)
Cadence (stride/min)	51.2 (42.1; 56.8)	50.5 (38.6; 54.6)	0.164	0.58 (0.46; 0.69)
Stance dur. (%)	57.3 (53.7; 61.9)	57.6 (53.9; 62.1)	0.445	0.53 (0.42; 0.65)
Double-support dur. (%)	7.4 (4.0; 11.7)	7.6 (4.0; 11.3)	0.295	0.55 (0.44; 0.67)
Regularity domain				
AP stride regularity (-)	0.66 (0.33; 0.88)	0.60 (0.17; 0.84)	0.109	0.64 (0.53; 0.75)
ML stride regularity (-)	0.68 (0.52; 0.84)	0.54 (0.10; 0.81)	**0.001**	0.71 (0.61; 0.81)
Symmetry domain				
AP iHR (%)	78.0 (67.3; 89.4)	73.3 (50.8; 81.8)	**<0.001**	0.73 (0.63; 0.83)
ML iHR (%)	72.4 (51.6; 87.1)	69.4 (51.8; 87.3)	0.239	0.57 (0.46; 0.68)
Dynamic stability domain				
AP sLyE (-)	0.71 (0.33; 1.14)	0.76 (0.36; 1.32)	0.347	0.55 (0.44; 0.67)
ML sLyE (-)	0.53 (0.26; 0.78)	0.66 (0.39; 1.06)	**<0.001**	0.73 (0.64; 0.83)
Trunk sway domain				
AP norm. trunk acc. (-)	0.41 (0.27; 0.57)	0.39 (0.26; 0.61)	0.719	0.52 (0.40; 0.64)
ML norm. trunk acc. (-)	0.40 (0.29; 0.55)	0.43 (0.31; 0.69)	0.363	0.54 (0.42; 0.66)

HS, healthy subjects; NW-PwMS, normal-walking people with MS; AUC, area under the receiver operating characteristic curve; AP, anteroposterior; ML, mediolateral; iHR, improved harmonic ratio; sLyE, short-term Lyapunov exponent. p-value: results of the Mann–Whitney U-test with Bonferroni–Holm correction for multiple comparisons. Statistically significant ($p < 0.05$) results are reported in bold.

2–2.5 [19/22 (86%)] vs. EDSS: 0–1.5 subgroup [21/37 (57%)] (**Figure 2B**). The same trend was found in clinical scales (**Figure 2B**), although not statistically significant ($p_{\chi 2} \geq 0.226$).

Correlation Analysis and Concurrent Validity

ML stride regularity, AP iHR, and ML sLyE showed low non-significant correlations between each other ($-0.23 \leq r_s \leq 0.17$, $p_{BH} \geq 0.222$).

As shown in **Table 5**, statistically significant correlations were found between the three instrumented metrics and FAB-s and FAB-s-Item 6 scores. ML sLyE moderately correlated also with MSWS-12.

DISCUSSION

A wearable-sensor-based assessment of WHHT was applied to HS and early-stage NW-PwMS to evaluate the presence of subclinical impairments not detected by clinical and instrumented measures of natural walking. This would help clinicians to discriminate between individuals with normal and abnormal dynamic balance, to identify, from the very early stages of the disease, those persons who may benefit from preventive rehabilitation exercise, and to track subtle impairments over the disease course. Three IMU-derived metrics, descriptive of regularity, symmetry, and stability of WHHT, were significantly impaired in NW-PwMS compared to HS and were able to discriminate between EDSS-based subgroups. The discriminant ability of the instrumented metrics was higher compared to FAB-s-Item6 and FAB-s clinical scores, and the significant correlations with the clinical scales demonstrated their concurrent validity.

Walking impairment is a hallmark of MS developing early in the disease course. Previous studies on walking in early-stage PwMS found altered spatiotemporal parameters (23, 31, 47), abnormal trunk sway (22), and increased variability (36, 48), instability (37, 38), and asymmetry (39, 49) compared to HS. No such abnormalities were found in the present cohort of NW-PwMS, at least during short-distance walking tests. The sample can thus be considered composed of PwMS showing normal natural locomotion, as highlighted also by the high gait speed derived from the T25FWT (1.9 ± 0.3 m/s) that is comparable with the mean velocity (1.8 ± 0.3 m/s) obtained from 31 studies, analyzed in a recent review (50), on the T25FWT in healthy subjects. Despite these results, the MSWS-12 scores indicated that 49% of participants perceived that MS influenced their walking capacity, at least minimally. Moreover, the FAB-s score was significantly reduced compared to HS, confirming that dynamic balance impairment is an early disease-related sign (46).

Regarding WHHT, both the FAB-s-Item6 sub-score and the instrumented parameters revealed significant anomalies in NW-PwMS vs. HS. In particular, ML regularity, AP symmetry, and ML dynamic stability were reduced in 31–42% of NW-PwMS and showed a moderate discriminant ability. Importantly, the three features were not correlated with each other, suggesting the presence of subclinical impairments affecting independent locomotor domains. Interestingly, the present results revealed

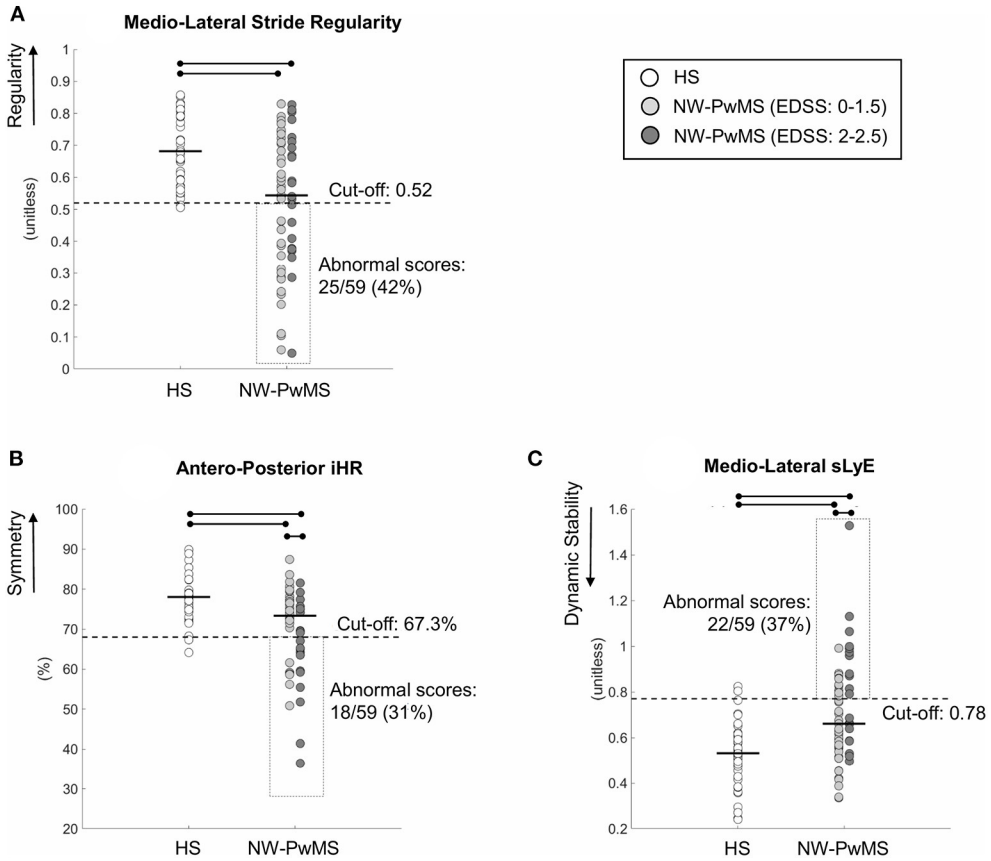

FIGURE 1 | Instrumented parameters describing walking with horizontal head turns (WHHT) in healthy subjects (HS) and early-stage people with MS showing normal walking (NW-PwMS). **(A)** Mediolateral Stride Regularity. **(B)** Anteroposterior iHR (improved harmonic ratio). **(C)** Mediolateral sLyE (short-term Lyapunov exponent). Each circle represents a single participant. Horizontal bold lines represent median values for each group. Horizontal lines and dots represent a statistically significant difference between groups ($p < 0.05$, Kruskal–Wallis and Bonferroni–Holm test). Cut-off scores, corresponding to the 5th percentile **(A,B)** and the 95th percentile **(C)** of HS, are reported together with the number (%) of NW-PwMS showing abnormal values.

subtle impairments also in the EDSS: 0–1.5 subgroup. Since both the present results on straight-line walking and previously published results on instrumented TUG (51) did not reveal abnormalities in EDSS: 0–1.5 patients, it can be suggested that the instrumented assessment of WHHT may be a more sensitive tool (than those mentioned above) to identify, already from the very early phases of the disease, incipient balance and locomotor anomalies that become clinically evident only in the most advanced stages of MS (EDSS≥4) (52–55).

The abnormalities found during WHHT could be primarily ascribed to the significant impairment of dynamic balance. The FAB-s score was abnormal in 39% of NW-PwMS and significantly correlated with the three instrumented metrics, indicating that poorer balance was associated with lower regularity, symmetry, and stability during WHHT. Although the Kurtzke Functional Systems scores (in particular Pyramidal, Cerebellar, Brainstem, and Sensory scores) (28) have not been addressed in this study, it can be speculated that sensory loss, a typical early sign of MS (25), may have been a significant factor affecting balance. Particularly, somatosensory and proprioceptive impairments may have increased the reliance on the vestibular system that could show alterations also in early-stage PwMS (56), especially when challenged during WHHT. Also, the possible impairments of the pyramidal system, representing the first clinical sign of MS in 22% of patients (57), may have played a role in reducing balance, as previously demonstrated by Martin et al. on early-stage PwMS (58), and in increasing step asymmetry, as found by Kalron and Givon on more severe patients (59). Another aspect that may be considered is that WHHT is, actually, a dual-task requiring attention to turn the head at the metronome beat while walking. Previous studies on PwMS have demonstrated that different dual-task paradigms adversely affect balance and walking also in early-stage subjects (60). This, in turn, may further explain the presence of abnormal WHHT patterns, even in participants with normal (single-task) walking.

Interestingly two of the three selected metrics (regularity and stability) were abnormal in ML direction. Previous studies on PwMS have demonstrated that several ML parameters descriptive of balance (61, 62) are more altered in fallers vs. non-fallers. Considering that falls/near falls have been reported in 30% of early-stage PwMS (46), future studies should assess if the WHHT metrics could be predictive of fall risk also in this population.

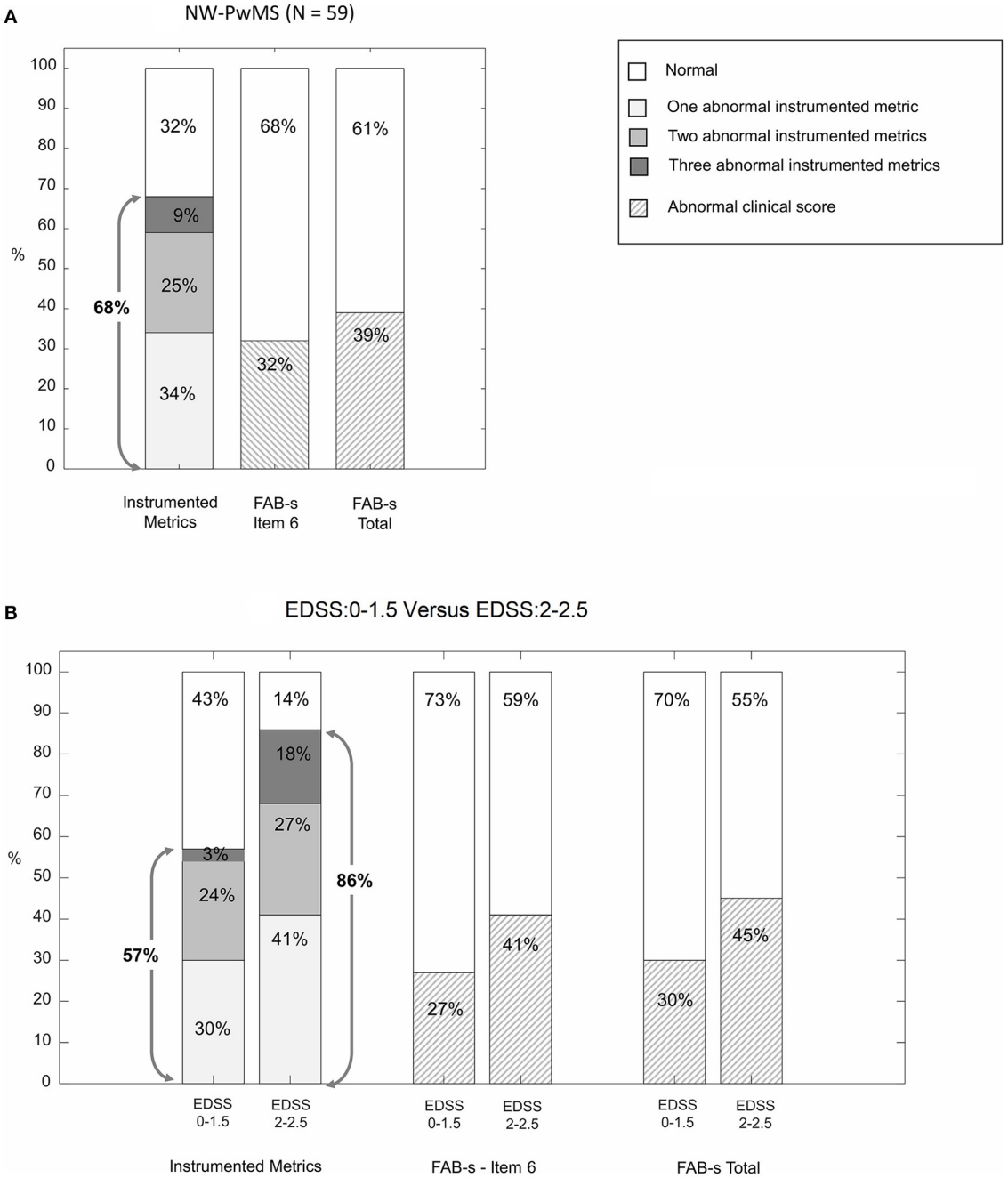

FIGURE 2 | Percentage of normal-walking people with MS (NW-PwMS) showing abnormal values of instrumented metrics descriptive of walking with horizontal head turns (WHHT) and abnormal clinical scores on FAB-s (Fullerton Advanced Balance scale-short version). **(A)** Whole sample of NW-PwMS. **(B)** NW-PwMS sub-samples showing, respectively, EDSS: 0–1.5 and EDSS: 2–2.5. Gray arrows indicate the percentage of NW-PwMS showing at least one abnormal instrumented metric.

While the clinical scores were comparable between EDSS subgroups, the instrumented WHHT revealed that the EDSS: 2–2.5 subgroup was characterized by lower AP symmetry and reduced ML dynamic stability compared to the EDSS: 0–1.5 subgroup. This indicated that the instrumented assessment of WHHT could be a sensitive tool to detect differences also between subgroups of PwMS in the lower range of EDSS. These findings suggest that AP symmetry and ML dynamic stability describing WHHT could be responsive indexes to monitor the disease progression. Further longitudinal studies including subjects with a larger spectrum of disability should be performed to corroborate this hypothesis.

Compared to the FAB-s clinical scores, the instrumented WHHT demonstrated a higher ability to discriminate between HS and NW-PwMS: the percentage of participants showing at least one abnormal instrumented metric (68%) was statistically

TABLE 5 | Spearman's correlation coefficient (r_s) between instrumented metrics and clinical scores.

	FAB-s Item 6 subscore	FAB-s score	MSWS-12 score
ML stride regularity (-)	0.37***	0.46***	−0.13
AP iHR (%)	0.39***	0.49***	−0.25
ML sLyE (-)	−0.44***	−0.48***	0.34*

*AP, anteroposterior; ML, mediolateral; iHR, improved harmonic ratio; sLyE, short-term Lyapunov exponent; FAB-s, Fullerton Advanced Balance scale—short version; MSWS-12, 12-item Multiple Sclerosis Walking Scale. *$p < 0.05$; ***$p < 0.001$ (Bonferroni–Holm correction).*

larger than that detected by FAB-s-Item6 subscore (32%) and FAB-s score (39%). This result was found also considering separately the two EDSS subgroups, further supporting the larger sensitivity of the instrumented WHHT. Finally, the correlation analysis between the FAB-s scores and the instrumented metrics revealed a moderate concurrent validity of the proposed indexes to measure dynamic balance impairments. Interestingly, ML dynamic stability, as measured by sLyE, was significantly correlated with the MSWS-12. This finding complements previous results showing that balance dysfunctions and instability are major contributors to the perceived MS-related walking disturbances also in the early stage of MS (39, 46). This result, together with previous findings of the responsiveness of sLyE to rehabilitation (24) and its association to fall risk in PwMS (55), suggests that this parameter, in particular, could be a promising sensitive biomarker to monitor the disease course from the beginning of MS and that exercises aimed at improving dynamic balance and stability should be proposed also to early-stage, high functioning PwMS. Future studies are necessary to confirm this hypothesis.

Study Limitations

First, the proposed instrumented metrics were computed on five strides that are those required by the FAB-s instructions but are less than those suggested to increase the robustness of the parameters (10–20 strides) (41, 63). However, the use of a test already validated is undoubtedly an advantage because of its clinical application. Future studies considering more consecutive strides or more repetitions of short walking bouts (64) should be performed to assess the test-retest reliability of the instrumented WHHT. Second, the Functional Systems scores have not been addressed since one of the aims of this study was to compare subgroups of PwMS with different EDSS global scores, independently from the functional systems involved. Third, although hearing loss is considered a rare symptom of MS, it is not uncommon (65). Even if none of the participants reported auditory problems, a dedicated exam was not performed. Hence, considering that the subjects had to turn their head at a metronome beat, we cannot exclude a possible influence of eventual hearing loss on the results. Further studies should address this aspect and the possible effect of the different functional systems. Finally, the tested sample consisted of early-stage high-functioning PwMS, thereby reducing the generalizability of present results.

CONCLUSION

The present results confirmed our hypotheses: the IMU-based assessment of WHHT provides valid objective metrics able to discriminate, with a higher sensitivity than clinical scores, between HS and NW-PwMS and between EDSS subgroups. The method is a promising tool to complement clinical assessments and detect subtle impairments in early-stage non-disabled PwMS who still show normal natural walking. This approach would help in tracking these impairments over time and identifying those individuals who may benefit from preventive motor exercise since the very early stages of MS, when rehabilitation may still have neuroprotective and disease-modifying effects, as recently suggested (26). Future studies, including more severe PwMS, are warranted to assess the reliability and the clinical responsiveness of the proposed metrics.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local Ethical Committee of each center. These were: Comitato Etico della Sezione "IRCCS Fondazione Don Carlo Gnocchi" del Comitato Etico IRCCS Regione Lombardia (IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy), Comitato Etico Interaziendale dell'A.O "SS. Antonio e Biagio e Cesare Arrigo" (Centro di Recupero e Rieducazione Funzionale Mons. Luigi Novarese, Moncrivello, Italy), and Comitato Etico Regionale della Liguria (Italian Multiple Sclerosis Foundation, Genoa, Italy). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conception and design of the study, software implementation, data processing, data analysis, data interpretation, and drafting the manuscript by IC. Instrumented data collection, clinical assessment, and data organization by EG, DA, and RD. Data collection and organization by AT. Recruitment of patients and clinical assessment by GB, PC, CS, and MR. Conceptualization and design of the study, data analysis and interpretation, and coordination by DC. Conceptualization and design of the study and coordination by MF, CS, and GB. All authors contributed to data interpretation, critically reviewed the manuscript, and approved the final version of the manuscript.

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Vestibulo-Ocular Reflex Is Modulated by Noisy Galvanic Vestibular Stimulation

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We investigated whether noisy galvanic vestibular stimulation (nGVS) modulates the vestibulo-ocular reflex (VOR) and whether this effect is correlated with the effect of nGVS on body sway. Thirty healthy young adults participated. The video head impulse test (vHIT) was used to estimate the ratio of eye motion velocity/head motion velocity to VOR-gain. The gain 60 ms after the start of head motion (VOR-gain-60 ms) and regression slope (RS) (i.e., gain in eye and head motion; VOR-gain-RS) were calculated. The total path length of the foot center of pressure (COP-TL) during upright standing was calculated to estimate body sway. Noisy Galvanic Vestibular Stimulation at 0.2, 0.6, 1.2 mA, or sham stimulation (direct current: 0 mA) was delivered to the bilateral mastoid process in random order during vHIT and COP measurements. Application of nGVS at 0.2 mA significantly reduced VOR-gain-RS, while application of nGVS at 0.6 mA significantly increased COP-TL. Vestibulo-ocular reflex-gain-60 ms differed significantly between 0.2 and 1.2 mA. There was no significant correlation between COP-TL and VOR-related parameters. These findings suggest that nGVS at 0.2 mA inhibits the VOR, while nGVS at 0.6 mA increases body sway during upright standing, although there may be no relationship between the respective effects in healthy individuals.

Keywords: noise stimulation, galvanic vestibular stimulation, video head impulse test, vestibulo-ocular reflex, postural control

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INTRODUCTION

The vestibulo-ocular reflex (VOR) is important for dynamic gazing in daily living (1), and patients with vestibular disease experience impairments in the VOR and dynamic visual ability (2). During the VOR, endolymph moves in the opposite direction of head movement, causing deflection of the ampulla (3), which in turn generates afferent action potentials in the primary vestibular nerve. In response to this impulse, the vestibular nucleus generates an action potential in the external eye muscles, resulting in eye movement. Thus, accurate assessment of VOR function is important for vestibular rehabilitation.

The head impulse test (HIT) is one of the most useful techniques for determining vestibular hypofunction and related vestibular disorders, and uses an impulsive VOR method first described by Halmagyi and Curthoys in 1988 (4, 5). Further, this HIT was implemented concomitant to the video discovered by Hamish McDougall (6), and this video head impulse test (vHIT) was compared with the gold standard search coil to highlight the saccades behavior in cases of chronic vestibular

deficit. Further, the vHIT test specifically explores Type I Hair Cells activity and consequently afferent transient systems (5).

The ratio of the velocity of eye movement to the velocity of head movement is considered the gain of the reflex and is used to evaluate VOR functionality (7). In patients with unilateral vestibular disorder, the VOR gain is reduced by approximately 30% compared to the intact side (5). Furthermore, the vHIT can detect a slight change in VOR gain (8) following intratympanic gentamicin treatment in patients with Ménière's disease (9). Therefore, restoration of VOR-gain in patients with vestibular disorders has become an important issue in vestibular rehabilitation.

Galvanic vestibular stimulation (GVS) is used to change the excitability of the vestibular reflex as a non-invasive neuromodulation method, and has been shown to improve vestibular rehabilitation results (10). Galvanic vestibular stimulation can induce impulses in primary otolithic neurons as well as primary semicircular canal neurons (11, 12). Recent studies have reported that noisy galvanic vestibular stimulation (nGVS) has the potential to alter the excitability of the vestibular reflex (13–15) via the application of a noise current to the bilateral mastoid process. A possible mechanism for this alteration is interference by nGVS in vestibular information carried by the irregular vestibular neurons originating from Type I Hair Cells (16). Although nGVS is thought to alter the degree of vestibulospinal reflexes and body sway in both patients with vestibular disease (17) and healthy participants (18, 19), it remains unclear whether nGVS alters the VOR. In the present study, therefore, we investigated whether nGVS induces changes in VOR-gain.

The effect of nGVS on body sway is dependent on the stimulus intensity; if it is too weak, it has no effect, and if it is too strong, it may increase the vestibulospinal reflex. This dependence may also be true for VOR. A previous study reported that the optimal stimulus intensity was approximately 0.2 mA (20), with exacerbation occurring at approximately 0.5 and 1 mA. Therefore, in this study, we also examined the hypothesis that VOR-gain would be increased at 0.2 mA and decreased at 0.6 and 1.2 mA.

The effect of nGVS varies among individuals (18, 20). Even at the same intensity, the center of gravity sway may decrease or increase. If the effect of nGVS on gravity oscillation and the effect on VOR are caused by the same effect of electricity on the vestibular apparatus, then the amount of both effects should be correlated. Therefore, the present study further examined whether there is a correlation between the center-of-gravity sway caused by nGVS and the gain of VOR.

METHODS

Participants

The appropriate sample size for one-sample tests and one-way repeated-measures analysis of variance (ANOVA) was estimated using G*power software (Version 3.1.9.4) (21) before the experiments. For one-sample tests, an *a priori* power analysis with the effect size (d) set to 0.8, the alpha error probability set to 0.05, and the power (1 – beta error probability) set to 0.95 indicated a required sample size of 23. For one-way repeated-measures ANOVA (OR-ANOVA), an *a priori* power analysis with the effect size (f) set to 0.4, alpha error probability set to 0.05, power (1 – beta error probability) set to 0.95, correlation among repetitive measures set to 0.5, and non-sphericity correction epsilon set to 1 indicated a required sample size of 15.

Thirty healthy adults (mean age, 20.5 ± 4 years; 23 women and 7 men) participated in the present examination. No participants had a history of neurological disease, including epilepsy, and none had experienced vertigo or dizziness within 3 weeks before participation in the study. All procedures of the present study were approved by the Ethics Committee of Shijonawate Gakuen University (approval code: 21-7) and were conducted with the understanding and written consent of each participant in accordance with the principles and guidelines of the Declaration of Helsinki.

General Procedures

This study was conducted using a single-blind, sham-controlled design. The stimulation conditions of nGVS were not known to the participants or assessors for vHIT. Before examination, we tested inducing body sway to the anodal side (22) by a 2.5-mA square wave pulse (spGVS) (23, 24) with 200 ms duration (25, 26) while participants maintained upright standing with their head facing forward (26), eyes closed, and feet together (25, 27). This test was conducted to determine whether they were responders to GVS, as per previously conducted methodology (19).

Next, the vHIT was conducted in each nGVS condition: sham, 0.2, 0.6, and 1.2 mA. In one vHIT, passive head rotation to the right and left was performed until 20 successes were achieved in each direction (28) under all of the nGVS conditions. The nGVS was delivered at 70 s, and the vHIT was completed within 40 s during nGVS. The order of stimuli was randomized for all participants. After the vHIT, we measured the center of pressure (COP) of the feet while standing upright during the sham, 0.2, 0.6, and 1.2 mA nGVS conditions. Similarly, the order of the nGVS conditions was randomized for all participants. The interval between tests was approximately 30 s. In summary, four vHITs (40 s) and four COP measurements (30 s) were conducted under random stimulation conditions.

vHIT

All vHITs (5) were administered by one tester, who is a skilled physical therapist specializing in otolaryngology. Left eye position and head velocity were recorded using the high-speed digital EyeSeeCam system (220 frames/s with an inertial measurement unit gyroscope; Interacoustics, Middelfart, Denmark) with infrared camera to estimate the gain of VOR, as per previously established methodology (29). During the test, participants wore tight-fitting goggles and were seated in a chair, instructed to make sure their pupils were clearly visible, and maintain their gaze on a red magnet (1 cm in diameter) attached to a whiteboard as a target positioned 1 m in front of them. The head was passively rotated by a tester at a velocity of more than 150°/s and a mean acceleration ranging from 1,000 to 2,500°/s^2 (29). The horizontal rotation amplitude was set at 5–10°.

Trials not meeting these conditions were omitted from the successful trials. Twenty suitable impulses of head rotational to the right and left were recorded in each stimulation condition, as previously described (29). Individual VOR gains were automatically calculated with the software included with EyeSeeCam system.

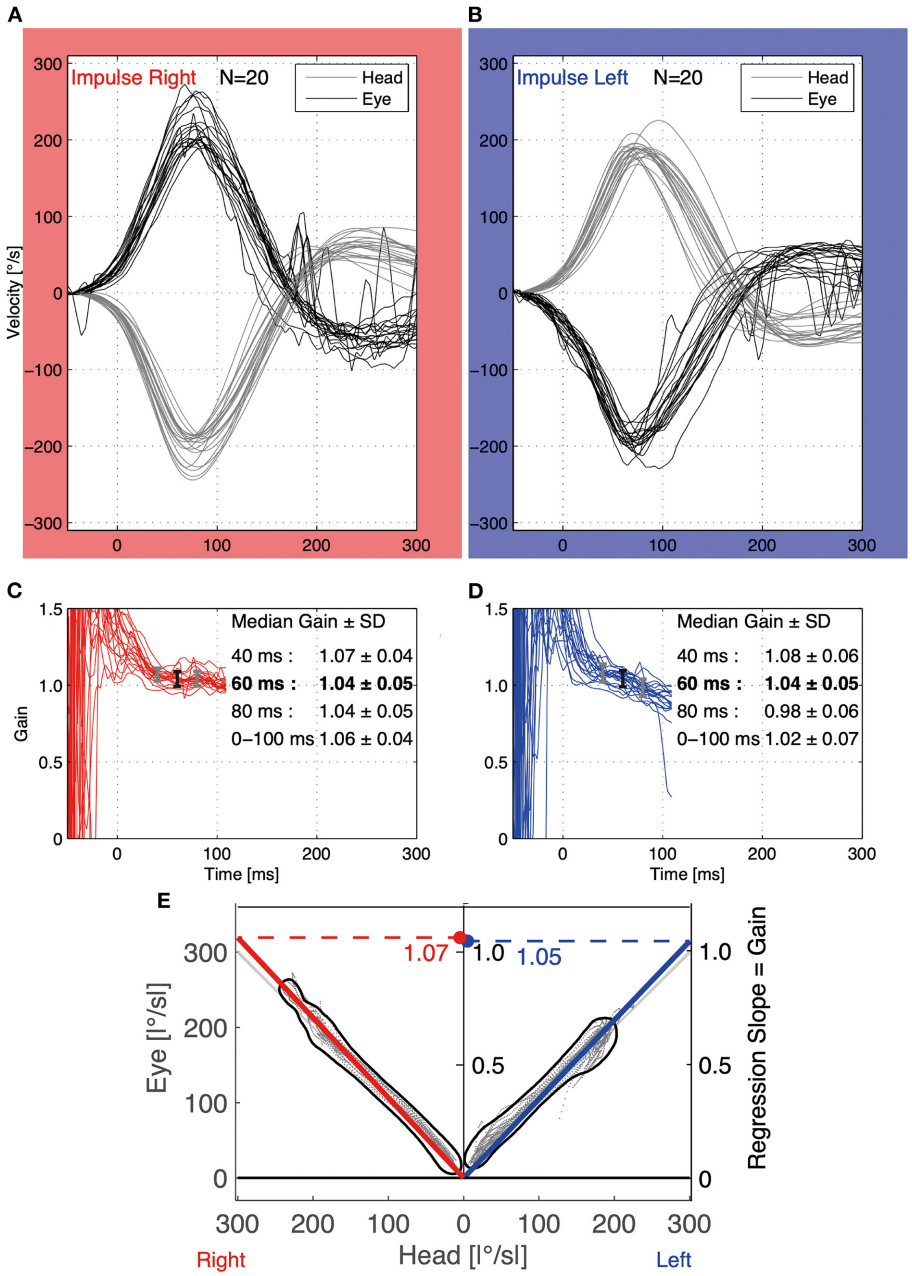

FIGURE 1 | Representative waveform of eye and head velocity for head impulses to the right **(A)** and left **(B)** in a participant during the vHIT (20 head impulses to the right and left). The vertical and horizontal axes indicate velocity and time from the start of head motion (head motion velocity >20°/s), respectively. The gray lines indicate head velocity, while the black lines indicate eye velocity. In the middle graphs, the 20 red **(C)** and blue **(D)** waves indicate VOR-gain calculated from eye and head velocity in each impulse, respectively. The vertical and horizontal axes indicate VOR-gain and time from the start of head motion, respectively. The vertical bars indicate the median and standard deviation (SD) at 40 ms (left gray bar), at 60 ms (middle black bar), and at 80 ms (right gray bar) in **(C,D)**. The median VOR-gain at 60 ms was used for analysis as in each vHIT, as this value especially reflects the function of the horizontal canal during horizontal rotational HIT. **(E)** The bottom graph is a scatter plot of absolute eye and head velocity for head impulses to the right and left in the vHIT, and the red and blue lines represent the respective regression lines. The regression slope (RS) was used as VOR-gain-RS for analysis, as this indicates the ratio of eye/head velocity during the whole motion. VOR, vestibulo-ocular reflex; vHIT, video head impulse test.

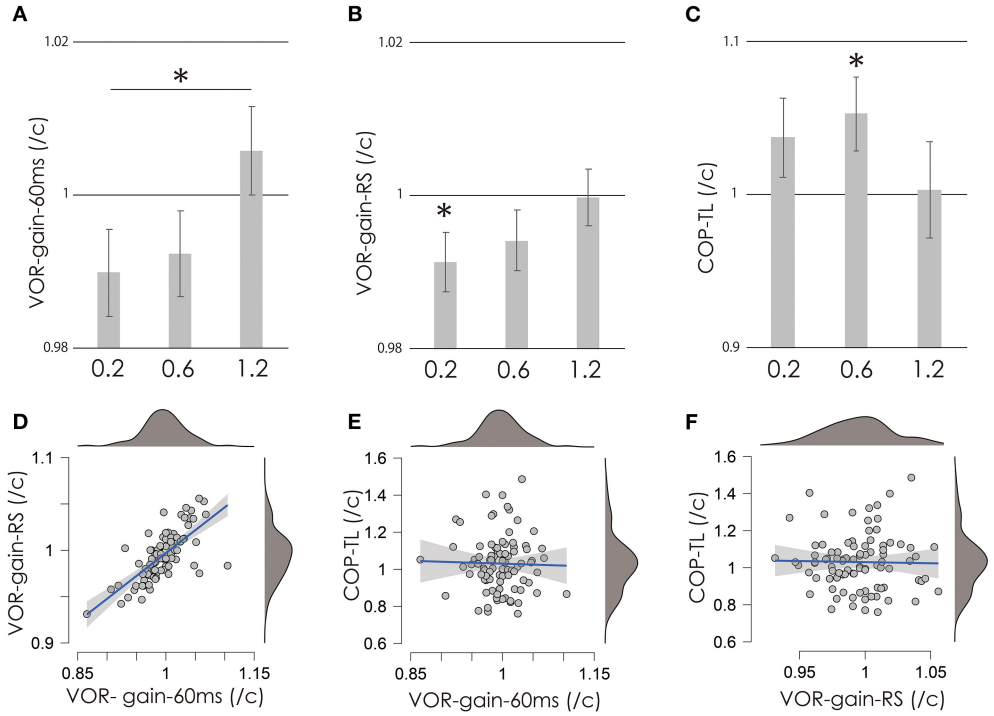

FIGURE 2 | VOR-gain-60 ms **(A)**, VOR-gain-RS **(B)**, and COP-TL **(C)** per control ratio at 0.2, 0.6, and 1.2 mA. Vertical gray bars indicate the mean, and error bars indicate standard errors. Asterisks indicate significance. **(D–F)** Scatter plots of COP-TL, VOR-gain-60 ms, and VOR-gain-RS over all stimulation conditions. Small gray circles indicate individual data, while the mean value of the right and left VOR was used as a representative value (see Methods and Results sections). The blue lines indicate regression lines, and the gray area indicates the 95% confidence interval. Upper and right dark gray areas indicate the density of the data (top: 100%; bottom: 0%). VOR, vestibulo-ocular reflex; vHIT, video head impulse test; COP-TL, total path length of the foot center of pressure; RS, regression slope.

COP Measurements

Participants were instructed to maintain an upright standing position on a force plate with both feet together while looking straight ahead to gaze at a blue magnet target (1 cm in diameter) 2 m in front of the participant. The ground reaction force during standing was recorded for 30 s with a force plate (Gravicorder G5500; Anima, Japan) at a sampling rate of 20 Hz. To estimate postural sway, the total path length of the foot center of pressure (COP-TL) during standing for 30 s was calculated as described in our previous studies (19, 25).

nGVS

The nGVS experiments were conducted in nearly the same manner as previous studies (14, 18, 19, 30). To deliver the noise electrical stimulation to the vestibular nerve, we used DC-STIMULATOR PLUS (Eldith, NeuroConn GmbH, Ilmenau, Germany) via Ag/AgCl surface electrodes on both mastoid processes as per our previous studies (14, 19, 30). The "noise" stimulation mode was used to generate a current in random level generated for every sample; the sample rate was 1,280 samples/s (14, 18, 19, 30, 31). The intensity was set to 0.2, 0.6, and 1.2 mA in this "noise" mode. In this setting, random numbers are normally distributed over time. The probability density follows a Gaussian bell curve, and all the coefficients have a similar size in the frequency spectrum in this "noise" mode. For the sham condition, direct current electrical stimulation was delivered using the same device with the intensity set to 0 mA (control trial) as described previously (19). These stimulations were delivered for 70 s during the vHIT and 50 s during the COP measurements.

Analysis

Figure 1 shows typical waveforms for eye and head velocity. Vestibulo-ocular reflex gain was calculated as eye motion velocity/head motion velocity at 40, 60, and 80 ms after the start of head motion by averaging the EyeSeeCam (Interacoustics, Middelfart, Denmark) results for 20 successful trials in each vHIT, as per previous methodology (29). The start of head motion was defined as the point when the velocity exceeded 20°/s, which is the default setting in the EyeSeeCam system and has been used previously (29). The VOR gain in 60 ms (VOR-gain-60 ms) is considered the most reflective parameter of the VOR function (32). The regression slope (RS) was calculated by determining the slope of the best-fitting line for the head and eye velocities (33) (**Figure 2**), which indicates the VOR gain in the whole eye and head (8). Therefore, we used the VOR gain in 60 ms and RS to estimate VOR function. Rotation to the right primarily reflects the function of the right horizontal semicircular canal, while rotation to the left primarily reflects the function of the left horizontal semicircular canal (5). Therefore, the VOR for the right and left impulses obtained from one participant were

TABLE 1 | One-sample test.

		Test of normality (Shapiro-Wilk)							95% CI for location estimate		
Parameter	**Intensity (mA)**	***W***	***p***	**Test**	**Statistic**	***df***	***p***	**Location estimate**	**Lower**	**Upper**	**Significant**
VOR-gain-60 ms	0.2	0.96	0.049	Student	−1.793	59	0.078	0.99	0.978	1.001	
				Wilcoxon	573.5		0.147	0.991	0.979	1.002	
	0.6	0.991	0.924	Student	−1.387	59	0.171	0.992	0.981	1.003	
				Wilcoxon	607.5		0.175	0.991	0.979	1.003	
	1.2	0.972	0.189	Student	0.983	59	0.33	1.006	0.994	1.017	
				Wilcoxon	840.5		0.27	1.008	0.994	1.019	
VOR-gain-RS	0.2	0.948	0.013	Student	−2.261	59	0.027	0.991	0.984	0.999	
				Wilcoxon	353		0.026	0.988	0.979	0.997	*
	0.6	0.975	0.265	Student	−1.501	59	0.139	0.994	0.986	1.002	
				Wilcoxon	608		0.176	0.992	0.983	1.002	
	1.2	0.945	0.009	Student	−0.084	59	0.933	1	0.992	1.007	
				Wilcoxon	677		0.917	1	0.987	1.008	
COP-TL	0.2	0.983	0.887	Student	1.436	29	0.162	1.037	0.984	1.09	
				Wilcoxon	296		0.198	1.03	0.982	1.084	
	0.6	0.946	0.134	Student	2.177	29	0.038	1.052	1.003	1.102	*
				Wilcoxon	329		0.047	1.052	1	1.092	
	1.2	0.911	0.016	Student	0.088	29	0.931	1.003	0.938	1.068	
				Wilcoxon	201		0.529	0.983	0.928	1.047	

*For the Student t-test, location estimate is given by the sample mean and the alternative hypothesis specifies that the mean is different from 1. For the Wilcoxon test, location estimate is given by the Hodges-Lehmann estimate, and the alternative hypothesis specifies that the median is different from 1. *p < 0.05.*

regarded as individual parameters (34). However, to estimate the correlation between the effect of nGVS on body sway (COP-TL) and VOR, the mean VOR for the right and left impulses was calculated as one parameter.

The total path length of the COP position (COP-TL) for 30 s was calculated to estimate the amount of body sway. The test/control ratio was calculated to normalize these parameters. A one-sample Student's *t*-test was performed to test the hypothesis that the test/control ratio differs from 1. However, if the normality test (Shapiro–Wilk) was significant, the Wilcoxon test was adopted. An OR-ANOVA was used to examine differences among intensities. If the Shapiro–Wilk test suggested an equal distribution for the ANOVA, the Friedman test was used. If the ANOVA suggested a significant effect of intensity, a *post-hoc* Bonferroni test or Kruskal–Wallis test was conducted. The JASP software (version 0.14.1; University of Amsterdam, Amsterdam, the Netherlands) (35) was used for all statistical analyses, and the alpha level was set to 0.05.

RESULTS

We made sure there were only the responders to GVS in this study because all participants induced lateral body sway to the anodal side by spGVS before the experiments. No participants experienced harmful side effects (i.e., headache, epilepsy, burns, or continuous dizziness after stimulation) throughout the entire experiment.

Figures 2A–C shows the test/control ratios for VOR-gain (60 ms), VOR-gain (RS), and COP-TL. **Table 1** shows the results of the one-sample *t*-test, which revealed significant changes in VOR-gain (RS) and COP-TL from the control at 0.2 at 1.2 mA, respectively. **Table 2** shows the results of the OR-ANOVA, which suggested a significant effect of stimulation on VOR-gain (60 ms), although there was no significant effect of stimulation on VOR-gain (RS) or COP-TL. The *post-hoc* analysis for VOR-gain (60 ms) revealed a significant difference between 0.2 and 1.2 mA (**Table 3**). **Figure 2** shows a scatter plot of VOR-gain (60 ms), VOR-gain (RS), and COP-TL over the stimulation conditions. **Table 4** shows the results of the correlation analysis for VOR-gain (60 ms), VOR-gain (RS), and COP-TL in the 0.2, 0.6, and 1.2 mA conditions and over all conditions. The results suggested that there was a significant correlation between VOR-gain (60 ms) and (RS), but not between VOR-gain (60 ms) and COP-TL.

DISCUSSION

The present study investigated the effect of nGVS on the VOR in humans. Specifically, we investigated whether nGVS modulates the VOR-gain in 60 ms and RS, and whether nGVS is correlated with VOR and COP-TL. Our findings indicated that VOR-gain-RS was significantly reduced by nGVS at 0.2 mA, and that COP-TL was significantly increased by nGVS at 0.6 mA. We also observed a significant difference in VOR-gain-60 ms between the 0.2 and 1.2 mA conditions. However, there was no significant correlation between COP-TL and VOR-related parameters. These findings indicate that nGVS at 0.2 mA can inhibit the VOR, while nGVS at 0.6 mA can increase body sway

TABLE 2 | ANOVA.

	Cases	Sum of squares	*df*	Mean square	*F*	η^2	*p*	Significant
VOR-gain-60 ms	Intensity	0.009	2	0.004	3.564	0.057	0.031	*
	Residuals	0.144	118	0.001				
VOR-gain-RS	Intensity	0.002	2	0.001	2.209	0.036	0.114	
	Residuals	0.059	118	4.970e−4				
COP-TL	Intensity	0.039	2	0.019	1.882	0.061	0.161	
	Residuals	0.597	58	0.01				

*$p < 0.05$.

TABLE 3 | *Post-hoc* test in VOR-gain-60 ms.

			95% CI for mean difference					
		Mean difference	Lower	Upper	*SE*	*t*	p_{holm}	Significant
0.2 mA	0.6 mA	−0.002	−0.018	0.013	0.006	−0.384	0.702	
0.2 mA	1.2 mA	−0.016	−0.031	−3.297e−4	0.006	−2.48	0.044	*
0.6 mA	1.2 mA	−0.013	−0.029	0.002	0.006	−2.096	0.076	

*P-value and confidence intervals adjusted for comparing a family of three estimates (confidence intervals corrected using the Bonferroni method). *$p < 0.05$.*

TABLE 4 | Correlation.

				Pearson			Spearman			
	Parameter 1	Parameter 2	Shapiro-Wilk	*p*	*r*	*p*	Significant	Rho	*p*	Significant
Total	VOR-gain-60 ms	VOR-gain-RS	0.883	<0.001	0.711	<0.001	***	0.712	<0.001	***
	VOR-gain-60 ms	COP-TL	0.98	0.167	−0.026	0.81		0.006	0.955	
	VOR-gain-RS	COP-TL	0.969	0.03	−0.021	0.848		0.002	0.986	
0.2mA	VOR-gain-60 ms	VOR-gain-RS	0.911	0.016	0.754	<0.001	***	0.669	<0.001	***
	VOR-gain-60 ms	COP-TL	0.905	0.011	−0.011	0.955		0.078	0.681	
	VOR-gain-RS	COP-TL	0.962	0.339	−0.249	0.184		−0.147	0.437	
0.6mA	VOR-gain-60 ms	VOR-gain-RS	0.924	0.034	0.677	<0.001	***	0.663	<0.001	***
	VOR-gain-60 ms	COP-TL	0.954	0.215	−0.096	0.614		−0.054	0.776	
	VOR-gain-RS	COP-TL	0.966	0.44	0.084	0.659		0.109	0.564	
1.2mA	VOR-gain-60 ms	VOR-gain-RS	0.71	<0.001	0.683	<0.001	***	0.829	<0.001	***
	VOR-gain-60 ms	COP-TL	0.954	0.215	0.077	0.685		0.073	0.702	
	VOR-gain-RS	COP-TL	0.933	0.059	0.124	0.513		0.112	0.554	

***$p < 0.001$.

while standing upright in healthy individuals, although there may be no relationship between the respective effects.

Administration of nGVS at 0.2 mA considerably reduced VOR-gain-RS, indicating that low-intensity nGVS inhibits the VOR. In contrast, VOR-gain-60 ms differed significantly between the 0.2 and 1.2 mA conditions, suggesting that high-intensity nGVS may increase the VOR. The vHIT explores Type I Hair Cells activity and consequently the afferent transient system (5). Ballistic rotation of the head in vHIT triggers action potentials in primary vestibular afferent neurons that project to vestibular nuclei, and induces eye movement (36). Galvanic vestibular stimulation can affect the synapses between hair cells in the semicircular canal and primary vestibular nerve, in addition to directly affecting the primary vestibular nerve including otolithic and semicircular canal neurons (11, 37). Furthermore, a previous *in vitro* study reported that stochastic noise electrical stimulation of the vestibular nuclei can modulate the neuronal gain of the medial vestibular nuclei (38). The nGVS can regulate the vestibular information carried by the vestibular neurons originating from Type I Hair Cells (16). Therefore, in this study, we propose that the nGVS modulated the VOR gain. However, the effect of nGVS is intensity-dependent; the optimal intensity decreases body sway, while non-optimal intensities increase body sway (20). Therefore, based on our results and these findings, we speculate that stimulation at 0.2 mA may be optimal for inhibition of the

VOR, while that at 1.2 mA may be optimal for facilitation of the VOR.

The COP-TL was significantly increased by nGVS at 0.6 mA. A previous study reported that nGVS at 0.2 mA decreased body sway in patients with vestibular disorder, while that at 0.5 mA increased body sway (20). Another previous study similarly reported that nGVS at 1 mA increased the COP-TL in a healthy young population (19). Therefore, our finding that nGVS at 0.6 mA increases COP-TL is consistent with those of previous studies. On the other hand, no significant decreases in COP-TL were observed at any intensity in the present study. A previous study reported that the effect of nGVS on body sway depends on the amount of body sway without stimulation (18), suggesting that only individuals with balance impairments can benefit from nGVS. As our study included healthy young adults without any neurological disorders, this may explain why nGVS only induced increases in COP-TL.

There was a significant positive correlation between VOR-gain-60 ms/control and VOR-gain-RS/control (**Table 4**). Vestibulo-ocular reflex-gain-60 ms reflects the ratio of eye motion velocity/head motion velocity at 60 ms after the start of head rotation, while the test/control parameter reflects the effect of nGVS. On the other hand, VOR-gain-RS reflects the ratio of eye motion velocity/head motion velocity during movement. A previous study indicated that values at 60 ms especially reflect the function of the ipsilateral horizontal semicircular canal, while those at other points reflect other functions. For example, values at 40 ms reflect the function of the ipsilateral otolith, while those after 100 ms, including compensatory catch-up saccades (5), reflect cerebellar function (39). Therefore, VOR-gain-60 ms may specifically reflects the function of the semicircular canal, while RS may include both otolith and cerebellar function. The correlation of the effect on both suggests that nGVS may exert effects not only on the ipsilateral semicircular canal, but also on organs common to both the primary vestibular nerve and the vestibular nucleus.

On the other hand, we observed no significant correlation between COP-TL and any VOR-gain parameters in any stimulation condition (**Table 4**). This suggests that there is no relationship between the effect on VOR and that on body sway in healthy young individuals, reflecting the function of the vestibulospinal reflex. There are some possible reasons for this decorrelation: First, the optimal intensity for the VOR and body sway was not 0.2, 0.6, or 1.2 mA. Therefore, a more rigorous search for intensity may be necessary (e.g., in 0.5 mA increments). Next, nGVS affects VOR and body sway via different organs. The origin of the vestibulospinal response for postural control is considered to arise from vertical canal input and otolith input (40). On the other hand, the horizontal head impulse of the VOR is related to the horizontal semicircular canal (41). Further studies are required to investigate the effect of nGVS on the vertical VOR and body sway.

There were some limitations to this study. First, only healthy young individuals were included, meaning that the effects of nGVS on VOR and body sway observed in this study may not apply to older populations and patients with vestibular disorders, as these effects may depend on vestibular function (42). Further, we tested the response to GVS before the examination, and further studies are required to determine the optimal intensity (20) of nGVS for the VOR in patients with vestibular disorders or healthy older individuals. Lastly, we could not rigorously separate and remove predictionary or compensatory saccades from all eye movements. As the methods for identifying and separating these saccades remain inconclusive, further research is needed.

In conclusion, our findings indicated that nGVS can modulate VOR-gain. The effects of nGVS on VOR-gain may not be related to the effect on body sway during upright standing requiring vestibulospinal control. Further studies are required to determine the optimal intensity for improving VOR in patients with vestibular disorders.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository and accession number can be found below: Akiyoshi Matsugi, Tomoyuki Shiozaki (2021), DATASET for vHIT-nGVS Mendeley Data, doi: 10.17632/dtj374wb2w.1, https://data.mendeley.com/datasets/dtj374wb2w/1.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Shijonawate Gakuen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM and TS: conceptualization and methodology. AM, TS, and HT: data curation, validation, writing—review, and editing. AM: formal analysis, funding acquisition, visualization, and writing—original draft. TS: resources and software. HT: supervision. All authors contributed to the article and approved the submitted version.

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Use of Stakeholder Feedback to Develop an App for Vestibular Rehabilitation–Input From Clinicians and Healthy Older Adults

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Close to half people over 60 years of age experience vestibular dysfunction. Although vestibular rehabilitation has been proven effective in reducing dizziness and falls in older adults, adherence to exercise programs is a major issue and reported to be below 50%. Therefore, this research aimed to develop an app with gaming elements to improve adherence to exercises that are part of vestibular rehabilitation, and to provide feedback to increase the accuracy during exercise performance. A clinician-informed design was used where five physical therapists were asked identical questions about the exercises they would like to see in the app, including their duration and frequency. Games were developed to train the vestibulo-ocular (VOR) reflex using VOR and gaze shifting exercises; and to train the vestibulo-spinal system using weight shifting and balance exercises. The games were designed to progress from simple to more complex visuals. The games were controlled by an Inertial Measurement Unit placed on the head or anterior waist. The app was tested on ten healthy females (69.1 ± 5.1 years) with no prior history of vestibular dysfunction or complaints of dizziness. Participants completed gaze stabilization and balance exercises using the app and provided feedback on the user interface, ease of use, usefulness and enjoyment using standardized questionnaires and changes they would like to see in the form of open-ended questions. In general, participants reported that they found the app easy to use, the user interface was friendly, and they enjoyed playing the games due to the graphics and colors. They reported that the feedback provided during the exercise session helped them recognize their mistakes and motivated them to do better. However, some elements of the app were frustrating due to incomplete instructions and inability to distinguish game objects due to insufficient contrast. Feedback received will be implemented in a revised version which will be trialed in older adults with dizziness due to vestibular hypofunction. We have demonstrated that the "Vestibular App™" created for rehabilitation with gaming elements was found to be enjoyable, useful, and easy to use by healthy older adults. In the long term, the app may increase adherence to vestibular rehabilitation.

Keywords: vestibular rehabilitation, physical therapy, vestibular ocular reflex, rehabilitation games, balance, rehabilitation application, dizziness

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INTRODUCTION

Vestibular hypofunction is a condition that results from damage to the vestibular organs in the inner ear and is associated with disabling symptoms including dizziness, vertigo, blurred vision, and postural instability. It is estimated that one third of US adults over 40 experience vestibular dysfunction and the prevalence increases sharply with age, with around half of those over age 60 experiencing vestibular dysfunction as documented by a balance test (1). It was found that those people who exhibit vestibular dysfunction symptoms (dizziness) are twelve times more likely to fall (1). Vestibular rehabilitation has been proven to be effective in reducing symptoms of dizziness and imbalance by providing exercise-focused interventions to promote adaptation and/or compensation for vestibular hypofunction (2–7). Clinical care is guided by best evidence, and in 2016 the Clinical Practice Guidelines (CPG) for vestibular hypofunction were created (8) and recently revised in 2021 (9). Based on CPG recommendations, vestibular-trained clinicians typically provide home exercise programs in written format as handouts and recommend patients perform the exercises consistently and accurately between 3 and 5 times a day, for a total of 15–20 min per day. However, adherence to the exercise program remains a major problem, with compliance rates below 50% (10). Many factors influence exercise adherence, however from a patient perspective the main factors that limit adherence to exercises are a lack of understanding of the exercises, fear of increasing symptoms during exercises, performing the exercises incorrectly, needing ongoing guidance and direction (10–13). Technology has made significant advances in the past two decades and can be harnessed to address some of these barriers.

Choi and colleagues found that persons who had suffered from a stroke and had resulting upper extremity impairments were more satisfied with a mobile game-based treatment vs. conventional treatment, they credit their success to the mobile game because it was specifically developed for their patients (14). For people with vestibular hypofunction, increased compliance and enjoyment was reported with the use of computer games, video games and using virtual reality (15–18). However, these games are not designed for vestibular rehabilitation at home, since they lack the specific head/body motions required to address gaze stability impairments, they are not customized based on each person's deficits, and cannot be advanced in visual or task complexity at a clinically relevant level as the person improves. Additionally, they do not provide patients with feedback to modify their performance, which currently is only possible when the person has direct supervision by a therapist.

Several studies have noted that 'multifaceted' strategies are necessary to implement clinical practice guidelines and modify therapist behaviors (15–17). When one introduces technology to deliver interventions the clinician must learn new skills. Molding and colleagues found that having clinician feedback early in the development phase of technology can be helpful to adopt new clinical skills (18). Having clinician feedback and involvement early in the development phases of technology can help to shape the elements of technology that are essential in the clinic, keeping in mind clinician time and effort. It is also necessary to consider different types of clinics and perspectives of clinicians in different healthcare sectors. This is an important step to form an alliance between researchers, industry, and clinicians to maximize the probability that a novel technology will be adopted in clinical practice.

The aims of this study were to use a clinician-informed design to develop, implement and test an app to deliver a rehabilitation program congruent with the CPG for peripheral vestibular hypofunction. The goals of this study were: (1) to use structured interviews and clinician feedback to design an application, including defining the type of exercises, progression of exercises, and safety during exercise performance; and to (2) test a prototype application in healthy controls so that feedback from participants could be used to make iterative changes to create an app that could be used in people with vestibular hypofunction.

MATERIALS AND METHODS

Clinician Feedback

To help shape the design of the virtual App-based technology for older adults with vestibular hypofunction, monthly focus group meetings were held with five physical therapists practicing in vestibular rehabilitation. All therapists hold a doctorate in physical therapy and have completed at least one course in vestibular rehabilitation. They work in a variety of settings including private practice, university hospital clinics, and Veterans' Affairs (VA) clinics. Years of experience range from 8 to 22 years, and they hold positions such as clinic owners, clinic directors, and lead vestibular therapists. Three therapists hold teaching positions. Each therapist participated in six one-hour sessions, that were setup at their convenience. The sessions were recorded and per session, identical questions were asked to all therapists involved. Responses were compared between therapists and with the CPG for peripheral vestibular hypofunction to identify gaps in practice.

Meetings focused on the following topics:

Session 1–Identifying exercises to include. The goal of this session was to identify and include all exercises that are required for older adults with vestibular hypofunction to perform their At-home rehabilitation session.

Session 2–Defining requirements and instructions for exercises. The purpose of this session was to define the instructions for each of the exercises that were included in the Vestibular Rehabilitation App™. The information obtained was used to design each exercise to ensure that each game accurately represented the intent of the rehabilitation exercise.

Session 3–Exercise progression. The purpose of this session was to understand and describe patient progression in clinical practice. This provided information to shape the automated progression prompts in the app.

Session 4–Techniques to improve adherence. In this session, therapists discussed the barriers to adherence and techniques that are currently used to overcome them. Elements were designed and added to the app with the goal to improve compliance.

Session 5–Patient education. The purpose of this session was to identify the education provided by clinicians over the course of rehabilitation, such as the time it takes for recovery, the importance of walking and movement in the recovery process,

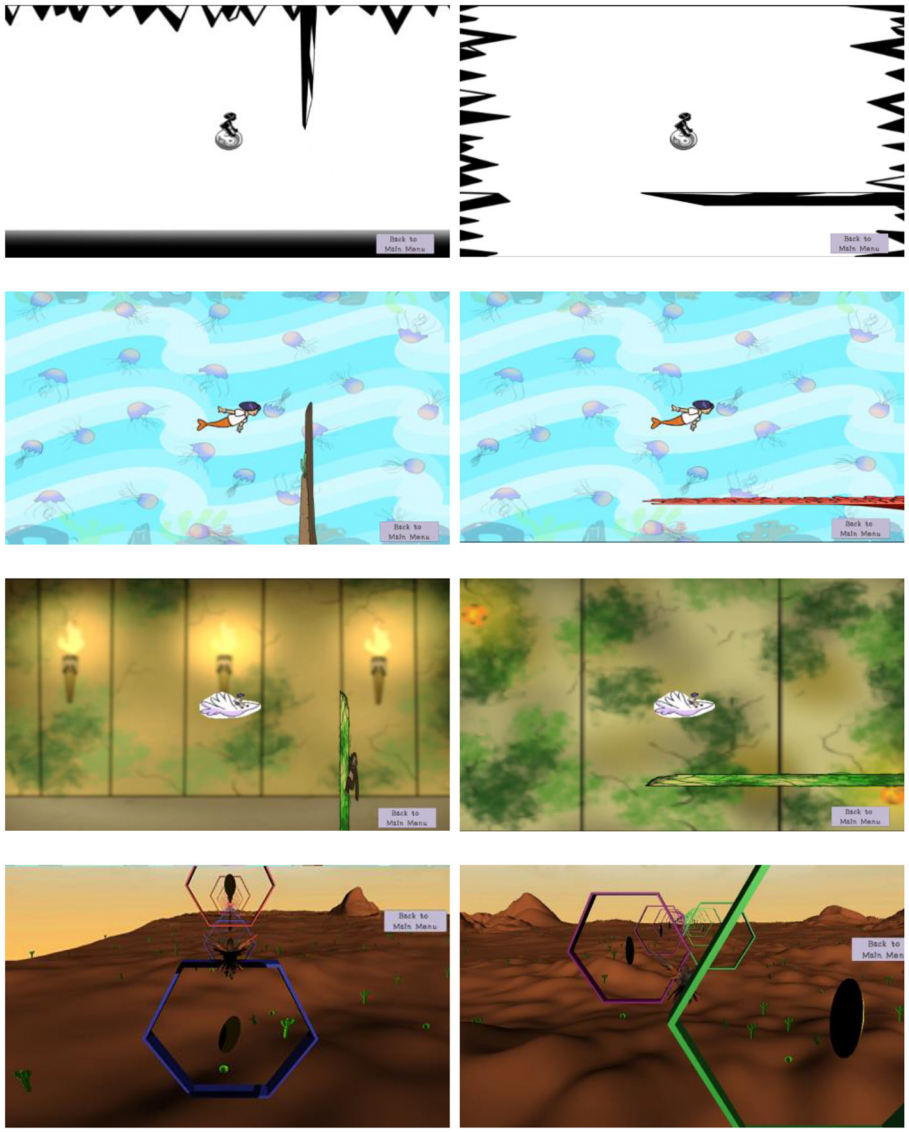

FIGURE 1 | Four different levels of exercise for VOR in the pitch and yaw direction (left and right column respectively). The various levels of visual stimuli are tailored to the severity of symptoms due to vestibular dysfunction. Patients progress from simple backgrounds (top row), to a complex static background (2nd row), a complex dynamic background (3rd row–torches flicker), to a 3D background with texture and the character and background moving (bottom row). Note that although the background was static for the first two rows, the obstacles and character still moved over the screen.

among others. This session provided information to shape the educational elements in the app.

Session 6–Safety measures. The goal of this session was to define the safety features that would need to be included in the app for people to perform the exercises at home safely.

The specific questions that were asked in each session are in the **Supplementary Material 1**.

Vestibular Rehabilitation Application

A mobile (smartphone or tablet) app containing games for the vestibular rehabilitation exercises was developed using Unity Pro (Unity Technologies) that could be used on an Android tablet. Games were controlled by an Inertial Measurement Unit [IMU; MetaMotionR (MBientlab)] that was connected to the tablet via Bluetooth. During gaze stability games, the IMU was placed on the forehead, and for the balance games, the sensor is secured with a waistband, just below the waist. The games developed were to train the vestibulo-ocular reflex (VOR) and gaze shifting or to train balance using weight shifting and single leg balance games. Artwork was developed specifically for the app. Care was taken to ensure that the artwork was appropriate for the target demographic (older adults) and has visual complexity that was tailored to patient severity.

Gaze Stability

VOR

The tablet was placed at arm's length for each individual so that they could reach the tablet easily to advance the games. A

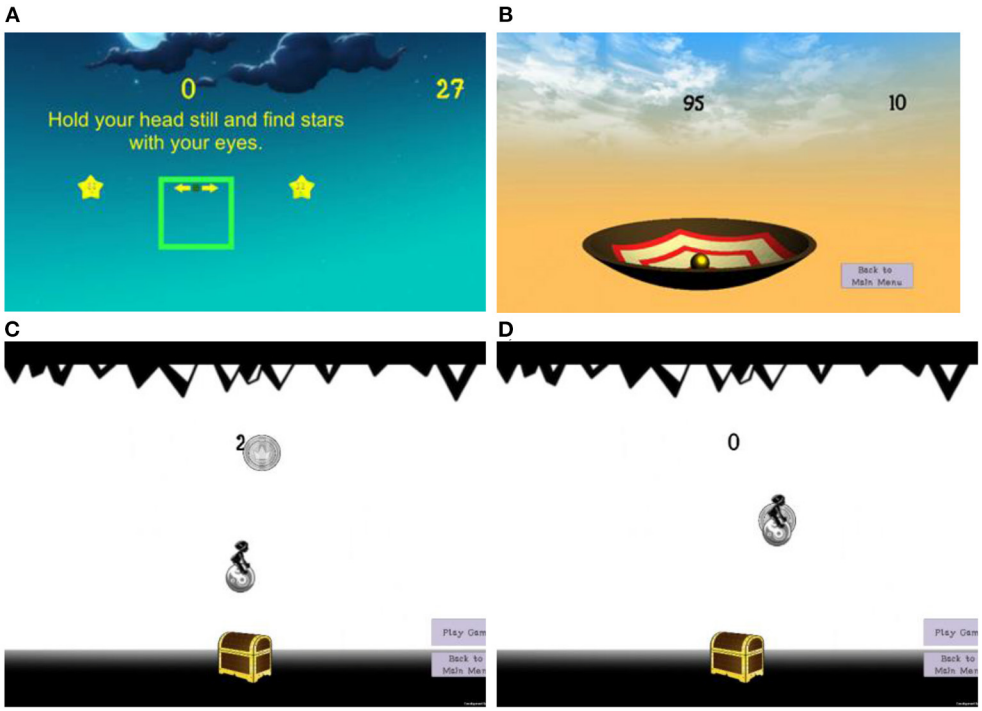

FIGURE 2 | Screenshots of the different vestibular rehabilitation exercise games: **(A)** gaze shifting, **(B)** single leg balance, and **(C)** weight shift with the character moving toward the coin and **(D)** weight shift with the character returning the coin.

character on the screen was controlled by moving the head Up-Down (pitch) or Left-Right (yaw) to avoid obstacles. Points were awarded with each successful obstacle avoided. Four different levels of exercises for the VOR were designed which could be tailored to the rehabilitation needs at the clinicians' discretion (**Figure 1**). The first level had few distracting elements, and as the exercises progressed the background distractors increased. The final progression (level 4) was a 3D version of the VOR game, where the environment was dynamic with the character moving through a moving 3D scene. The app allowed the desired head range of motion and head angular velocity of the head motion to be changed. Changes in head range of motion were associated with the change in the amount of character movement relative to the head motion, so that the character was at the edge of the screen at the desired range of motion. Similarly, the head angular velocity setting of head motion controlled the speed at which the obstacles appeared on the screen. Speed was calculated using the range of motion and the desired angular velocity to set the amount of head rotations that needed to be made per second.

Gaze Shifting

The tablet shows a 360° panoramic view of a night sky (**Figure 2**). With the tablet in hand, the participant has to move the tablet to find stars with their eyes only, without moving their head. On screen arrows point at the stars to guide the participant in the right direction. Once a star is aligned in the center of the screen, a message is provided with direction to move their head to align a box on the screen with the star. Success in this task is defined as a successful gaze shift exercise, with the eyes moving first followed by the head.

Balance Games

Single Leg Standing

A large bowl on the screen tilts anterior/posterior or laterally based on the movement of the IMU placed on the waist (**Figure 2**). The objective is to remain still and vertically aligned during single leg standing, keeping the ball in the center of the bowl (tilting causes the ball to roll away). Points are scored based on how close the ball is to the center of the bowl.

Weight Shifting

The person controls a character on the screen by shifting their body weight. Leaning forward moves the character up and leaning left/right moves the character horizontally. Instructions are given to move from the ankle and not from the hips or bend the knees. The goal is to collect the most coins and put these in a treasure chest to gain points (**Figure 2**). The coins appear at different locations on the screen so that the person must shift their weight in different directions.

Human Subject Testing

The study was approved by the Institutional Review Board at the University of Kansas Medical Center (site PI-LD). The Vestibular Rehabilitation App™ was tested with 10 adults, all participants signed informed consent before the study began. Inclusion criteria were: (1) Adults between 60

and 75 years of age; (2) Able to fluently read and speak English, (3) Able to give informed consent, (4) Able to get out of a chair independently. Exclusion criteria were as follows: (1) Pre-existing neurological disease, vestibular disease, or uncorrectable visual problem; (2) Lower extremity musculoskeletal injury or pain that would impede performing the balance exercises.

Human subject testing was performed in a laboratory setting at the University of Kansas Medical session, as a one-time session. During testing subjects were seated in a comfortable chair for the VOR exercises and standing for the balance exercises while facing a stand that the tablet was placed in with the tablet at eye level. The MetaMotionR IMU was placed on the subject's forehead for the gaze stability game and on the anterior waist for the balance games using hypoallergenic adhesive tape. The experimenter introduced the Vestibular Rehabilitation App^{TM} to the subject and only helped when needed. Subjects were asked to complete VOR games in both pitch and yaw exercise games at all four levels of visual complexity. Next, subjects completed the gaze shifting and balance games. Subjects played one set of each game and were given the option to rest between each game. After each game, participants were asked for feedback using a questionnaire that was developed specifically for the study. They rated the following questions using a 7-point Likert scale ranging from completely agree to completely disagree: (1) I enjoyed playing the game; (2) I understood what I was supposed to do in the game; and (3) It was easy for me to play the game. Followed by the following Open-Ended questions: (1) what I liked most about the game; (2) what I disliked most about the game. The questionnaire that was developed is included in the **Supplementary Files**.

After the participant has completed all exercises, they completed the following questionnaires.

1) Game Evaluation Questionnaire–The Game Evaluation Questionnaire was developed specifically for this study to evaluate each game separately (see **Supplementary Material 2.1**).
2) User Interface Questionnaire–The User Interface questionnaire (19) evaluates the overall reactions to the software. This rates several reactions on a scale of 0 to 9 (with 5 being a neutral answer).
3) Perceived Ease of Use Questionnaire–The perceived ease of use questionnaire by Davis (20) evaluates the ease of use of technology (see **Supplementary Material 2.2**).
4) Usefulness, Motivation, and Enjoyment Questionnaire–The usefulness, motivation and enjoyment questionnaire by Silveira et al. (21) was adapted to evaluate usefulness, motivation, and enjoyment when using the Vestibular App (see **Supplementary Material 2.3**).
5) Open Ended Feedback: At the end of the entire session, participants were asked five open-ended questions that were: (1) How challenging was the entire session? (2) What are the positive features of the app? (3) What did you not like about the app? (4) What changes would you like to see? (5) Do you see any barriers to using this app at home?

RESULTS

Clinician Feedback

Outcomes of the structured interviews with the clinicians and how the feedback was incorporated in the Vestibular Rehabilitation App^{TM} are outlined below.

Session 1–Identifying Relevant Exercises

The main exercises prescribed were similar between therapists, with small variations in prescription of additional strengthening, habituation, and balance. Educational and motivational opportunities were also noted by each of the therapists, such as grounding exercises to aid in reduction of dizziness.

Based on this feedback, the exercises that were included in the Vestibular Rehabilitation App^{TM} were the VOR exercise in the pitch and yaw directions, the gaze shift exercise, weight shifting, and single leg balance exercise. Although some clinicians prescribed habituation exercises, these were not included in this preliminary version of the app. They will be included in future versions.

Session 2–Defining Requirements and Instructions for Exercises

Instructions for the VOR exercise were similar between therapists, with small differences such as focusing on a dot vs. a word on a card. Therapists agreed on the definition of correct exercise performance, however, differences were seen in exercise dosing. Questionnaires that were used by clinicians ranged from ABC (22), to DHI (23), to dizziness scales, to therapeutic outcomes questionnaires. All clinicians ask patients about activities that caused dizziness, however, they varied in the manner the information was used for further exercise prescription.

Based on this feedback, the Vestibular Rehabilitation App^{TM} was developed with flexibility to prescribe exercise duration and the support used (e.g., single vs. double leg stance, holding a chair) during balance exercises. A dizziness visual analog scale from 0 to 10 was added to the app to rate dizziness after the VOR exercises, as well as DHI and ABC questionnaires.

Session 3–Exercise Progression

There was consensus that patients could progress to performing exercises at a more difficult level after achieving the time and accuracy needed without increasing symptoms of dizziness excessively (as determined by a VAS Pre- and Post-exercise). Symptom resolution was factored into exercise progression where symptoms mostly resolved in 15–20 min after exercise performance. Typically, patients were progressed to a higher level after consistently accurate performance for 2 days.

Since the Vestibular Rehabilitation App^{TM} is intended to be a helpful tool for the clinician and not replace clinical expertise, an algorithm has been developed to alert the clinician when a patient may be ready to progress. This algorithm takes into account if the patient is doing the exercise correctly (consistently high scores and achieving prescribed motions) and without causing excessive dizziness (low reported change in dizziness after VOR exercises).

Session 4–Techniques to Improve Adherence

Therapists identified the hurdles to compliance to home exercises as: finding the time to do the exercises; not seeing immediate results; remembering to do the exercises; exercises increase symptoms of dizziness; exercises are boring; not sure if they are doing exercises correctly / uncomfortable doing exercises; patients think they should not do exercises when they are dizzy; no appropriate expectations of level of symptoms during exercises.

The following methods to improve adherence to exercise programs were identified: provide information on the importance of exercises and how to do them correctly; limit duration of exercise program (up to 15 min total); ask the patient how much time they could dedicate; recommend techniques to alleviate symptoms; Self-motivation and reward. All therapists reported that being responsive to patient's symptoms, identifying goals, and tracking progress toward these goals were key components for improving adherence.

Based on this feedback, automated reminders were incorporated in the Vestibular Rehabilitation App^{TM}, providing reminders on the device where the app is installed. Exercises were turned into fun games. Rewarding elements, such as trophies and game scores were included to show progress made and to increase motivation. Future work will incorporate a storyline that is linked to patient progress toward their rehabilitation goals.

Session 5–Patient Education

Primary goals of education were to inform the patient on recovery trajectory, such as time to recovery, what to expect during rehabilitation and alternative strategies to help reduce their dizziness and improve balance.

Based on this feedback, educational messages in the Vestibular Rehabilitation App^{TM} are focused on positive messages that reinforce the importance of rehabilitation based on scientific evidence. The app has been programmed so that educational messages appear at random time points after completing a game. A link to patient resources is also included in the app, with background on vestibular disorders (24, 25), resources to get more active (26), and healthy living (27).

Session 6–Safety Measures

The safety measures identified when performing the exercises included: standing with the back to a corner and near a sturdy surface they could hold on to if needed; start in sitting before doing exercises in standing, clear the floor of clutter; make sure pets were out of the way; wear Non-skid shoes (no flip flops or slippers); stand on a firm surface (preferably no carpet); and not walking around while looking at the tablet.

Based on this feedback, safety instructions have been included in the Vestibular Rehabilitation App^{TM}. Patients must acknowledge and agree to abide by the safety instructions to proceed to the exercise program.

Application Testing

Subjects were 10 females aged 60–74 years, average age 69.1 $\pm$ 5.1 years. There were no adverse events noted during testing.

Results Game Evaluation Questionnaire

A mixed methods design was used to obtain detailed information about participant interaction with each game (gaze stability and balance) at each level. As well as elements of progression through levels 1–4. Subjects' response to questions regarding enjoyment, understanding game play and ease of play are shown in **Figure 3**. Responses to Open-Ended questions are summarized in the **Supplementary Material 3**.

In general, participants preferred the VOR Levels 1–3 and single leg balance games. Both games were easy to understand and were found enjoyable unlike the 3D VOR game which was difficult to understand. The gaze shifting game was the most difficult to understand and all agreed that they did not enjoy it. Although the instructions of the weight shifting game were clear, it was not easy, and participants had difficulty performing this exercise.

Results of the User Interface Questionnaire

Average ratings for each item are presented in **Figure 4**. Specific comments in response to each item can be found in the **Supplementary Material 4**.

Results of the Perceived Ease of Use Questionnaire

All participants indicated that learning to operate the "Vestibular Rehabilitation application" would be easy for them, their interaction with the app was clear and understandable, and it would be easy for them to become skillful at using the app (**Figure 5**). Eight out of the 10 subjects indicated that they found it easy to get the Vestibular Rehabilitation App^{TM} to do that they wanted it to do. Nine out of 10 people indicated that they found the Vestibular Rehabilitation App^{TM} to be flexible to interact with.

Results of the Usefulness, Motivation, and Enjoyment Questionnaire

All participants agreed that if they had to use the app at home, it would help them do the exercises independently (**Figure 6**). They agreed that they would use the app and that they would recommend the app to their friends and family members with dizziness or a balance problem. All participants liked the different levels and felt motivated when playing the games. Nine participants felt motivated when they saw their scores or trophies in the application and 4 reported that they would feel more motivated using a social version of the application. All subjects responded that it was fun to carry out the vestibular rehabilitation exercises. Four subjects indicated that they felt worry and frustration, and only two subjects that they felt nervous while doing the exercises.

Open Ended Feedback

Five Open-Ended questions around the entire session concluded the session. Responses to the questions are reported below.

1) "How challenging was the session?" 5 subjects responded that the session was a good challenge, 2 responded that it was minimally challenging, 2 said that it was not challenging, but some games were difficult to understand, and 1 person responded it was challenging as she was not familiar with

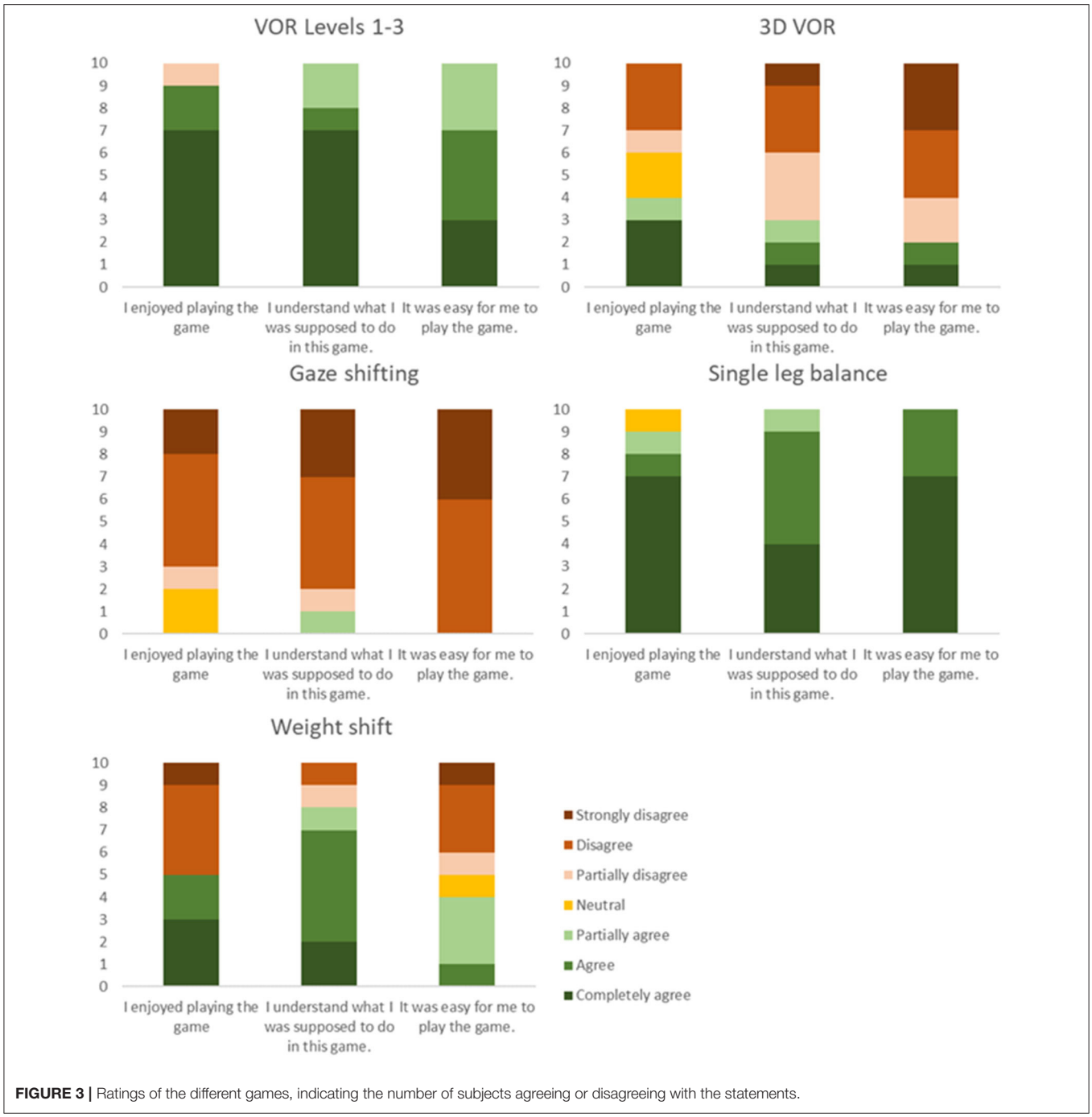

FIGURE 3 | Ratings of the different games, indicating the number of subjects agreeing or disagreeing with the statements.

tablets or games. Most subjects indicated that some games were more challenging than others.

2) "What are the positive features of the app?" subjects responses included: visuals are great; active games; colorful and variety of games, enjoyed the competitiveness, liked the practice opportunity, instructions were straightforward, exercises got more challenging, using the sensor to control the games.
3) "What did you not like about the app?" were as follows: visibility and speed were too fast on some games, instructions on some games (3D VOR and gaze shifting) were confusing, frustration because they could not succeed in the games due to sensor not moving accurately.
4) "What changes would you like to see?" participants suggestions include: too hard to play the 3D VOR game, screen and character color similarities made it difficult to see the screen; Single-Leg balance was too easy, create varying degrees of difficulty; provide clearer instructions; improve graphics, identify goals or levels you try to reach, more positive

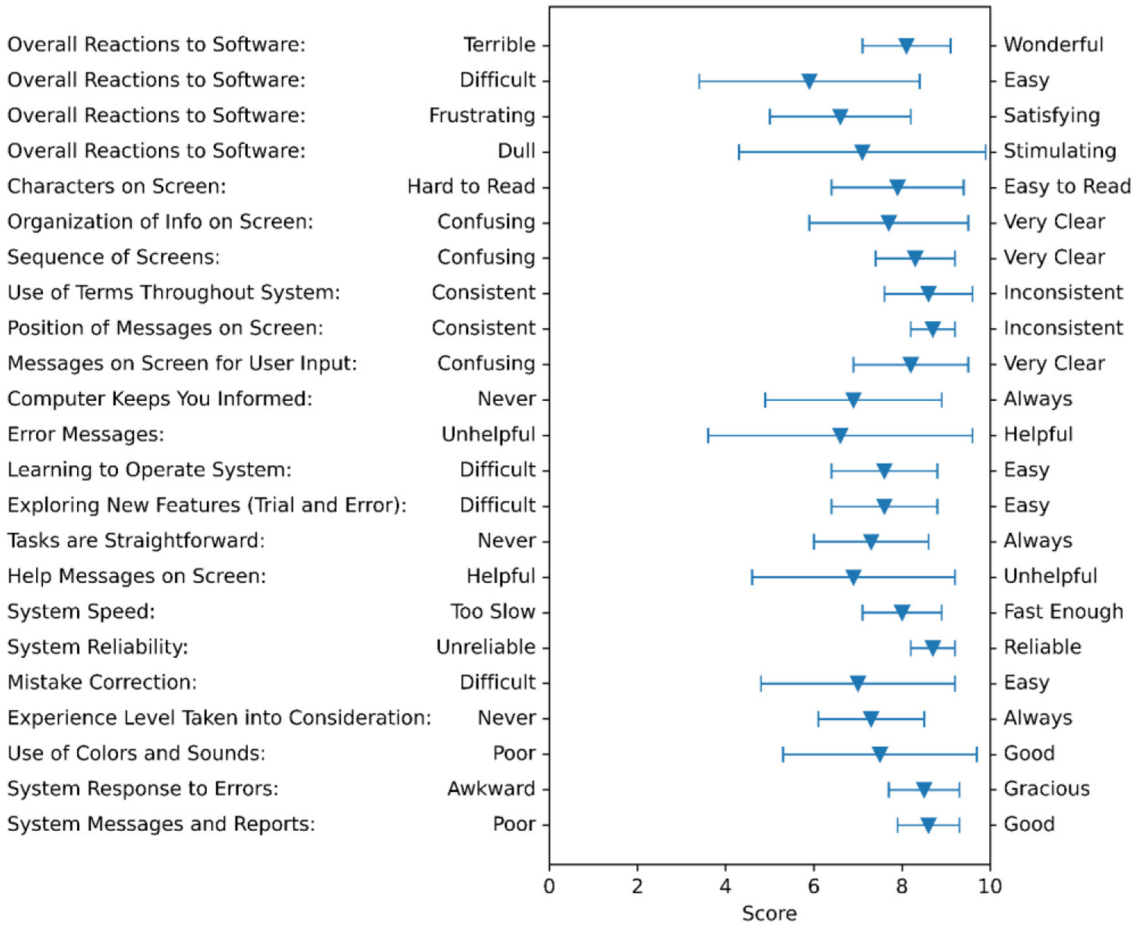

FIGURE 4 | Feedback summary on the User Interface Questionnaire. The triangles show the averages of all subjects and the bars show the standard deviation.

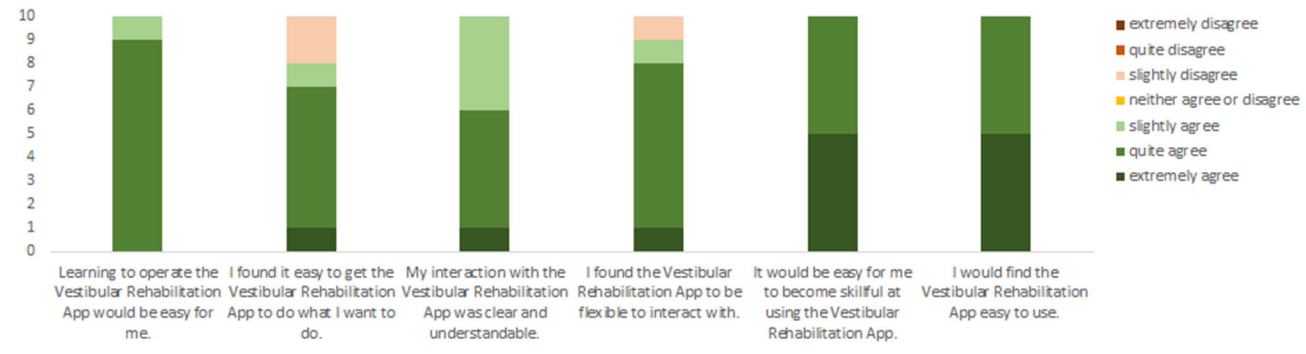

FIGURE 5 | Rating for the six questions on the perceived ease of use questionnaire.

reinforcement; toggle on/off audio–music or sound effects; provide feedback during the game about quality of movements (e.g., pause the game and give a reminder); explain the scores, as there was no reference to know if it was a good or a bad score.

5) "Do you see any barriers to using this app at home?" The main barriers identified were related to use of technology, the need to be comfortable using the tablet and sensor. Concerns about finances and having to buy a tablet and stand for the tablet, and placement of the tablet in a safe space in the home with adequate lighting and no glare.

DISCUSSION

The aims of this study were to use a Clinician-Informed design to develop, implement and test an app to deliver a rehabilitation program congruent with the CPG for peripheral vestibular hypofunction. Although technology has the potential to keep

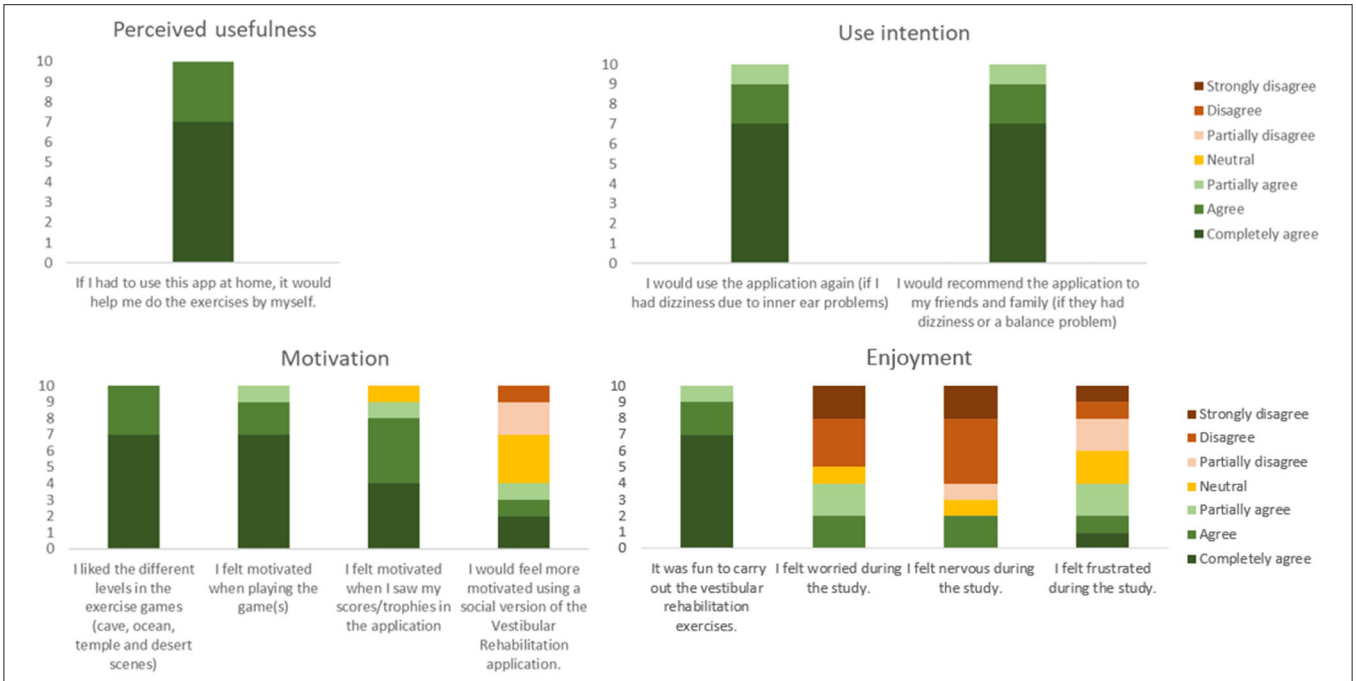

FIGURE 6 | Overview of responses to the usefulness, motivation, and enjoyment questionnaire.

patients engaged by providing the exercises in a game format, with interesting storylines and graphics, exercises adapted into technology must be evidence based. The Clinical Practice Guidelines for Vestibular Hypofunction were used to guide exercise selection, prescription, and progression (8). Clinicians were included in the app design from the beginning and their feedback was considered at every stage to include elements in the app that addressed patient deficits, education, safety, and overall wellbeing.

Vestibular rehabilitation is an Exercise-Based approach that includes exercises to promote gaze stability, exercises to improve balance, habituation exercises to reduce symptoms, and walking for endurance. Of these, gaze stabilization exercises can be used either for adaptation or substitution of the vestibulo-ocular reflex depending on the severity of the hypofunction and if the involvement is unilateral or bilateral. Adaptation exercises require head movement while maintaining focus on a target, while substitution exercises use other strategies such as smooth pursuit eye movements to compensate for lost function. These exercises are effective in reducing symptoms of dizziness and fall risk after acute (28, 29) and chronic (6, 7) vestibular lesions as well as in older adults with complaints of dizziness without vestibular dysfunction (30). During structured interviews, all therapists involved in this study identified gaze stability and balance exercises as essential components of the rehabilitation program.

Poor adherence to vestibular rehabilitation exercises is a barrier that was reported by all clinicians involved in the study. To overcome the repetitive nature of the exercises and to engage patients during the program, the Vestibular Rehabilitation App™ was designed with gaming elements, engaging graphics, and feedback on performance. We found that older adults with no prior experience with these games found the exercises engaging, the app interface easy to use, and felt motivated to do their best. However, results of our study show that to make the experience enjoyable, the games need to be clearly explained and the user interface needs to be intuitive. Additionally, the games that were too easy did not seem motivating but the games that were too difficult to perform or when the link between the sensor and the character on the screen was not precise, caused frustration. These factors such as simple instructions, intuitive user interface, and the right amount of challenge must be considered to keep patients engaged.

Participants were eager to know how they performed and reported that they appreciated the instant feedback to improve the accuracy of game performance but also wanted the terminal feedback to know what their total score was compared to the highest score possible. These are important factors that can increase motivation and thus adherence to the exercise program. Future iterations of the Vestibular Rehabilitation App™ will include feedback strategies such as adding a story line, showing progress toward goals, and visually representing change over time. Artwork is important. Our findings show that artwork is a good way to get people to engage with the games. Several subjects remarked that they liked the graphics, though some also noted problems with contrast. When designing games for people who are sensitive to visual stimuli, it is important to consider color and graphics. For example, Whitney et al. (31) found that age and presence of dizziness can affect strategies to find objects in a virtual environment.

This study was to inform the design of the initial prototype version of the Vestibular Rehabilitation App™ and to see where improvements were needed. Findings from this study will be considered in the development of future versions of the app. Future directions include creating a Web-Based prescription portal for therapists so that the number of exercises and their frequency can be easily prescribed. Additionally, accuracy of exercise performance and symptom severity with each exercise will be built into the portal and so that the results can be viewed easily in the form of graphs and tables, showing recovery trends over days, weeks, and months. Machine learning algorithms will be used to identify when mistakes in exercise performance are made so that the app can stop the exercise to provide feedback and ensure accurate performance. Validated questionnaires such as the Dizziness Handicap Inventory (23), and Activity-specific Balance Confidence scale (ABC) (22) will be incorporated into the app so that clinicians can track progress over time. This future development will get the app ready for testing on vestibular patients as well as clinical trials to demonstrate effectiveness of the app.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board at the University of Kansas Medical Center. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PR and NP contributed to conception and design of the study. LD contributed to the design of the human subject testing and collected and summarized all data. PR analyzed, presented data, and wrote the first draft of the manuscript. LD and KS wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.836571/full#supplementary-material

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ORIGINAL RESEARCH
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Evaluation of the Psychometric Properties of Jebsen Taylor Hand Function Test (JTHFT) in Italian Individuals With Multiple Sclerosis

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Introduction: The Jebsen Taylor Hand Function Test (JTHFT) is a non-diagnostic assessment scale for hand and upper limb dexterity that is commonly used in various countries around the world for diseases, such as muscular dystrophy, stroke, spinal cord injury, Parkinson, carpal tunnel syndrome, and rheumatoid arthritis. This study aimed to evaluate the psychometric properties of the JTHFT in Italian adults with Multiple Sclerosis (MS).

Materials and methods: The test's internal consistency was evaluated with Cronbach's alpha, whereas its concurrent validity was evaluated by comparing the JTHFT with the Health Assessment Questionnaire (HAQ) and by calculating Pearson's correlation coefficient.

Results: The JTHFT was administered to 29 Italians with MS. The Cronbach's alpha showed that the nondominant hand has a value of 0.76 and 0.91 for the dominant hand. Pearson's correlation coefficient showed significant correlations between JTHFT and HAQ.

Discussion: The JTHFT is a reliable tool to evaluate the functionality of the upper limb and hand in patients with MS. This tool is useful for testing the effectiveness of a treatment in various diseases. The results obtained in this study are coherent with previous studies that are conducted in populations with different diseases. In particular, the correlation between JTHFT and HAQ showed that a disability related to the upper limbs can often have repercussions, not only on activities of daily living, but also on walking. Based on this correlation, the motor deficits that emerged may be linked to a brain marrow disease rather than a spinal disease, even if an essential deepening can confirm this hypothesis.

Keywords: disability, multiple sclerosis, occupational therapy, psychometric properties, rehabilitation

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease that affects the central nervous system. It is the main cause of progressive neurological disability (1). Individuals with MS usually present with neurological deficits, cerebellar symptoms, fatigue, and cognitive deficits. Previous studies showed that sensory function (85%), fatigue (81%), impaired hand function (60%), and mobility (50%) were the most frequently reported symptoms in the first year of the disease. A combination of symptoms results in disability, which often impairs the ability to perform activities of daily living (ADL) and social activities, resulting in reduced quality of life (2).

Nowadays, several studies highlight the importance of addressing the rehabilitation of upper limb function in people with MS. Recent funding has shown a high percentage of individuals reporting upper limb dysfunction, even in the early stages of the disease (3–6). Kierkegaard et al. found in 2012 (7) that manual dexterity (Nine Hole Peg Test) is an important predictor of overall activity and participation within the community (Frenchay Activity Index). The upper limb dysfunction in MS contributes to a decrease in the ability to perform ADL, resulting in reduced independence and quality of life (8). Upper limb dysfunction is, in addition to walking, fatigue, and cognitive deficits, one of the critical dysfunctions present in MS (2, 9).

During the pathology progression, the fatigue and sensory and motor disorders to the lower and upper limbs can reduce the independence in the ADL with consequent reduction of quality of life. Therefore, it is important to base a proper rehabilitation program after a careful evaluation based on interviews and observation of occupational performance, especially on the administration of scales that give an objective judgment to the patient's upper limb and hand clinical conditions. A systematic review reports the following assessment scales used for the upper limb in multiple sclerosis: Fugl Meyer Assessment, Motricity Index, Modified Ashworth Scale, Fahn tremor Rating Scale, the Nine-hole peg test (NHPT), the Box and Block test (BBT), Action Research Arm Test (ARAT), Jebsen Taylor Hand Function Test (JTHFT), Purdue Pegboard Test, ABILHAND, Motor Activity Log (MAL), Disabilities of the Arm, Shoulder, and Hand (DASH), and Manual Ability Measure-36 (MAM-36) (2).

The evaluation of upper limb and hand functions is essential to develop a proper rehabilitation program, to identify limits and residual abilities, and to monitor the progression of symptoms. Clinicians need clear and complete information to use when making patient care decisions; there is a need for standardization in the outcome assessment. These would benefit patients, researchers, and clinicians. Universally validated outcome measures are needed to allow comparisons across the practice (10).

The JTHFT is a non-diagnostic assessment scale for hand and upper limb dexterity that is commonly used in various countries around the world (11–20) for diseases, such as muscular dystrophy (21), Stroke, (15, 18) Spinal Cord Injury (22), Parkinson (23), carpal tunnel syndrome (24), and rheumatoid arthritis (12). The tool is already used for people with MS (25), however, its psychometric properties for this population have never been studied.

This scale is classified by the International Classification of Function (ICF) as an activity assessment tool, and it evaluates changes in functional activities (26). This feature is an advantage and the only scale that evaluates the dexterities of the hand and the upper limb solely concerningtime-based and most common daily activities, such as writing and power simulation.

In addition, the "participation" assessment tools assess the difficulties that a person may encounter in engaging in the activities of life. The Katz Basic and Instrumental ADL Index, the Frenchay Activities Index, and the Functional Independence Measure are frequently used outcome measures to assess the restriction at the "activity" and "participation" levels. These assessment tools, however, strongly influence the individual's ability to walk, perform transfers, and cognitive condition. In contrast, the JTHFT appreciates the ability to perform various ADL-like tasks that require the handling or transport of standardized small and large objects using different gripping functions (8).

Although developed by Jebsen et al. in 1969, it is still widely used in rehabilitation especially in assessing dexterity in daily activities (27). It is validated and used in many languages and many countries worldwide, and it also allows to compare the outcomes of different clinical studies. It is useful for evaluating the effectiveness of a treatment in various diseases and using the same outcome measure can define which intervention is more effective than others.

This study aimed to evaluate the Italian version of JTHFT (JTHFCT-IT)'s psychometric properties on a population of adults with MS.

MATERIALS AND METHODS

This study was carried out by a research group from the Sapienza University of Rome and the Rehabilitation & Outcome Measure Assessment (R.O.M.A.) Association (28–34).

Participants

According to previous validation studies of the same assessment tool, the minimum number of participants considered was 25 (34). The sample was recruited from February to October 2020 in the Department of Human Neurosciences of Polyclinic Umberto I of Rome. Those at the neurology clinic with a diagnosis of MS (according to the McDonald's standard) (35) were invited to participate in the study. They had to have the ability to understand instructions and perform the scale's activities, to have a range of Expanded Disability Status Scale (EDSS) between 0 and 9, and shall not have comorbidities that affect upper limb's functionality.

All participants were informed about the procedures and purposes of the study, and those who were interested in participating in the study gave their written consent before inclusion (36, 37).

TABLE 1 | Demographic characteristics of the population.

	Mean (Standard Deviation)
Age	47.59 (9.57)
Years from diagnosis	13.82 (8.88)
Gender	**Frequency (%)**
Male	14 (48.3)
Female	15 (51.7)
Occupation	**Frequency (%)**
Unemployed	7 (24.1)
Employee	14 (48.3)
Freelancer	6 (20.7
Retired	1 (3.4)
Student	1 (3.4)
EDSS	**Frequency (%)**
0–2	4 (13.8)
2.5	7 (24.1)
3.0–4.5	3 (10.3)
5.5	2 (6.9)
6.0	4(13.8)
6.5	5 (17.2)
7.0–8.0	2 (6.9)

TABLE 2 | Mean SD and Cronbach alpha values of one of the items of the scale.

		Mean	**Std. deviation**	**Cronbach's Alpha if item deleted**
Non dominant hand	Writing	52.15	30.23	0.79
	Turning pages	8.99	6.89	0.71
	Pick up small objects	11.12	5.51	0.73
	Simulate feeding	20.85	21.27	0.65
	Stacking Checkers	9.73	6.05	0.74
	Moving light cans	6.92	3.02	0.76
	Moving weight cans	7.19	3.74	0.76
Total alpha non dominant hand = 0.76				
Dominant hand	Writing	16.73	7.94	0.91
	Turning pages	6.93	4.04	0.91
	Pick up small objects	9.08	3.54	0.89
	Simulate feeding	13.54	8.08	0.89
	Stacking Checkers	6.88	3.86	0.89
	Moving light cans	5.80	2.32	0.90
	Moving weight cans	6.03	2.42	0.90
Total alpha dominant hand = 0.91				

Validation Procedures

Three clinicians (a neurologist and two occupational therapists) screened all patients of neurology's clinic and applied inclusion/exclusion criteria for recruitment. After being included, the raters recorded demographic and clinical characteristics and administered the tests. The tests were administered in the same order: JTHFT-IT, Jamar dynamometer (12), and the Health Assessment Questionnaire (HAQ).

Tools

The JTHFT consists of seven elements administered with verbal instruction and standard verbal instruction modalities. The tasks are as follows: (1) write a 24-character sentence; (2) flip three 7.62 cm × 12.7 cm (3" x 5") sheets, simulating turning a page; (3) collect small common items, including a penny, paper clips, and bottle caps, and place them in a container; (4) stackable pawns; (5) pick up small items with a spoon; (6) moving light cans; and (7) moving heavy cans. Tests are evaluated by recording the number of seconds it takes to complete each task. The increase in the time to complete the test correlates with the decrease in hand function. Each activity is initially done with the non-dominant hand, and then with the dominant hand.

The HAQ, developed in 1980, is among the first Patient-Reported Outcome Measures. The HAQ includes items that assess the upper extremity's fine movements, lower limb activities, and tasks that involve both the upper and lower limbs. It is composed of 20 items divided into eight categories, which represent a comprehensive set of ADLs: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Each item is scored from 0 to 3, with higher scores indicating more disability (0 = without any difficulty; 1 = with some difficulty; 2 = with much difficulty; and 3 = unable to do). Scores of 0 to 1 generally represent mild to moderate difficulty, 1–2 represent moderate to severe disability, and 2 to 3 indicate severe to very severe disability (38).

Data Analysis

The psychometric properties were assessed by following the Consensus-Based Standards for the Selection of Health Status Measurement Instruments (COSMIN) checklist (39).

The internal consistency was evaluated using Cronbach's alpha (α) to assess the items' correlation and the homogeneity of the scale; the coefficient must be at least 0.7 to indicate the acceptable homogeneity of all the items within a scale (13). The concurrent validity of the JTHFT-IT was evaluated by calculating the Pearson's correlation coefficient (ρ) between the test and dynamometer (40), and HAQ. The following values were considered in interpreting the results: $\rho > 0.70$ = strong correlation, $0.50 < \rho < 0.70$ = moderate correlation, and $\rho < 0.50$ = weak correlation. Any $p \leq 0.05$ were considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows (13).

RESULTS

The scale was administered to 29 people, of whom 51.7% were women, with an average age of 47.59 years (9.57 in standard deviation). The demographic characteristics of the population are shown in **Table 1**.

The Cronbach alpha value from the statistics showed an internal consistency of 0.76 for the non-dominant hand and 0.91 for the dominant hand. **Table 2** shows the mean, SD, and Cronbach alpha values if one of the items of the scale is removed,

TABLE 3 | Pearsons' correlation coefficient for nondominant hand between the Jebsen Taylor Hand Function Test (JTHFT) and the Health Assessment Questionnaire (HAQ).

Correlations non dominant hand								
	Dressing	**Arising**	**Eating**	**Walking**	**Hygiene**	**Reaching**	**Grip**	**Activity**
Writing	0.63**	0.50**	0.33	0.44*	0.49**	0.37*	0.36	0.54**
Turning pages	0.69**	0.63**	0.48**	0.57**	0.54**	0.39*	0.20	0.53**
Pick up small objects	0.78**	0.70**	0.44*	0.65**	0.66**	0.54**	0.37*	0.65**
Simulate feeding	0.67**	0.56**	0.45*	0.51**	0.57**	0.40*	0.12	0.60**
Stacking Checkers	0.69**	0.55**	0.47*	0.53**	0.58**	0.38*	0.13	0.57**
Moving light cans	0.82**	0.71**	0.57**	0.66**	0.68**	0.53**	0.38*	0.70**
Moving weight cans	0.79**	0.68**	0.61**	0.59**	0.68**	0.53**	0.29	0.68**

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

TABLE 4 | Pearsons' correlation coefficient for dominant hand between JTHFT and HAQ.

Correlations dominant hand								
	Dressing	**Arising**	**Eating**	**Walking**	**Hygiene**	**Reaching**	**Grip**	**Activity**
Writing	0.37*	0.41*	0.32	0.34	0.28	0.31	0.23	0.35
Turning pages	0.77**	0.65**	0.57**	0.58**	0.60**	0.52**	0.59**	0.62**
Pick up small objects	0.81**	0.71**	0.58**	0.68**	0.69**	0.54**	0.67**	0.73**
Simulate feeding	0.58**	0.49**	0.46*	0.46*	0.46*	0.44*	0.61**	0.46*
Stacking checkers	0.75**	0.74**	0.61**	0.70**	0.66**	0.54**	0.27	0.63**
Moving light cans	0.84**	0.72**	0.57**	0.63**	0.73**	0.52**	0.40*	0.76**
Moving weight cans	0.80**	0.64**	0.64**	0.54**	0.67**	0.47*	0.37*	0.69**

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

higher results have been found for the dominant hand. The criterion validity and analysis of the JTHFT-IT results were performed in the dominant and non-dominant hand, where statistically significant variations with the HAQ were found in **Tables 3**, **4**. These tables report the statistically significant correlations within all subscales and strong correlations ($\rho >$ 0.70) for "pick up small objects", "moving light cans," and "moving weight cans". The subscale of "grip" correlates only in the results of the dominant hand.

DISCUSSION

The present study aimed to evaluate the psychometric properties of the JTHFT-IT scale in Italian people with MS. The results of this study have shown that the scale taken into consideration is a reliable and valid tool for the population studied. Cronbach's alpha was used to assess the scale's internal coherence, with values of 0.76 for the non-dominant hand, and 0.91 for the dominant hand. In both cases, the values exceed the minimum value of 0.7 necessary to consider the instrument reliable. Many other studies found the first item (writing) to have an important weight compared to other items, because they considered populations with a specific disorder (Parkinson's disease, stroke, etc.), For this study, however, a difference in time between writing and the other tasks was not found (12, 15, 23).

Interesting results have been found with Pearson's correlation analysis, which reported a statistically significant correlation between the non-dominant and dominant hand items, and the HAQ subtests.

For the non-dominant hand, statistically significant data are given between:

- Item 1 (writing) and the subtest dressing, and arising with a moderate linear relation
- Item 2 and item 3 (page rotation simulation and small object gripping) and all HAQ-scaled subtests with a linear relationship between moderate and strong
- Item 4.5 (simulate feeding and stacking) except for grip 6.7 (collect and lift large, light, and heavy objects) and all HAQ-scaled subtests with a linear relationship between moderate and strong.

As for the dominant hand, on the other hand, they were correlated with a linear relationship between moderate and strong with all JTHFT items except:

- Item 1 (writing) with the subtest "eat" and "grip."

- Items 2, 4, 5, and 7 (simulate turning a page, simulate feeding, stacking, collecting, and moving large and heavy objects) with "Grip".

Strong correlations ($\rho > 0.70$) were found for Jebsen subscales' "pick up small objects," "moving light cans," and "moving weight cans" with HAQ subscales' "Dressing," "Arising," "Walking," "Hygiene," and "Activity", showing that daily activities are correlated with a better gross motor hand function instead of fine motricity. Another interesting result was that the subscale of "grip" correlates only in the analysis with the dominant hand.

Finally, the correlation between JTHFT and HAQ suggests that a disability related to the upper limbs can often have consequences on walking. This correlation found in literature a study on motor function of the upper and lower extremities and cognitive deterioration in multiple sclerosis (41) showed a statistically significant correlation between a Timed 25 Foot Walk T (T25FW) and an NHPT upper limb function test. The motor deficits that emerged from the T25FW and the NHPT may be linked to a brain marrow disease rather than a spinal disease, even if in the same study (41), we refer to a deepening through MRI that can confirm this hypothesis.

Limitation of the Study

This study has some limitations. Even though the number of participants is enough to examine the psychometric properties, a larger sample would allow the examination of the influences of the various sociodemographic variables. Finally, the authors agree with previous studies that the JTHFT itself has some limitations (18, 21, 24). The score of the test does not reflect different compensation mechanisms for positioning the upper limb. Hence, it is important to provide appropriate instructions before starting the test and to ask patients to not change their strategy while being tested or, in clinical trials that use the JTHFT score as an endpoint, to not change strategies in follow-up evaluations. Furthermore, the patients with moderate-to-severe functional impairment are often not testable with the JTHFT.

CONCLUSION

In conclusion, it can be said that the JTHFT is a reliable tool to evaluate the functionality of the upper limb and hand in patients with MS. The JTHFT, in line with previous studies, is a valid tool for the evaluation of the upper limb. Moreover, in addition to the simplicity and speed of administration, it is an instrument that requires materials that are readily available and can be produced by hand.

However, the appearance of Item 1 must be considered, that is, the writing item, which requires much more time than the other items on the scale. Although no test used in isolation can provide a realistic assessment of hand function, it is important to consider the potential usefulness of JTHFT compared to other tests (12).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB, GG, GF, and AC contributed to conception and design of the study. FP organized the database. GG performed the statistical analysis. AB and FP wrote the first draft of the manuscript. MTo, MTa, VB, and SC wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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CASE REPORT
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Bechterew's Phenomenon in Bilateral Sequential Vestibular Neuritis: A Report of Two Cases

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The brain can compensate for the vestibular imbalance. When the unilateral labyrinthine function is lost, the asymmetry between the peripheral vestibular inputs is compensated centrally by readjusting the signal difference from both ears and regaining vestibular balance. If the other healthy labyrinth is destroyed, the vestibular nuclei become imbalanced again, creating spontaneous nystagmus even though there is no input to the vestibular nuclei from either labyrinth. This is called Bechterew's phenomenon; a rare and not widely recognized phenomenon that occurs in cases of bilateral sequential vestibular neuritis. This is of clinical importance because spontaneous nystagmus with bilaterally absent or diminished caloric responses may give a misleading impression of a central lesion rather than a second peripheral lesion superimposed upon the effects of central compensation for the first. Although well-documented in experimental animals, this phenomenon rarely occurs in human beings. The objective of this study is to highlight the characteristics and the progression of test results from two patients from our own experience. Along with careful history taking and physical examination, a complex interpretation of various vestibular function tests, including induced nystagmus, head impulse test, caloric test, and fundus photography, is needed to make an accurate diagnosis of bilateral sequential vestibular neuritis (BSVN).

Keywords: bilateral sequential vestibular neuritis, Bechterew's phenomenon, vibration-induced nystagmus, headshaking nystagmus, ocular torsion

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INTRODUCTION

Vestibular neuritis (VN) is a common peripheral vestibular disease, accounting for 7% of patients in a vertigo clinic (1, 2). The VN presents with acute vertigo that lasts over 24 h, spontaneous nystagmus that beats toward the unaffected ear, and a positive head impulse test. Resolution of the acute and severe rotatory vertigo ensues after 2–3 days in 70% of the patients, but, in 4%, it can last longer than 2 weeks (3, 4). The VN was traditionally known as a non-recurrent disease (5); however, reports of recurrence have been made (6).

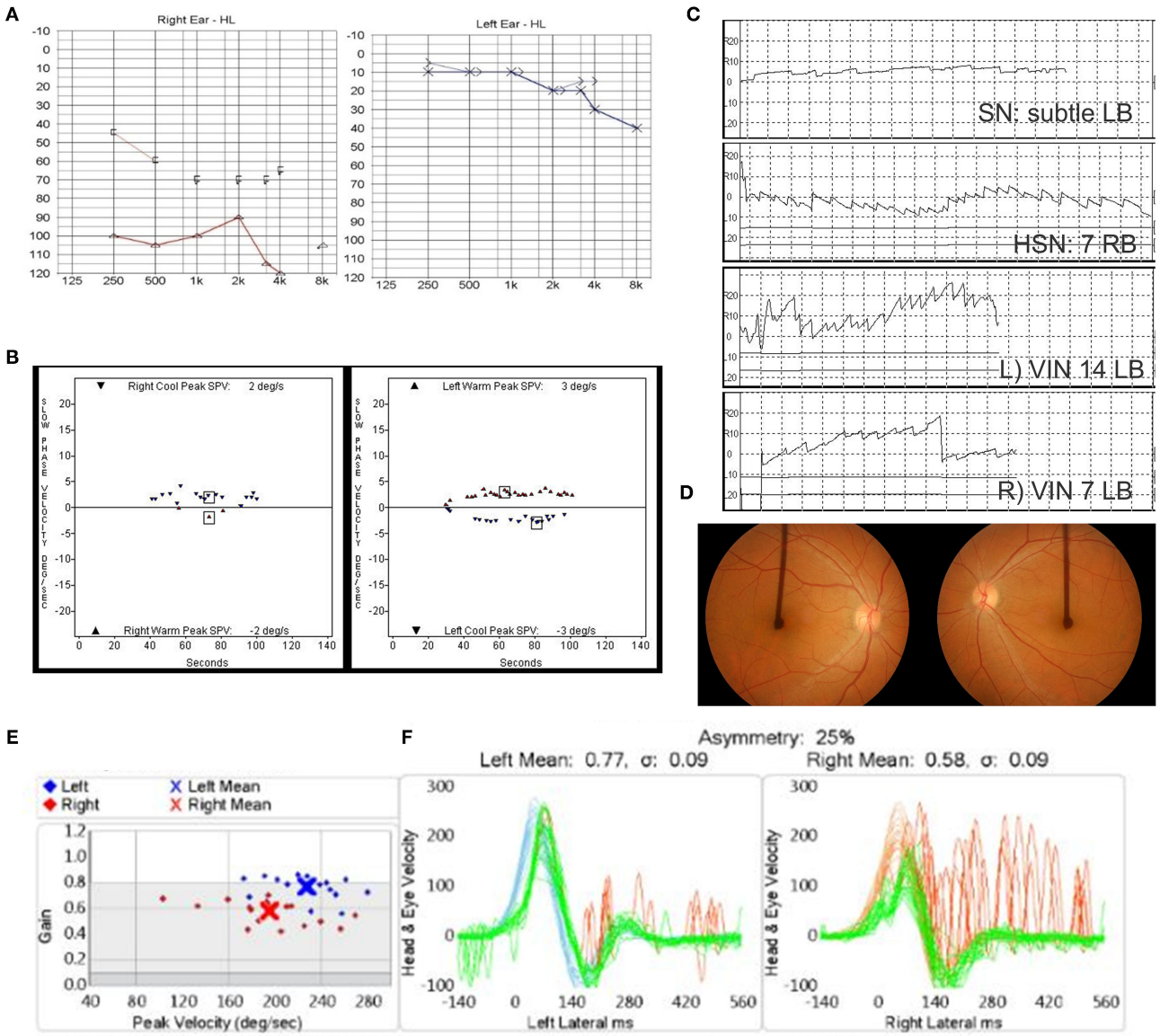

FIGURE 1 | (A–D) Clinical assessment of Case 1 at 4 months after the onset of left vestibular neuritis. **(A)** Audiometric assessment shows right-side deafness. **(B)** The bithermal caloric test shows bilateral canal paresis. **(C)** Subtle left-beating spontaneous nystagmus, headshaking nystagmus (HSN) beating to the right, and vibration-induced nystagmus beating to the left. **(D)** Fundus photography revealed conjugate counterclockwise torsion from the viewpoint of the patient with extorsion of the right eye (4°) and increased extorsion of the left eye (17°). **(E)** The video head impulse test showed vestibulo-ocular reflex (VOR) gain of 0.58 on the right side and 0.77 on the left side 4 years later.

Recurrence of VN can either be ipsilateral (7) or contralateral (5). Contralateral involvement of VN after completion of central compensation from initial VN is referred to as bilateral sequential vestibular neuritis (BSVN). The BSVN is a rare condition that has only been described in a limited number of publications (5, 6, 8–13). If the vestibular function from the first episode of VN is not recovered, the patient will develop spontaneous horizontal nystagmus beating away from the side involved during contralateral VN, while vestibular test results will show findings of bilateral vestibular hypofunction. These findings may give a misleading impression of central vertigo if the clinician is not aware of the first episode of unilateral VN that the patient has already gone through.

Bechterew first described this phenomenon after a series of surgical labyrinthectomies performed on animals (14); a pioneering work that revealed central compensation mechanisms that follow asymmetry of bilateral vestibular tones. Vestibular compensation readjusts the signal difference from both ears to regain vestibular balance; however, this dynamic process occurs at different rates to a different extent for different

TABLE 1 | A summary of changes of vestibular function in case 1.

	Right VN (10 years before left VN)	Left VN (4 months)	Left VN (1 year)	Left VN (4 years)
SN (°/s)	NT	subtleLB	3 RB	0
HSN (°/s)	NT	7RB	9 RB	8 RB
VIN (°/s)	NT	R) 7 LB L) 14 LB	R) 7LB L) 9 LB	R) 18 LB L) 16 LB
Ocular torsion (°)	NT	R) 4° L) 17°	R) 4° L) 17°	NT
Caloric test	NT			
RW+RC (°/s)		4	5	0
LW+LC (°/s)		6	7	5
vHIT gain of horizontal canal	NT	NT	NT	R) 0.58 L) 0.77
cVEMP	NT	R) NR L) NR	NT	NT

VN, vestibular neuritis; SN, spontaneous nystagmus; NT, not tested; RB, right beating; LB, left beating; HSN, headshaking nystagmus; VIN. Vibration-induced nystagmus; RW, right warm; RC, right cold; LW, left warm; LC, left cold; vHIT, video head impulse test; cVEMP, cervical vestibular evoked myogenic potentials; NR, no response.

vestibular responses (15). For example, spontaneous nystagmus (static imbalance) resolves within days, whereas in post-head shaking nystagmus, nystagmus induced by position change and vibration-induced nystagmus (dynamic imbalance) persist, and their resolutions are less complete.

Earlier reports of BSVN are somewhat anecdotal (9, 10, 12, 13), but, with advancements in vestibular function tests, recent reports have provided a more in-depth description of the status of the vestibular periphery and the compensatory stage of patients with BSVN. To highlight the clinical characteristics of BSVN, we report 2 cases from our own experience. Especially, we discuss the progression of objective findings after the second insult in the contralateral ear using vibration-induced and headshaking nystagmus (HSN), video head impulse test (vHIT), and ocular torsion (OT) as seen on fundus photography, which, to our knowledge, is the first report of its kind in BSVN.

CASE DESCRIPTION

Case 1

A 54-year-old female was presented to the clinic, complaining of oscillopsia and ataxia after sudden spontaneous vertigo accompanied by nausea and vomiting 4 months ago. Ten years previously, she reported another spell of spontaneous vertigo and hearing loss of the right ear. The vertigo spell resolved over time, but the hearing loss remained. Apart from the hearing loss, the patient did not recall other past or present medical conditions. Physical assessment revealed subtle right-beating spontaneous nystagmus under Frenzel glasses, a positive sign on impulse head rotation to both sides, no skew deviation, and no cerebellar signs. Audiometry showed right side deafness and age-appropriate hearing on the left with mild sensorineural hearing loss of the high frequencies (**Figure 1A**). The bithermal caloric test identified bilateral vestibular hypofunction. The sum of peak slow phase velocity (SPV) of warm and cold stimulation was 4°/s (right ear) and 6°/s (left ear) (**Figure 1B**). Cervical vestibular-evoked myogenic potentials (VEMPs) were bilaterally absent. Video nystagmography showed subtle left-beating spontaneous nystagmus (1°/s) at a sitting position. Headshaking evoked horizontal nystagmus beating to the right with a maximum SPV of 7°/s. A vibrator applied to the patient's left mastoid induced a horizontal nystagmus beating to the left with an SPV of 14°/s and left-beating nystagmus with an SPV of 7°/s when applied to the right mastoid (**Figure 1C**). The OT was assessed using fundus photography with a scanning laser ophthalmoscope (Fundus camera CF-60 UVI, Canon, Tokyo, Japan), with the patient's head upright. The OT was determined by measuring the angle between the horizontal line running through the center of the optic disc and a line connecting the center of the optic disc and fovea. A negative value of the angle indicates intorsion, and a positive value indicates extorsion. This patient revealed conjugate counterclockwise torsion from the viewpoint of the patient with extorsion of the right eye (4°) and increased extorsion of the left eye (17°) (**Figure 1D**). Brain MRI revealed a 7-mm lesion in the right frontal lobe, consistent with hemangioma, but no other noticeable findings in the posterior fossa or the temporal bone. A diagnosis of BSVN (the onset of the right side: 10 years ago, the onset of the left side: 4 months ago) was made, and she underwent vestibular rehabilitation. Four years later, the vHIT showed a VOR gain of 0.58 on the right side and 0.77 on the left side (**Figure 1E**). The sequential changes of the patient's vestibular function are summarized in **Table 1**.

Case 2

A 65-year-old male, with no underlying medical conditions, was presented to the emergency room with a 12-h history of severe acute rotatory vertigo (visual analog scale, VAS 10) without hearing impairment. Bed-side examination found right-beating spontaneous nystagmus under Frenzel glasses and showed a positive sign on the head impulse test to the left. Neurological evaluation revealed no skew deviation and no cerebellar signs. The bithermal caloric test revealed canal paresis of 91% of the left side (**Figure 2A**). vHIT showed decreased gain of the left lateral semicircular canal (**Figure 2B**). The patient was discharged with a diagnosis of left VN. Four years later, the patient returned to the emergency room complaining of another vertigo attack, which was milder in severity (VAS 8). Spontaneous nystagmus was beating to the left (12°/s), and the bedside head impulse test showed a positive sign in both directions. The bithermal caloric test revealed bilateral vestibular hypofunction. The sum of SPVs of warm and cold stimulation of right and left was −3 and 1°/s, respectively (**Figure 2C**). Substantial directional preponderance was shown due to strong spontaneous nystagmus. The vHIT showed markedly decreased gains of bilateral anterior and lateral semicircular canals (**Figure 2D**). A central cause was excluded by

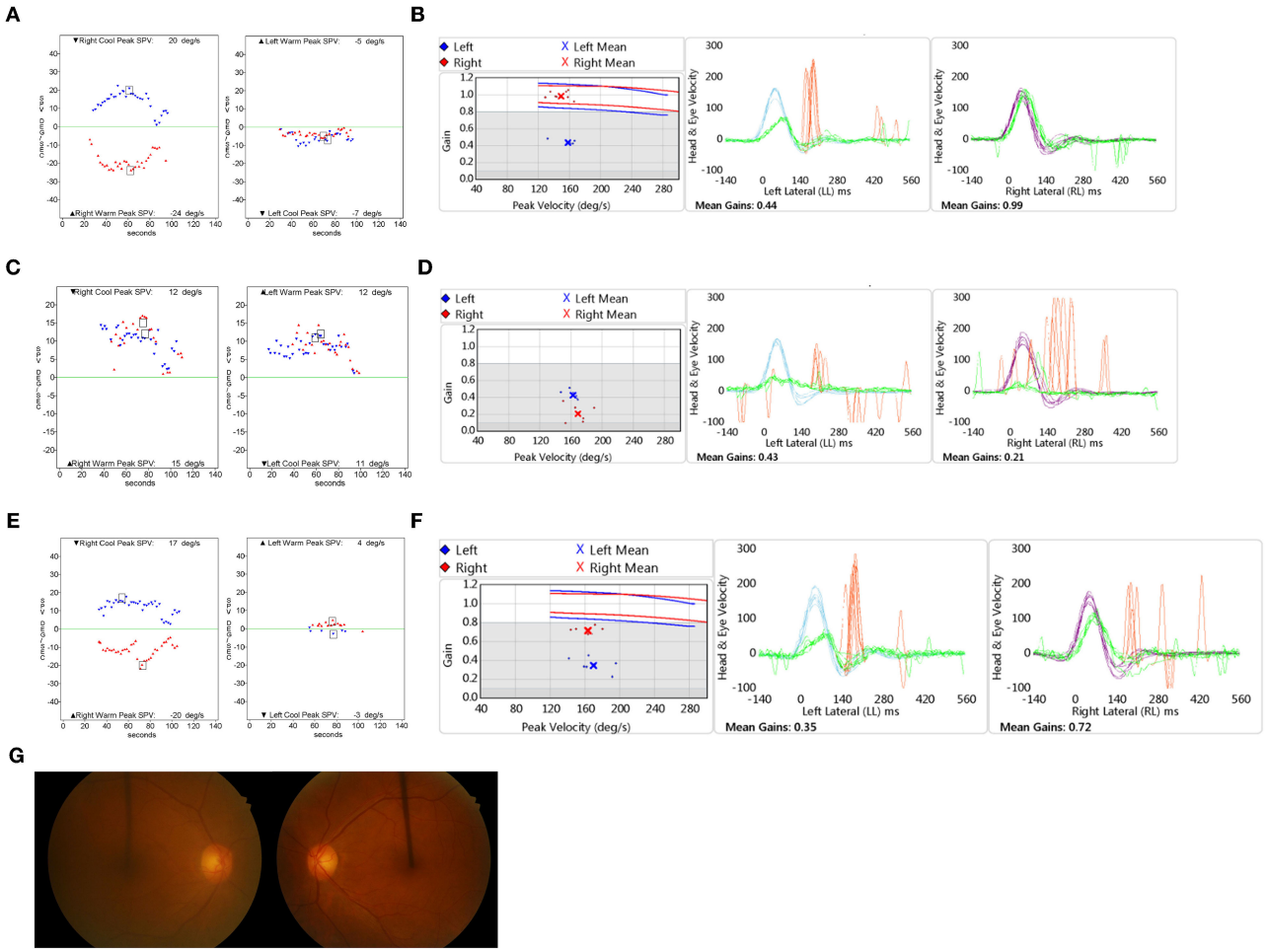

FIGURE 2 | Clinical assessment of Case 2. The bithermal caloric test **(A)** and video head impulse test (vHIT) **(B)** results show unilateral vestibular hypofunction when the patient was diagnosed with left vestibular dysfunction initially. The bithermal caloric test **(C)** and vHIT **(D)** results show bilateral vestibular hypofunction when the patient was diagnosed with right vestibular dysfunction. The bithermal caloric test **(E)** and vHIT **(F)** performed 1 year later revealed partial recovery of the right side. **(G)** Fundus photography showed symmetric ocular torsion. vHIT: video head impulse test.

neurological examination, including the abovementioned head impulse, nystagmus, test of skew (HINTS), cerebellar function test, and a gadolinium-enhanced brain MRI. After corticosteroid treatment and vestibular rehabilitation, subjective discomforts of dizziness, imbalance, and oscillopsia were resolved over time. Four months later, headshaking evoked subtle horizontal nystagmus beating to the left with a maximum SPV of 1°/s. A vibrator was applied to the patient's left mastoid-induced horizontal nystagmus beating to the right with an SPV of 11°/s and right-beating nystagmus with an SPV of 8°/s when applied to the right. The bithermal caloric test showed partial restoration of canal response of the right side. The sum of SPVs of right warm and cold stimulation was 18°/s, while VOR gain of the right horizontal canal on vHIT was still 0.53. The sum of SPVs of left stimulation was 0. Fundus photography showed symmetric revealing extorsion of the right eye (4°) and extorsion of the left eye (5°). Cervical VEMPs were normal on both sides, whereas ocular VEMPs were bilaterally absent. Caloric response (**Figure 2E**) and VOR gain on vHIT of the right side after 1 year were further improved, while those of the left side was not much improved (**Figure 2F**). Fundus photography showed symmetric ocular torsion (**Figure 2G**). The sequential changes of the patient's vestibular function are summarized in **Table 2**. Both participants voluntarily participated in the study and provided written informed consent. This study was reviewed and approved by the Institutional Review Board.

DISCUSSION

The BSVN is a rare condition in which 1.9–5.3% of patients with unilateral VN develop later (1, 5, 8). During the first episode, the patients complained of severe whirling-type vertigo, whereas the main symptoms of the second episode were imbalance with slight vertigo. The direction of the spontaneous nystagmus of the first and second episodes changed. Although results of the vestibular function

TABLE 2 | A summary of changes of vestibular function in Case 2.

	Left VN (4 years ago)	Right VN (1 day)	Right VN (4 months)	Right VN (1 year)
SN	8 RB	12 LB	0	0
HSN	20 RB	Not augmented	1 LB	0
VIN	R) 30 RB	NT	R) 8 RB	R) 19 RB
	L) 65 RB		L) 11 RB	L) 5 RB
Ocular torsion	NT	NT	R) 4 ex	R) 5 ex
			L) 5 ex	L) 6 ex
Caloric test				
RW+RC (°/s)	44	−3	18	37
LW+LC (°/s)	2	1	0	7
vHIT gain of horizontal canal	R) 0.99	R) 0.21	R) 0.53	R) 0.72
	L) 0.44	L) 0.43	L) 0.32	L) 0.35
cVEMP	NT	NT	Symmetric response	NT
oVEMP	NT	NT	Both no response	NT

VN, vestibular neuritis; SN, spontaneous nystagmus; NT, not tested; RB, right beating; LB, left beating; HSN, headshaking nystagmus; VIN: vibration-induced nystagmus; RW, right warm; RC, right cold; LW, left warm; LC, left cold; vHIT, video head impulse test; cVEMP, cervical vestibular-evoked myogenic potentials; oVEMP, ocular vestibular-evoked myogenic potentials; NR, no response.

test showed bilateral hypofunction, spontaneous nystagmus was formed toward the side originally (the first episode) involved. This can be a rather strange and misleading clinical finding, raising the false suspicion of central nystagmus or cerebellar clamp, in which cerebellar inhibition suppresses the vestibular signal of the intact side to rebalance the asymmetry (16). However, the cerebellar clamp resolves within days after unilateral insult, a feature that is distinguishable from BSVN (17).

A phenomenon associated with Bechterew's nystagmus includes recovery nystagmus, which is spontaneous nystagmus beating toward the affected side observed temporarily for a few months after the initial insult (18). It results from persistent central compensation for an imbalance in vestibular tone after the need for this amount of compensation has diminished (19), and, possibly, restoration of end-organ function. Bechterew's phenomenon occurs because, after the central vestibular tone has been rebalanced following the first lesion, the second lesion creates a new imbalance (12).

In the 2 cases presented as our own experience, the ocular torsion on the fundus photography, HSN, and vibration-induced nystagmus were applied. In Case 1, the extorsion of the left eye (the side recently affected) was increased, and it was maintained over years, whereas the ocular torsion of the right eye was within a normal range for the patient's age (20). In Case 2, a fundus photograph was taken 4 months after the second ear attack. Unfortunately, the fundus photography was not taken immediately after the contralateral insult. If it was tested, increased extorsion to the newly affected side would be documented. The fundus photograph at 4 months after the second attack did not show asymmetric ocular torsion, which would be normalized with the gradual recovery of the end-organ function.

The HSN is generated by repetitive headshaking and usually beats toward the better ear in unilateral inhibitory vestibular lesions (19). The mechanism behind HSN is explained by Ewald's second law and the central velocity-storage system. During each head movement, the directionally asymmetric responses accumulate in the velocity-storage mechanism to be discharged after the head stops shaking (21). To interpret HSN, the condition of the velocity-storage mechanism must be taken into account (22). In BSVN, at the time of the second insult, the velocity-storage mechanism from the first insult would have recovered, thereby eliciting dynamic asymmetry of the recently affected side.

Vibration-induced nystagmus is not modified by vestibular compensation, so it is useful for differentiating bilateral areflexia. Patients with no caloric responses (a test for low frequencies) and decreased VOR gain for all 6 canals in vHIT (middle-range frequencies) show vibration-induced nystagmus due to residual hair cells still responding at high frequencies (100 Hz) (23).

CONCLUSION

The BSVN is a rare condition but an interesting human model to understand the change of central compensation after deafferentation of peripheral vestibular input. To accurately diagnose BSVN and recognize current vestibular status, it is necessary to understand the pattern of induced nystagmus resulting from the central compensation mechanism and change of a peripheral vestibular function. A collective interpretation of the patient's history, as well as physical examination and comprehensive vestibular function tests, including headshaking and vibration-induced nystagmus, head impulse test, caloric test, fundus photography, is needed to understand and diagnose BSVN.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Seoul National University Bundang Hospital Institutional Review Board. The patients/participants provided

their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participants for the publication of this case report.

AUTHOR CONTRIBUTIONS

YK and J-WK designed the study and wrote the article. YK, SJ, J-SK, and J-WK collected and analyzed data. All authors read and approved the final manuscript.

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ORIGINAL RESEARCH
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Evaluation of the Psychometric Properties of the Health Assessment Questionnaire (HAQ) in a Population of Individuals With Multiple Sclerosis

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Introduction: The Health Assessment Questionnaire (HAQ) has been translated into many languages and it has been classified as the predictor of disability and medical costs, however, the psychometric properties of the HAQ have never been studied in a population with neurological disease. The purpose of this study was the evaluation of the psychometric properties of HAQ in a population of individuals with multiple sclerosis (MS).

Materials and Methods: This cross-sectional study was conducted with patients diagnosed with MS. The evaluation tools administered were the 36-item short form health survey (SF–36) to evaluate the health state of the patients and HAQ and to evaluate the limitations of the activities of daily living (ADL).

Results: A total of 34 patients were included in this study. Cronbach's alpha assessed the internal consistency of the HAQ, and it is equal to 0.94. The study revealed some significant correlations between the dimensions of the SF-36 and the sub-categories of the HAQ using Pearson's Correlation Coefficient. Significant correlations emerged between the demographic and clinical characteristics of patients and the subcategories of HAQ.

Discussion: The HAQ is a valid and reliable tool to assess the limitations of the activities of daily living, and it could provide for the healthcare and rehabilitation sector with an additional evaluation tool.

Keywords: disability, occupational therapy, rehabilitation, psychometric properties, multiple sclerosis

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INTRODUCTION

Chronic symptoms of multiple sclerosis (MS), such as physical functioning impairment, cognitive impairment, emotional burden, and fatigue, considerably affect the quality of life (QOL) of people with MS with an important impact on daily activities and social participation. More than half of the individuals with MS reported physical symptoms that negatively affected activities of daily living (ADLs), such as weakness, problems with balance/coordination, heat/cold sensitivity, numbness/tingling, and trouble moving/muscle

stiffness; most patients also reported fatigue and low energy. People also reported a negative effect on emotional and social factors, including self-esteem, general outlook, wellbeing, maintaining/starting relationships, ability to advance in one's career/keep one's job, and coping with life roles (1).

Thus, these symptoms have an important impact on the ability to participate in meaningful activities with repercussions on individuals and societies (2–4). Overall, participation is defined as the "involvement in a life situation," which includes daily activities, leisure, social activities, and work (5, 6). Participation is associated with life quality, self-efficacy, and self-esteem and has been proposed as a determinant of health status. Thus, currently, the rehabilitation process tends to focus on improving the participation level among patients (6). When a person with MS starts a rehabilitation process, it is essential to identify the needs, based not only on the symptoms but also on the difficulties encountered in daily life. Standardized, valid, and reliable tools are essential to effective evaluation. Internationally, there are several evaluation scales capable of achieving these objectives (7). Compared to these scales, however, it was decided to use the Health Assessment Questionnaire (HAQ) because it has been translated into most languages and it has been classified as the best predictor of mortality, work disability, joint replacement, and medical costs. The US Food and Drug Administration accepts it as a measure for the evaluation of the prevention of disability (8). Furthermore, it is used in most clinical trials and observational outcome studies. To date, the HAQ questionnaire is available in English (9), Dutch (10), Swedish (11), Portuguese (Brasil) (12), French (13), Spanish (Mexico) (14), Spanish (Spain) (15), Italian (16), German (17), Arabic (Kuwait) (18), Korean (19), Chinese (Singapore) (20), Danish (21), Slovak (22), Indian (23), Arabic (Egypt) (24), Spanish (Argentine) (25), Estonian (26), Greek (27), Thai (28), Turkish (29), Bengali (30), Nepali (31), Malay (32), Persian (33), and Japanese (34).

The psychometric properties of the HAQ have never been studied in a population of people with neurological disease. The validation of this measurement tool for people with MS allows the comparison of studies that analyze the same treatment in different diseases. Moreover, using the same assessment tool can define which treatment is more effective than others. This study aims to evaluate the psychometric properties of HAQ in a population of individuals with MS and compare the results with their QOL.

METHODS

This study was conducted by a research group from "Sapienza" the University of Rome (35–44).

This cross-sectional study was performed in line with Consensus-based Standards for the selection of health Measurement Instruments (COSMIN); refer to the COSMIN checklist to examine the psychometric properties of the HAQ (45).

Participants and Recruitment

A survey was conducted on a cohort of consecutive patients about the neurologic outpatient clinic at the Policlinic Umberto I in Rome between February and October 2020. There were no inclusion or exclusion criteria for participants except that they should be diagnosed with MS, per the "McDonald's" clinical diagnostic criteria for MS and a score with a range of 1–8 (46). Individuals in the MS Center of the clinic were verbally informed about the study's methods and purposes by their neurologist. All participants were informed about the study, and their interest in taking part was recorded; those who subsequently entered the study gave their written consent before inclusion (47, 48).

Assessment Tools

1. The Expanded Disability Status Scale (EDSS) is the most commonly used scale in patients with MS. The EDSS is a very effective method of reflecting disability. The EDSS, with a scoring system between 0 and 10, reveals the patient's morbidity. Zero points are normal neurological examinations. Ten points show the MS-related death cases. Patients with an EDSS score up to 5 are fully ambulatory patients. Up to this point, the main determinant of EDSS are functional systems (FS), the ambulation status is the main determinant in the degree of disability after 5 (49);
2. The HAQ consists of 20 questions relating to the ability to carry out common daily life activities, which are divided into eight sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities. There are four possible responses for each question, with the degree of difficulty that the requested action involves: 0 = without any difficulty; 1 = with some difficulty; 2 = with much difficulty; 3 = unable to do. For each category, the highest score is considered and the sum of the scores (from 0 to 24) divided by 8 represents the final HAQ score, which can vary from a minimum of 0 to a maximum of 3. The higher the score, the greater the disability; The time of administration ranges between 10 and 20 min (9);
3. The Short Form (36) Health Survey (SF-36) consists of eight scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health). Each of those consists of 1–10 questions. Also, a single-question assessment on the change in health conditions is not used for scoring in any of the eight scales. Synthetic indices that globally describe the state of physical and mental health were obtained from the aggregation of the different subscales. The questions and subscales of SF-36 are organized so that the higher the score, the better the health of the subject. Standardized mathematical procedures establish the algorithms relating to the scoring phases (50).

Data Collection

At the beginning of the study, the patients' data were collected (name and surname, date of birth, education, marital status, profession, city of residence, type of house, presence of architectural barriers, people living in the house, caregiver, if in possession of a mobility aid, years of duration of the illness, and availability for any future studies). The questionnaire choices were based on the study objectives. The EDSS, administered by the neurologist, was used to define the progression of the

disease, SF-36, to evaluate the health state of patients, and HAQ to evaluate the limitations in the QOL due to disease.

Two occupational therapists administered the questionnaire. The patients were interviewed separately at a neurological clinic. The questionnaires are self-administered by the patient if he could, or by the caregiver if the patient was not cognitively fit.

Data Analysis

All the data were coded, inputted, and analyzed into Microsoft Exce (One Microsoft Way, Redmond, Washington, USA). The data were analyzed with descriptive statistics measures. The reliability of the test was assessed by measuring the value of Cronbach's alpha for internal consistency. As recommended, the acceptable alpha coefficient was set to at least 0.70 (51). The correlations between the instruments were assessed using the Pearson correlation coefficient. The Pearson's correlation coefficient was interpreted as follows: 0 indicated no linear relationship; +1/−1 indicated a perfect linear relationship (positive/negative); a value between 0 and 0.3 indicated a weak linear relationship; values from 0.3 to 0.7 indicated a moderate linear relationship; values between 0.7 and 1 indicated a strong linear relationship (52). Any p-values $\leq$0.05 were considered statistically significant. All statistical analyses were performed using IBM-SPSS version 23.00 [International Business Machines Corporation (IBM), Armonk, New York, USA].

RESULTS

Table 1 presents the demographic and clinical characteristics of the study subjects. Of the 34 patients, 17 are women (50%) and 17 are men (50%), with a mean age of 49 years. A total of 4 patients (11.8%) are in EDSS grade 0, 2 (5.8%) in grades 1 and 1.5, 7 (20.5%) in grades 2 and 2.5, 2 (5.9%) in grade 3, 4 (11.7%) in grades 4 and 4.5, 3 (8.8%) in grade 5.5, 10 (29.4%) in grades 6 and 6.5, 1 (2.9%) in grade 7, and 1 (2.9%) in grade 8. Approximately 79% of the patients are diagnosed with relapsing-remitting MS (RRMS), and 21% are diagnosed with MS Secondarily Progressive (SMSP). Furthermore, 19 patients (55.9%) out of 34 reported being autonomous in the activities of daily life (ADL), and, therefore, they do not need a caregiver.

Table 2 shows the mean results and standard deviation of the HAQ score for each sub-category (dressing, arising, eating, walking, hygiene, reach, grip, and activity), highlighting the interrelationships. From these, a total Cronbach's alpha of 0.94 emerged.

Table 3 shows the correlation between the dimensions of SF-36, the sub-categories of the HAQ, and its total according to the Pearson Correlation Coefficient. To evaluate a possible linearity relationship between SF-36 and HAQ, the Pearson Correlation Coefficient was used, from which significant correlations ($p <$ 0.01) emerged. As shown in **Table 3**, it was found that the eight sub-categories of the HAQ are inversely proportional to the dimension of physical functioning and activity limitations due to the physical health of SF-36. It also emerged that HAQ sub-categories are inversely proportional to the dimension of the limitations of activities due to emotional problems and energy/fatigue, especially in the grip, where there is a significant correlation at the 0.01 level. All items of the HAQ are inversely proportional to emotional wellbeing, significantly in eating and grip. There is a significant correlation ($p < 0.01$) between social functioning and eating, the action of arising, grip, reach, and activity; therefore, social functioning decreases as the difficulty in eating increases. The categories of arising and activity turn out to be significantly inversely proportional to general health. As it is

TABLE 1 | Demographic and clinical characteristics of the participating population.

	Mean (standard deviation)
Age	49 (9)
EDSS	4 (2.5)
	Frequency (%)
Diagnosis	
Relapsing remittent	27 (79.4)
Secondary progressive multiple scale	7 (20.6)
Gender	
Women	17 (50.0)
Education	
High school	19 (25.9)
Gratuated	7 (20.5)
Middle school	8 (23.6)
Marital status	
Single	11 (32.3)
Married	16 (47.1)
Unmarried	5 (14.7)
Widowed	2 (5.9)
Employment status	
Unemployed	7 (20.6)
Employed	17 (50.0)
Freelance professional	7 (20.6)
Retired	2 (5.9)
Student	1 (2.9)
Caregiver	
Nobody	19 (55.9)
Formal	2 (5.9)
Informal	13 (38.2)

TABLE 2 | Internal consistency of the Health Assessment Questionnaire (HAQ).

	Mean (standard deviation)	Cronbach's alpha if item Deleted
Dressing	0.88 (1.04)	0.931
Arising	1.12 (1.15)	0.925
Eating	0.94 (1.15)	0.936
Walking	1.24 (1.05)	0.932
Hygiene	1.18 (1.14)	0.930
Reach	1.06 (1.18)	0.932
Grip	0.41 (0.86)	0.946
Activity	1.41 (1.21)	0.929
Total alpha 0.94		

TABLE 3 | Correlations between Health Survey—Short Form 36 (SF36) and the HAQ.

	Physical functioning	Role limitations due to physical health	Role limitations due to emotional problems	Energy/ fatigue	Emotional wellbeing	Social functioning	Pain	General health
Dressing	−0.765**	−0.474*	−0.087	−0.246	−0.215	−0.249	−0.023	−0.309
Arising	−0.784**	−0.453*	−0.199	−0.305	−0.330	−0.403*	−0.170	−0.388*
Eating	−0.750**	−0.679**	−0.314	−0.374	−0.384*	−0.396*	−0.279	−0.327
Walking	−0.793**	−0.377*	−0.048	−0.306	−0.105	−0.218	−0.055	−0.260
Hygiene	−0.854**	−0.567**	−0.117	−0.363	−0.174	−0.249	−0.087	−0.343
Reach	−0.689**	−0.551**	−0.305	−0.286	−0.235	−0.400*	−0.207	−0.221
Grip	−0.421*	−0.465*	−0.445*	−0.417*	−0.469*	−0.494**	−0.298	−0.235
Activity	−0.840**	−0.600**	−0.267	−0.371	−0.287	−0.445*	−0.193	−0.377*

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

TABLE 4 | Correlations between the clinical and demographic characteristics of the population and items of HAQ.

	Dressing	Arising	Eating	Walking	Hygiene	Reach	Grip	Activity	HAQ total
Type of MS	0.509**	0.568**	0.473**	0.281	0.388*	0.585**	0.280	0.486**	0.517**
Years from diagnosis	0.058	0.048	0.180	−0.073	−0.005	0.049	−0.220	0.056	0.090
EDSS	0.678**	0.802**	0.590**	0.798**	0.750**	0.560**	0.292	0.834**	0.829**
Age	0.333	0.194	0.180	0.078	0.384*	0.027	−0.104	0.344*	0.259
Gender	−0.129	−0.044	−0.058	−0.175	−0.044	−0.179	0.024	0.006	−0.102

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

possible to find in the current literature, invisible MS symptoms negatively affected the patients' social lives. Programs should be designed to improve the work integration and daily activities of patients with MS (53).

Table 4 shows the cross-cultural correlations between the clinical and demographic characteristics of the study participants, the sub-categories of the HAQ, and their total scores.

DISCUSSION

This study evaluated the psychometric properties of HAQ in a population of individuals with MS and has been shown that these properties are satisfactory, with good reliability and validity, in patients with MS.

In the study, from the mean of the HAQ sub-categories' intercorrelations, it emerged that the total Cronbach's alpha is equal to 0.94 (**Table 2**). These data are in line with other studies, for example, the HAQ showed an alpha value of 0.90 in the Spanish (Mexican) version (54) and 0.98 in the Chinese version (55). Therefore, it has excellent internal consistency and good consistency between the items in the questionnaire. The Italian version of SF-36 was used as a gold standard to assess construct validity. The construct validity analysis showed a linear correlation between activity limitation and quality of life; this correlation was higher for physical functioning. A recent study of the Chinese version showed a strong correlation between HAQ in a patient with rheumatoid arthritis with SF-12, also for the mental health component (55).

Finally, a cross-cultural analysis was made with the HAQ, from which, as reported in **Table 3**, it emerged that according to the type of diagnosis (relapsing remittent or progressive), there is a significant direct proportionality with difficulty in all sub-categories of the HAQ and the total score of the HAQ, except for walking and grip. Furthermore, it is shown that the degree of EDSS of the subjects has a significant direct proportionality with all the items of the HAQ, except for grip; therefore, the higher the EDSS stage, the greater the difficulties in the aforementioned activities. This means that people with progressive MS and with higher levels of EDSS have a greater impact on ADLs. The last significant correlation occurs between the patient's age, hygiene, and activity in a directly proportional way.

Limitations of the Study

The study's limitations are mainly due to the historical period in which it was conducted during the pandemic due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. For this reason, there was no possibility of administering the questionnaires to the population. Consequently, the number of participants is not very large. Future studies should include larger samples of patients with MS to overcome this limitation.

Conclusions

In conclusion, with these psychometric properties, HAQ appears to be a valid tool to evaluate the ability to carry out in a population with MS. It could provide the healthcare and rehabilitation sector with an additional tool for assessing patients' disabilities with

MS. The validation of this measurement tool for people with MS allows comparing outcomes of various studies. It is useful for testing the effectiveness of a treatment in various diseases, and using the same assessment tool can define which treatment is more effective than others.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB, GG, AC, and GF contributed to conception and design of the study. LC and CC organized the database. GG performed the statistical analysis. AB wrote the first draft of the manuscript. MTo, MTa, VB, and SC wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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BRIEF RESEARCH REPORT
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Toward a Digital Health Intervention for Vestibular Rehabilitation: Usability and Subjective Outcomes of a Novel Platform

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Digital technologies are increasingly available and are reducing in cost. There is an opportunity to move to a digital health approach in vestibular rehabilitation (VR), but there is a paucity of suitable systems available and a consequent lack of evidence to support their use. This study aimed to investigate a novel digital platform developed specifically for VR (comprising clinician software, a wearable sensor, and a patient-facing app). Participants ($n = 14$, 9F:5M, mean age 59) with vestibular dysfunction and imbalance used the app for treatment, and therapists ($n = 4$) used the platform to deliver VR in the form of individualized exercise programmes over a mean of 17.4 ± 8.8 weeks. Outcomes included the system usability scale, the patient enablement instrument (PEI), change in subjective symptoms (numerical rating scales), percentage adherence to prescribed exercise, and a semi-structured interview on utility. A significant reduction was found in symptoms of vertigo/dizziness ($p < 0.004$), imbalance ($p < 0.002$), oscillopsia ($p < 0.04$), and anxiety ($p < 0.02$) after use. System usability scores were high for both clinicians (mean 85/100) and participants (mean 82.7/100) and high enablement was reported (mean PEI 6.5/12). Overall percentage adherence to the exercise prescription was highly variable and ranged from 4 to 78% when measured digitally. At semi-structured interviews, participants reported a high level of acceptance and satisfaction with digital delivery, and no adverse events were recorded. When COVID-19 restrictions eased, 2 participants trialed the head sensor with the application and found it highly usable. Further research is required to investigate the efficacy and how the wearable sensor impacts the delivery of care.

Keywords: vestibular rehabilitation, digital health, exercise adherence, usability, enablement

INTRODUCTION

Across all fields in healthcare, digital health is on the rise, but its role in vestibular rehabilitation (VR) remains to be elucidated. The World Health Organization has defined digital health as "a broad umbrella term encompassing eHealth (which includes mHealth), as well as emerging areas, such as the use of advanced computing sciences in "big data," genomics and artificial intelligence" (1). Within this definition, e-health is further defined as "the use of information and communications technology" and mHealth as "the use of mobile wireless technologies" (1). Traditionally, VR has been delivered face to face, with fewer than 5% reporting the use of telerehabilitation before the COVID-19 pandemic (2). One of the obvious benefits of digital health is to improve access, which is a challenge in VR (3). It is estimated that between 53 and 95 million adults have peripheral vestibular hypofunction across Europe and the US (4), and VR is a first-line, evidence-based treatment for these adults (5, 6). In a recent European Survey of VR in 22 countries, almost 50% of therapists reported that VR was difficult to access (2). Furthermore, the mainstay of VR is the home exercise programme. Gaze stabilization exercises are recommended at frequencies of 3–4 times per day (6), and meta-analysis of studies in fall prevention estimate a cut-off of at least 50 hours of targeted exercises to achieve therapeutic effects (7). It is likely not necessary and probably not feasible to have direct therapist supervision at these required intensities. Physical therapy fundamentally aims to improve movement and the ability to accurately track movement when the patient is exercising provides major opportunities for a better understanding of FITT (frequency, intensity, type, and time) principles. In turn, this would provide a much-needed evidence on the effectiveness of different components of exercise regimes. To advance the science of exercise prescription in VR, it is axiomatic that accurate data of exercise parameters are collected. This data would provide rich information for clinical and research purposes.

It is therefore anticipated that digital health will be embedded in future care, will solve the problems of access, and allow a greater understanding of exercise parameters. In a recent VR specific survey, 80% of therapists agreed that telehealth was an effective mode of delivering treatment but reported challenges with providing the written exercise programme and concerns about testing balance remotely with no caregiver present (8), and in a large survey of US physical therapists, 40% reported using telehealth software for the first time in 2020 (9). A benefit of the pandemic has been the requirement to use technology for daily human interactions beyond health care, and this has likely increased acceptance and familiarity with remote interactions. There are thus many opportunities for VR professionals to harness technology to solve the problems of prescribing and delivering exercise programmes remotely. However, therapists face many considerations when transitioning to digital care, and barriers are often cited as cost, IT infrastructure, data privacy and security, and uncertainty around efficacy (10, 11). Also, amongst therapists and patients, there remains a preference for face-to-face care, in a profession that is known for its "hands-on" approach (8).

Some studies are now appearing in the literature comparing conventional face-to-face VR with internet-based rehabilitation and have provided support for a digital approach and valuable insights on patient behavior and outcomes using digital technology. Geraghty et al. (12) and Pavlou et al. (13) both reported high attrition rates of 21 and 55%, respectively, in the groups allocated to unsupervised remote forms of VR, much higher than those who received face-to-face care. More recently, however, van Vugt et al. (14) reported similar attrition rates of ∼5% in groups receiving internet-only based VR or therapist-supported home VR, perhaps heralding an increased acceptance of remote VR amongst patients.

Considerable challenges remain in proving efficacy and cost-effectiveness. The opportunity costs of a telerehabilitation infrastructure and associated technology (wearables, hardware, software, etc,) need to show a benefit for both the patient (in terms of time and money saved by being treated in the home, faster and better outcomes reducing loss of productivity, and increasing quality of life) and the health care provider (decreased consultation time, better outcomes, and more timely and targeted care). Therefore, it is not an easy task to integrate telerehab or technologies into rehabilitation. Major obstacles such as reimbursement by insurers also exist, although these are beginning to be addressed and will greatly assist with more widespread adoption.

The aims of this study were, first, to investigate the usability of a newly developed VR-specific digital platform and, second, to investigate its safety, exercise adherence, and outcomes with use.

MATERIALS AND METHODS

This was a usability study using a pre-treatment–post-treatment design to investigate the use of a novel digital VR platform for the rehabilitation of vestibular dysfunction and imbalance. The objectives of the study were to quantify patient and therapist usability of the platform, patient outcomes after using the platform, and to obtain, using a structured questionnaire, patients' views on the use of the app developed for the platform in their rehabilitation.

The study endpoints were:

1. The system usability scale (SUS) score (15) (patient and therapist) and the patient enablement instrument (PEI) score (16, 17) at 6 weeks (patient).
2. Change in visual analogue scores of subjective symptoms of dizziness/vertigo, imbalance, nausea, anxiety, and oscillopsia (18).
3. Percentage adherence to exercise (digitally measured by the application) and safety of the platform (number of adverse events).
4. Patient's views on the utility of the platform in their rehabilitation using a semi-structured phone interview (see **Supplemental Material**).

Data collection took place at the Neurotology Clinic and Physiotherapy Department at a large University teaching hospital. Ethical approval was obtained from the Hospital's Medical Research Ethics Committee. The study aimed to recruit

12–15 participants to gather sufficient data on patient's subjective views on using the platform. A sample size of 12 participants is deemed appropriate for usability studies (19).

Patients with vestibular dysfunction, confirmed with a positive video head impulse test (gain of <0.7 unilaterally) (https://www.synapsys.fr/en/home/), caloric testing (Canal Paresis > 20%), or in the absence of lab testing, a positive clinical head impulse test and nystagmus with fixation removed, and reporting at least one of the following subjective complaints: disequilibrium, gait instability, vertigo/dizziness, or motion sensitivity (20) were eligible for the study. They were excluded if they had previous VR, fluctuating vestibular disease (active Meniere's disease, migrainous vertigo), active benign paroxysmal positional vertigo, or other medical conditions in the acute phase (orthopedic injury). They were also excluded if they were unwilling or unable to use, or did not own a smartphone/tablet to use during the study.

Eligible patients were identified at the neurotology clinic by two of the researchers (RMW and DMu) who acted as gatekeepers and informed eligible patients about the study. Where there was a willingness to discuss the study, a third researcher (DMe) contacted the patient with information and obtained written informed consent after a cooling-off period of up to 1 week.

Procedure

At baseline, participants underwent the following assessments. A physical in-person assessment was often not fully possible due to the COVID-19 second (October 2020) and third waves (January 2021), when some or all of rehabilitation moved to a telerehabilitation approach. Subjective assessments were collected remotely by the platform or during phone interviews and included the following:

1. The SUS (15) was designed as a subjective assessment of the usability of interface technologies. Levels of agreement with ten statements are scored using a five-point Likert scale anchored with "strongly disagree" and "strongly agree." The SUS provides a point estimate of percentage usability. Scores above 70 are acceptable, and highly usable products score above 90. Scores below 50 indicate unacceptably low levels of usability. The validity, reliability, and sensitivity of the SUS have been extensively evaluated.
2. The PEI (16, 17) measures on a four-point Likert scale how enabled a patient feels to cope with their disease based on a consultation with their health care professional. Six questions are included and they enquire about the patient's understanding of illness, ability to cope with their illness and life, keep themselves healthy, and be confident about their health. A maximum score of 12 is attainable with higher scores indicating greater enablement. A score of 6–7 is considered to represent acceptable enablement (16, 17).

Intervention

Subsequent to completion of baseline measures and an initial assessment, the treating physiotherapist prescribed an individualized treatment programme on the platform which was then sent to the patient's smartphone and accessed *via* the App (**Figure 1**). The platform consisted of a digital clinical portal where the patient could be "on-boarded" and prescribed their individualized exercise programme. The exercises were broadly categorized into gaze stabilization, balance and gait, habituation, strengthening, breathing exercises (for anxiety), and optokinetic exercises. The FITT parameters could be individually adjusted by the therapist ensuring a customized individualized programme, which is considered the gold standard prescription approach (6, 21). Once prescribed, the patient application was used by the participant to perform their exercises; the app tracked the programme and symptoms, and these metrics were sent back to the portal in real-time. The participant was instructed on how to access and download the app to their smartphone or electronic tablet. Participants were pseudonymised on the clinical portal to prevent their identification by the technical personnel who were outside of the hospital setting. At each subsequent clinical visit (usually every week or 2 weeks) and until discharge, prescriptions were adjusted by the treating physiotherapist as appropriate. These visits mostly took place with a teleconsultation platform that was being used by the hospital during the pandemic.

The patient application on the smartphone provided the following information and support to the patient:

1. A video of each exercise with aural and text instructions.
2. Automatic guidance through their exercise programme. The app provided auditory feedback on head frequency during any gaze stabilization exercises (with an adjustable built aural metronome in the software).
3. Measurement of symptoms responses daily on a 10-point numerical rating scale (vertigo/dizziness, nausea and disequilibrium, anxiety, and oscillopsia). These were inputted by the participant once a day *via* the app. The first time a participant opened the app each day, the five scales would appear and they would be prompted on the screen to select the score that best described their symptoms that day.

Finally, the therapist could also select specific educational materials on the portal relating to balance and inner ear problems that were considered beneficial for their particular presentation and send them to the patient app. These included reading materials about what to expect from VR, symptoms of dizziness, vertigo and imbalance, and safety guidelines for exercising.

After using the application for 2–3 weeks, the participant was contacted by a researcher to explore their view on its utility and to collect the usability and enablement scores.

When COVID-19 restrictions were lifted, two participants attended the clinic and trialed the head sensor (**Figure 1**) with the app. The sensor (VG02; www.vertigenius.com) consists of an inertial measurement unit (IMU) to measure inertial motion of the head during gaze stabilization exercises. The IMU contains a gyroscope to measure the angular velocity of head movement (°/s) with yaw and pitch axis orientation. This angular velocity is used to estimate accurately the frequency in beats per minute (BPM) of the head rotation on either axis.

The participants were provided with the head sensor which connected *via* Bluetooth to the smartphone app. During gaze

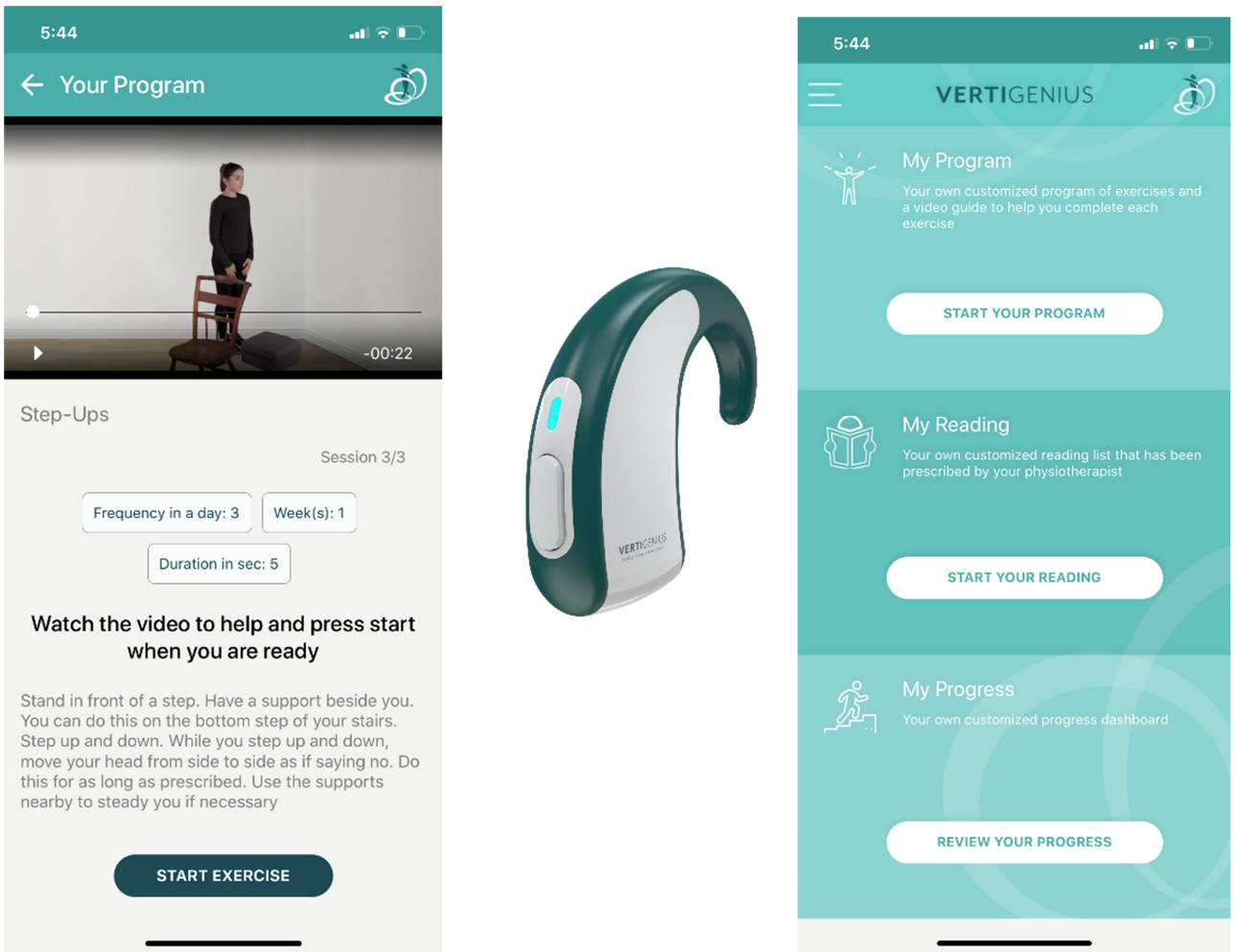

FIGURE 1 | Patient-facing application and wearable head sensor.

stabilization exercises, the sensor gave real-time feedback on the prescribed vs. actual head frequency during their exercises. A traffic light system was employed. For example, if the therapist had prescribed a head frequency of 120 beats per minute, the target displayed on the screen that the participant was fixating on turned red if the head was moving at a higher frequency, yellow if slower, and green if correct. Post-session, they were interviewed on their views of head sensor use during rehabilitation and asked to score the usability of the whole system on the SUS.

Data Analysis

Data relating to the participant's interaction with the application was processed by one of the researchers (DM). Descriptive statistics were used for the analysis of SUS and PEI scores. Data were examined for normality using histograms and QQ plots. Paired *t*-tests and Mann–Whitney *U*-tests were used to investigate pre- and post-treatment NRS scores in normally and non-normally distributed outcomes respectively. Data from the semi-structured questionnaire were analyzed descriptively.

RESULTS

The study took place from August 2020 to August 2021. In total, 14 participants (9F:5M mean age 59 years, range 38–76 years) were recruited to the study. Baseline data and demographics are shown in **Table 1**. All participants had evidence of vestibular dysfunction and age-related abnormality in at least one balance test at baseline. Due to the fluctuating COVID-19 restrictions on face-to-face visits, testing was not uniform. Participants used the application for 17.4 ± 8.8 weeks and were prescribed 5.3 ± 3.6 programmes during this time. Three patients dropped out of the study, one reporting they did "not like technology" and preferred to use conventional methods of pen and paper for exercise prescription. Another dropped out before starting to use the application reporting that English was not her first language. One more participant dropped out after 1.5 months without giving a reason.

The average SUS was 82.7 ± 17 (range 32.5–92.5) (**Figure 2A**). Only one participant scored below 80. This was a female

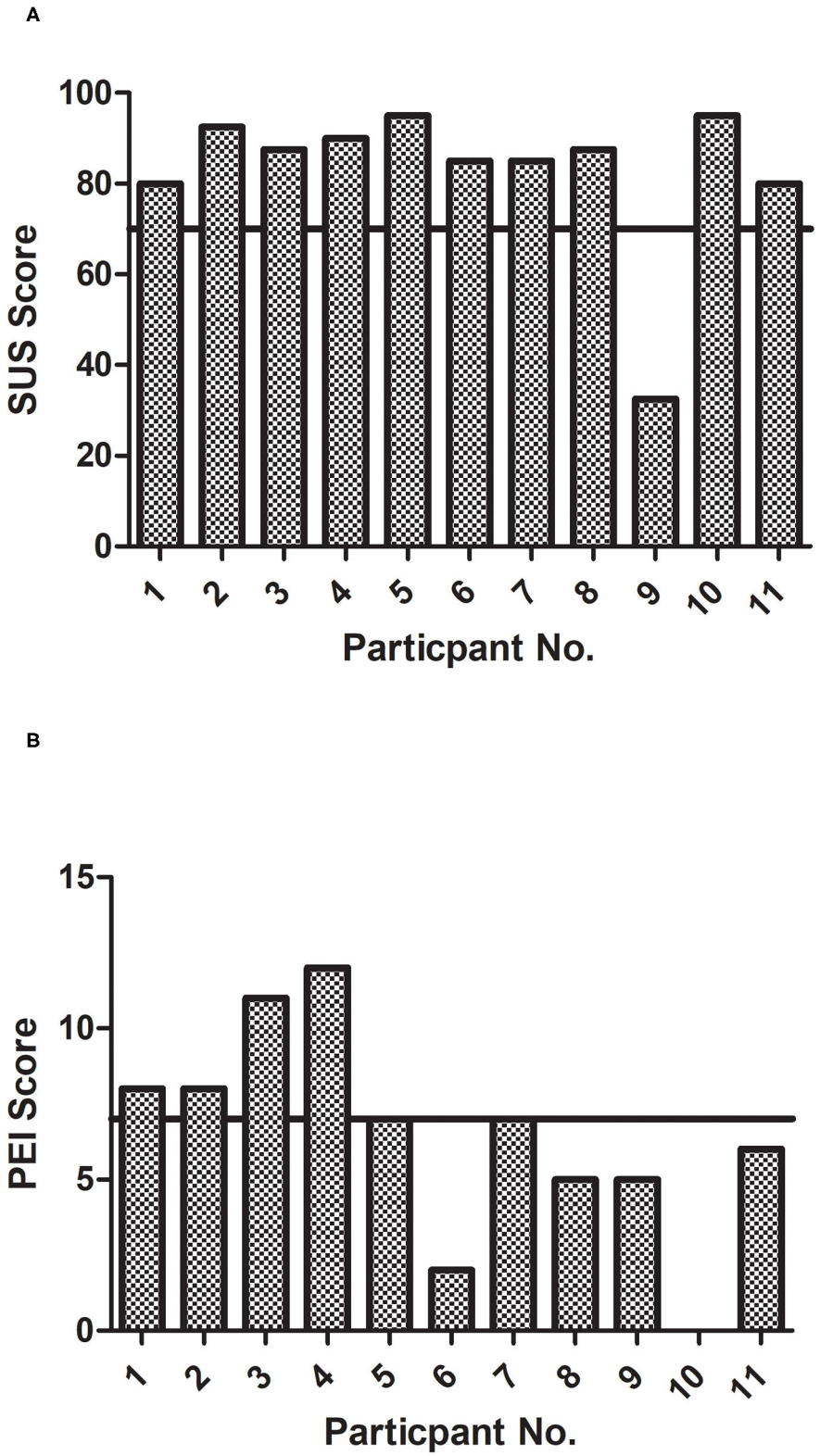

FIGURE 2 | (A) System usability scale scores for each participant. The cut-off point of acceptable usability is shown on the y axis at 70/100 and **(B)** patient enablement instrument scores for each participant. The acceptable cut-off score of 7 is depicted by the line on the y axis at 7/12.

TABLE 1 | Participant baseline clinical data.

Participant	Gender	Age	Clinical/laboratory assessment	Baseline abnormality of balance	Length of time with symptoms	Duration of rehab in weeks
1	F	58	Positive Right cHIT, Left Beating Horizontal Nystagmus with fixation removed	SOFEC Abnormal: 6, 10, 10 Secs	14 months	11
2	F	53	25% Left Canal Paresis, Caloric Testing	Condition 5 on SOT abnormal: Scores 0, 50, 50	4 Years	12
3	F	53	Abnormal Left vHIT Gain of 0.70	Condition 5 on SOT abnormal: Scores 59, 40, 64	2 years	20
4	F	45	28% Left Canal Paresis, Caloric Testing	SOFEC denoted Abnormal	1 year	2
5	M	76	Positive Left cHIT, Right Beating Horizontal Nystagmus with fixation removed	Condition 5 on SOT abnormal: Scores 0, 0, 26	1 year	30
6	M	38	32% Left Canal Paresis, Caloric Testing	Conditon 5 on SOT abnormal: Scores 50, 57, 76	9 months	34
7	M	72	Positive R cHIT, Right Beating Horizontal Nystagmus with fixation removed	SLS denoted abnormal	20 years	9
8	F	60	23% Right Canal Paresis, Caloric Testing	SOFEC abnormal: Scores 2, 2, 2 Secs	6 years	16
9	F	62	Clinical Diagnosis of UVL in Notes, Lab data not available	SLS abnormal: 10 Secs Eyes Open, 4 Secs Eyes Closed	10 years	**
10	F	66	Positive Right cHIT, Left Horizontal Nystagmus with fixation removed	SLS denoted abnormal	2 years	17
11	M	74	Positive Right cHIT, Left Beating Horizontal Nystagmus with fixation removed	SOFEC abnormal: 6 secs, SLS abnormal: 0 Secs	3 months	18
12	F	61	Abnormal Right vHIT Gain of 0.30	Condition 5 on SOT abnormal: scores 0, 0, 56	4 months	21
13	M	38	Abnormal Left vHIT gain of 0.77, Positive Right cHIT	SLS abnormal: 4 Secs Eyes Closed	1 year	19*
14	F	73	Positive Right cHIT, Left Beating Horizontal Nystagmus with fixation removed	SOFEC abnormal 9, 11, 15 Secs	9 months	**

*cHIT, clinical head impulse test; vHIT, video head impulse test; SOFEC, Stand on Foam Eyes Closed; Secs, seconds; SOT, Sensory Organization Test (Equitest); SLS, Single Leg Stance Test. *Dropped out without giving a reason, **Dropped out of study.*

participant who scored 32.5 and who had dropped out due to a preference for conventional care.

Change in Numerical Rating Scale Scores

The numerical rating scales were completed for the five subjective symptoms, namely, dizziness/vertigo, imbalance, nausea, anxiety, and oscillopsia. **Figure 3** shows the pre–post treatment scores, and **Table 2** shows the results of the paired *t*-tests for each symptom. All symptoms were significantly reduced by at least 40% ($p < 0.05$) (indicating improvement) except for the nausea NRS, which was reduced by only 9.1% ($p = 1.0$). No adverse events were recorded during the study.

PEI Scores

The mean PEI score was 6.5 ± 3.7. One participant scored 0/12, which is a very low score indicating little or no enablement with treatment. On closer inspection of their numerical rating scores, improvements were seen in all five except the complaint of imbalance, which did not change. Another participant scored 2/12 but all numerical rating scores were improved. The remainder had acceptable PEIs (**Figure 2B**).

SUS Scores: Health Care Practitioners

Four physical therapists used the platform during the study. Each completed a SUS. The mean score was 85 ± 10.2 (range 70–92.5). Two specifically reported needing time to become familiar with the application to onboard the patients, but after that phase they found it highly usable.

Adherence

Once an exercise was completed, i.e., the patient opened and completed each exercise on the app, data on completion was sent back to the portal immediately allowing the therapists to easily view adherence in a graphical form. The average percentage adherence in counts of prescribed exercises (the frequency per day of each exercise multiplied by the duration of the programme in weeks) was 30.3 ± 23.5% (range 4.4–77.8%).

Results From Semi-structure Interviews

Eleven participants completed a phone interview about using the application for their phone. Ten (91%) reported they would recommend the app to others for rehabilitation (reporting "yes definitely," "yes absolutely," and "yes 100%," amongst other responses). One participant had macular degeneration and visual impairment and was using the app on an iPad. She specifically reported she liked accessing exercises on the iPad as "they were there at a touch, didn't have to fumble around with paper and if it was on paper, I wouldn't have been able to see it."

A female participant who dropped out before using the app reported she "maybe" would recommend it. This participant was "afraid" to log in to the application, had needed help from a family member to download the app, and reported being "just lost" when trying to log in. This participant reported not "being one for apps" and not "a phone person." A lower PEI score (5/12) and a lower SUS score (32.5) were recorded by this participant

Broad themes relating to the question of what participants liked and disliked about the app are shown below in **Table 3**.

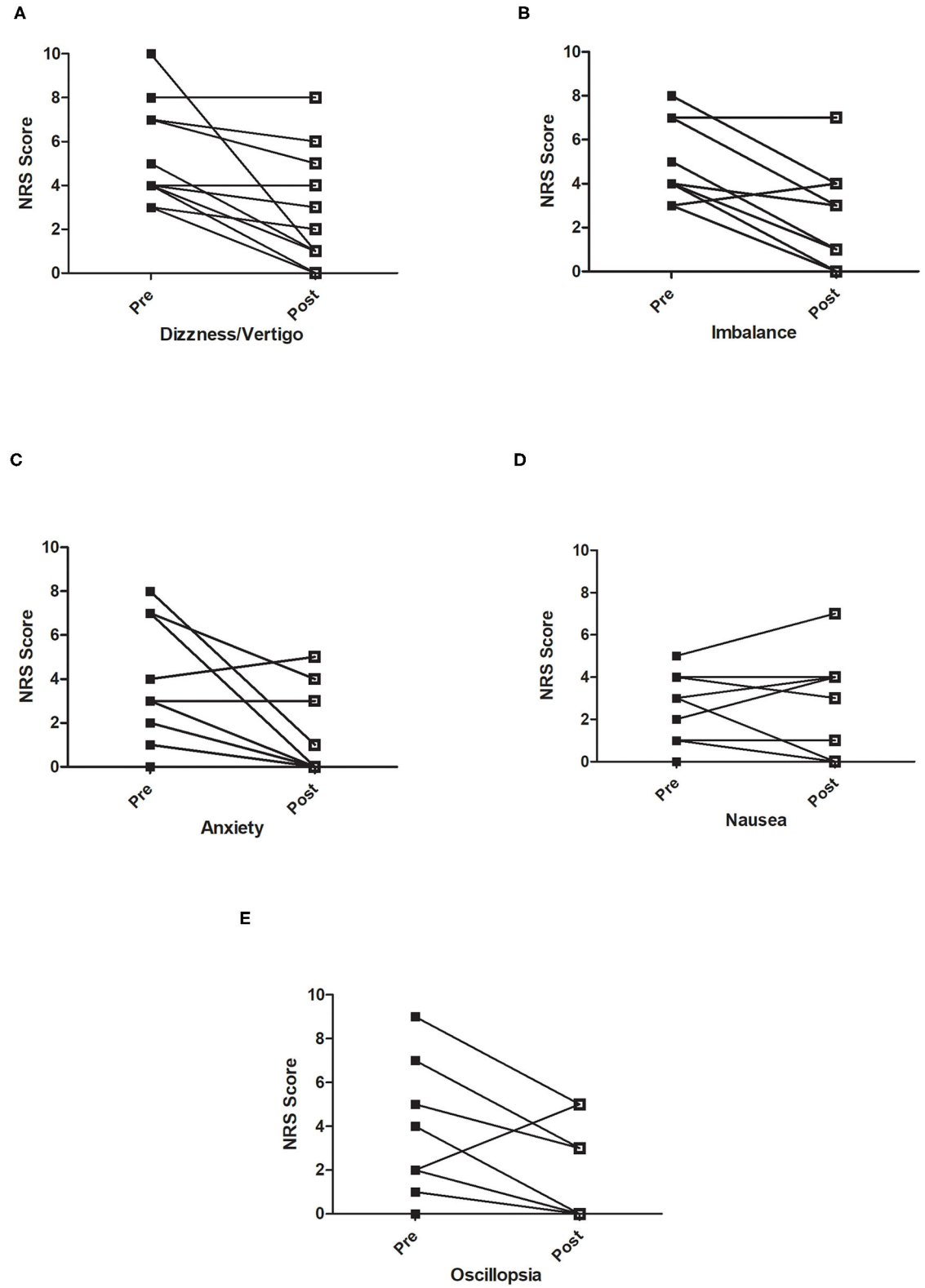

FIGURE 3 | Pre- and post-treatment numerical rating scale scores for **(A)** Dizziness/vertigo, **(B)** Imbalance, **(C)** Anxiety, **(D)** Nausea, and **(E)** Oscillopsia. Participants rated symptoms daily on a 0–10 scale with 0 anchored as "none" and 10 as "symptom as bad as it could be." Each participant is represented on a graph with closed squares showing the pre-treatment score and a line linking to the post-treatment score (open square).

TABLE 2 | Mean change in numerical rating scale scores of subjective symptoms, where 0 is "no symptoms" and 10 is marked as "symptoms as bad as they can be."

Symptom	Pre-treatment NRS (/10) Mean (SD)	Post treatment NRS (/10) Mean (SD)	Change NRS (/10)	*P*-Value	95% CI
Vertigo/dizziness	5.26 (2.2)	2.6 (2.6)	2.67	0.004	1.1–4.3
Imbalance	5 (1.8)	2.8 (2.5)	2.25	0.002	1.0–3.4
Nausea	1.9 (1.8)	1.9 (2.4)	0	1.0	−0.9–0.9
Anxiety	3.2 (2.8)	1.1 (1.8)	2.2	0.02	0.4–3.7
Oscillopsia	3.1 (3.2)	1.6 (2.1)	1.5	0.04	0.1–2.9

TABLE 3 | Results from the semi-structured interviews on the utility of the app in vestibular rehabilitation.

Likes

- High ease of use, even for those who self-declared they were not "big" app users and had not used them for treatment before.
- High perceived usefulness of videos to correct performance, ease of access to the treatment (a few reporting its in "your pocket," easier to follow than a "sheet of paper."
- Benefits of the app over pen and paper adding structure and motivation to the exercise program. Comments on the "age we live in, it's all about the phone."
- High levels of satisfaction with color scheme, simplicity and clarity of layout- app was easy to navigate.
- Improved self-efficacy in exercise, reports that the app was tangible, accessible in the home, reduced the anxiety of not performing exercises correctly, helped them remember to do exercises, stay "on-top" of the program.
- Educational materials were useful.
- Reduced the need for clinic visits (COVID-19 related concern).
- Information on progress in the app and symptom collection allowed me "to see some days are better than others" and "liked that it was telling me I was making progress."

Dislikes

- Occasionally technical problems (screen freezing).
- There was no audible prompt for timer when doing balance exercises with eyes closed.
- Sometimes it was not clear that they had completed exercises.
- Unable to use the app and have others working in the background (for example listening to music when doing their walking program).
- Symptoms only being recorded once a day was an issue for $n = 2$ who pointed out the exercises often increase the symptoms and they would like this to be recorded.
- No specific information/feedback provided by the app as to whether they were performing the exercise correctly.
- Requests to see more information on progress and mindfulness or other strategies for anxiety.

Head Sensor Usability

For the two participants who were observed using the head sensor during their prescribed exercise programme, SUS scores were 97.5 and 100, respectively, indicating very high usability. Both had been using the app only with the inbuilt metronome at home, and both remarked that the head sensor made the system "much better." One participant likened the head sensor to a hearing aid and remarked it might be easily lost due to its small size. It was also observed that instructions were needed for participants to place the head sensor correctly on the ear. Participants reported that the visual feedback correcting their head frequency in real-time was helpful and the traffic light visual feedback was easily understood. They also stated that the head sensor could be easily incorporated into treatment at home and that they were in favor of the feedback on their performance and the additional information on their progress that could be obtained from the head sensor.

DISCUSSION

This study was performed to investigate both clinician and patient usability and experiences when using a novel digital health platform for the delivery of VR. During data collection, Ireland experienced waves 2 and 3 of the COVID-19 pandemic, which resulted in challenges to the recruitment process (recruitment is usually done face to face with baseline outcome measures performed in clinic). However, the platform easily enabled remote treatment in the home, and whether the participant had face-to-face or remote sessions with their therapist, did not negatively impact its use. In agreement with others, the study found that the benefits of digital delivery were augmented during COVID-19, conferring a feeling of safety and continuation of care when face-to-face visits were curtailed (11, 22). In addition, positive outcomes on the distressing subjective complaints of dizziness/vertigo, oscillopsia, imbalance, and anxiety were evident.

For "naïve" patient users, the app had high system usability scores. Generally, a score above 70 is deemed acceptable, and the mean score in this study was 83 (19, 23). There were three drop-outs, one did not speak English as a first language and one declined to use the application after downloading it as she was "just lost." This was expected as technology is difficult for some.

High levels of enablement were also recorded by participants. Enablement is a key feature for patients to feel they can cope

with and understand their illness. Scores of 6–7 are considered acceptable and the mean score was 6.5. Scores were higher than reported in other studies who reported lower mean scores of between 3 and 4 (24, 25).

All participants, except one, reported they would recommend the app to other patients with dizziness and vertigo. A high level of user acceptance was evident, and participants had little fault to find with the ease of use, layout, and look and feel of the application. The app can be considered to be usable.

For the 4 "naïve" Health Care Practitioners, the clinician portal also had high SUS scores at 83.3. They reported that it was easy, intuitive, and quick to use, and it streamlined and facilitated care remotely, the latter being a key benefit during the pandemic.

There were no adverse events recorded during the study. Participants used the application for an average of 17 ± 8.8 weeks, and there was preliminary evidence that a reduction in subjective symptoms of dizziness/vertigo, imbalance, nausea, anxiety, and oscillopsia occurred with the usage of the application, indicating the effectiveness of the treatment, in line with what is expected with VR. Due to COVID-19, we were unable to systematically collect physical outcome measures, and this must be evaluated in future studies to determine efficacy.

Two participants were non-English speakers, one of these dropped out due to difficulties with the English language and comprehension, but the other was able to engage with the patient app. It is thus a recommendation that when employing patient apps they are translated into the local language.

One key benefit of the platform was the automated collection of exercise adherence. Diaries are commonly used to this end but are frequently criticized as being inaccurate and time-consuming. This is the first study to report actual adherence to exercise and found a low mean adherence to exercise of 30%. This may be because the recommended frequency for gaze stabilization exercises in VR programmes is 3–4 times per day (6). However, significant improvements were seen in subjective symptoms, and future work is planned to investigate the minimum exercise adherence necessary to achieve benefits. Therapists personalized the exercise prescription according to participants' presenting impairments, and whilst this meant participants completed different exercises, this is the recommended practice (6, 21). However, all participants were prescribed gaze stabilization exercises, balance, and gait exercises. Further study of the effects of individual exercises with controls is required to determine optimal programmes.

Only two participants used the head sensor during the study and in a face to face setting. Although reported usability was high and the integration of the head sensor providing real-time corrective feedback was easily understood, these findings can only be considered preliminary.

STUDY LIMITATIONS

The study took place during the second (October 2020) and third waves (January 2021) of the COVID-19 pandemic, therefore the physical outcome measures that were planned for the study were not feasible to collect as the face-to-face contact with the researchers, which would be usual in data collection, was not permitted. More complete data on physical outcomes of balance and gait would have provided a valuable addition to the findings. We were unable to provide all the participants with this head sensor, but initial trials with two participants were favorable, and a future study is underway to investigate the effect of the head sensor. Several participants who did not use the head sensor reported they would like more feedback on their exercise performance and personalized direction on what to do if exercises increased symptoms. The wearable sensor was designed to address this problem so it will be interesting to see how it impacts treatment.

Finally, the sample size was small but considered adequate for usability studies. Larger sample sizes will be required to demonstrate efficacy and cost-effectiveness.

In conclusion, this usability study has provided initial evidence that a novel digital platform incorporating a clinician portal and a patient-facing app are highly usable and accepted by health care practitioners and patients for VR. Significantly reduced symptoms were recorded with use, suggesting benefit. A "naïve" user of either can be easily onboarded and interact with the platform relevant to them. Importantly over the time frame of use, improvement in subjective symptoms was significant, supporting its use in vestibular and balance rehabilitation programmes. As with all applications, feature improvements were suggested, but the current workflows are usable and mirror the clinical pathway sufficiently to integrate the system easily into healthcare settings. Future studies planned include incorporating the platform's wearable sensor in a randomized controlled trial to investigate efficacy and cost-effectiveness.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was reviewed by Beaumont Hospital Medical Research Ethics Committee, Beaumont Hospital, Beaumont Road, Dublin 9. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DMe and DMu conceived the study. RM and OH were gatekeepers, recruited patients, and assisted with preparations for the Ethics Committee Submission. SM, SC, DMu, and RV treated the participants. DMe interviewed the patients and collected the outcomes, analyzed the data, and wrote the paper. DMe and RV commented on the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.836796/full#supplementary-material

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Conflict of Interest: DMe is the inventor of the digital intervention that was employed in the study. It is patent pending and she is named on the patent. This research is being commercialized and she is a shareholder in a start-up company formed before the end of the study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Eye Position Shifts Body Sway Under Foot Dominance Bias in the Absence of Visual Feedback

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Purpose: The purpose of this study was to investigate whether information on extraocular muscle proprioception without visual information affects postural control.

Methods: Thirty-five healthy young volunteers participated in the study. Postural control outcomes included the center of pressure (CoP) for static standing, the total length of the sway of the CoP (LNG), and the sway area (SA), as well as the mean CoP in the mediolateral and anteroposterior directions. The following five eye-fixing positions were used: eye-up (E-Up), eye-down (E-Down), eye-right (E-Right), eye-left (E-Left), and eye-center (Center eye position). One-way ANOVA and Bonferroni correction was performed for statistical processing. Electrooculograms were recorded to detect eye orientation errors, measured with the eyes closed.

Results: The results of this study showed no significant difference between the LNG and SA results when comparing respective eye positions (E-up, E-down, E-right, E-left) relative to E-Center (control). However, the average CoP was shifted to the right at E-Up, E-Down, and E-Left.

Conclusion: These findings indicate that postural control may be affected by eye-body coordination depending on the position of the eyes, even without visual information.

Keywords: eye position, body sway, postural control, dominant foot, visual reference, electrooculography

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INTRODUCTION

Visual information contributes to postural stability in humans (1). Closing one's eyes increases body sway (2), and the change in optical flow in the peripheral visual field induces displacement of the foot center of pressure (CoP) during upright standing (3). Human vision captures targets through saccadic movements. The position of the retinal image is different before and after the saccade. This retinal displacement also affects postural instability (4). Gaze position (5, 6) and distance (7–9) are also factors that affect body sway. In terms of gaze direction, Paulus et al. (9) found that back-and-forth sway was induced by changes in target disparity over a short distance, while longitudinal sway was induced by the movement of the gaze following an object. In terms of gaze distance, Kapoula and Lê (6) and Moraes et al. (8) reported that postural sway in the left-right and front-back directions in healthy subjects was smaller when they gazed at a closer object than when they gazed at an object further away. In addition, eye movement accompanied by changes in visual reference affects postural control in humans (10). The lateral rhythmic movement of the eyes while following a moving target induces body sway in the mediolateral (ML) direction without inducing head

movement (11). As these previous studies have shown, factors, such as eye position and focusing distance, along with visual information, affect postural control when the eyes are open. On the other hand, it is not clear whether changes in eye position alone affect body sway in the absence of external stimuli, such as when the eyes are closed. There is a substantial increase in body sway when the eyes are closed (9). In other words, the position of the eyes during eye closure is considered to affect the body sway. However, the way in which visual stimuli are integrated into postural control is not fully understood, and much research is needed to clarify the dynamic relationship between visual information and motor behavior (8). This interdependence of perception and action is thought to arise from the so-called action-perception cycle (12, 13).

The foot CoP is often used to assess body sway during upright standing. To determine the magnitude of body sway, the total length of the sway trajectory of the CoP (LNG) (14) and the area of the surface surrounded by CoP (SA) (15) have been used in previous studies. To determine the deviation in posture, the mean position of the CoP in the ML and anteroposterior (AP) directions is often used (14). As mentioned in these previous studies, it is well known that visual information contributes to postural control, in such a way that we can manipulate visual information with balance exercises. However, if not only visual information but also eye position itself influences postural control, then balance training programs should be updated to consider both visual information and eye position manipulation, for higher effectiveness. In the present study, we aimed to clarify whether proprioceptive information coming from the external ocular muscles involved in eye position affects body sway in the absence of visual information during the eyes-closed state.

MATERIALS AND METHODS

Participants

In this study, the appropriate sample size was estimated with the G*power software (Version 3.1.9.4) (16) for one-way analysis of variance (ANOVA) with repeated measures for LNG and mean CoP to compare between eyes-directions. The type of power analysis was set to "A priori: Compute required sample size- given α, power, and effect size." Effect size (f) was set to 0.5 (middle level), the α-error probability was set to 0.05, power (1-β-error probability) was set to 0.8, and correlation among repetitive measures was set to 0.5. The calculated sample size was 35. Therefore, 35 healthy subjects were recruited (male, 18; female, 17; mean age, 22.3 ± 2.4 years) in this study. All participants were right-footed, defined as habitually kicking a ball with the right foot (17). None of the participants had a history of neurological diseases. All participants were informed of the aim of the study and provided signed informed consent before participation, following the guidelines approved by the Shijonawate Gakuen University Faculty of Rehabilitation research ethics committee (Approval No. 18-10), and this study was conducted in accordance with the tenets of the Declaration of Helsinki.

Experimental Procedure

The participants were asked to stand motionless on a footprint that was pre-printed on a force plate, with both toes of the first digit of the feet pointed outward at an angle of 15°, with heel contact and eyes closed during all experiments (see **Figure 1A**). Next, participants were instructed to fix their eyes in five positions: E-Up, E-Down, E-Right, E-Left, E-Center (see **Figure 1B**). The eye position was initiated by an external cue. The participants were asked to maintain their eye position for 60 s without inducing body sway or head movements. We conducted the randomization of the task order regarding eye direction using Microsoft Excel software for Mac (version 16.16.10; Microsoft Corp., Redmond, WA, USA). Trials were conducted at 180-s intervals. One attempt was made for each position. Electrooculography (EOG) of the right eye was performed and monitored online during the task, while the CoP measurement began after approximately 5 s into the 30-s holding of the eye position (see **Figure 1C**). In the EOG waveforms of this study, E-Up and E-Right were shown as positive waveforms, and E-Down and E-Right were shown as negative waveforms. In each trial, subjects fixed their eyes in the position specified by an external stimulus from the examiner, which was confirmed by the appearance of the EOG waveform. If the EOG value, which reflects the position of the eye in the horizontal and vertical directions, exceeded ±50 μV in a different direction from that of the attended direction, the trial was reconducted (see **Figure 1D**).

EOG and CoP Measurements

EOG was used to confirm the direction of movement of the right eye with eyes closed, without contaminating visual information. EOG was assessed as described previously (18) using JINS MEME EOG glasses (JINS Inc., Tokyo, Japan) (19). The dry electrodes of the ocular potential sensors were placed on the left and right nose pads, and the reference electrode was placed on the upper part of the nose pad (see **Figure 1B**). The sampling frequency was set to 100 Hz. The device has an EOG sensor that can measure in the X and Y-axes. The EOG data were simultaneously transferred from this EOG system to a smartphone device using Bluetooth during the experiment. The data were also transferred to a computer via the ES_R Development Kit application (JINS Inc., Tokyo, Japan), as in a previous study (18). To estimate the deviation of the body from that in the no-movement eye task, the CoP of each participant's foot while standing was measured using a force plate (Gravicorder G5500; Anima, Tokyo, Japan). The sampling rate was set to 20 Hz. To estimate body sway, the LNG and SA were calculated. To estimate the deviation of the CoP, the mean CoP position in the AP and ML directions was assessed.

Statistical Analysis

The Shapiro–Wilk test was used to confirm that the data had a normal distribution. We conducted the parametric statistical analysis, as normality was confirmed. One-way ANOVA was used to compare whether the difference in eye position affects the mean in the AP and ML directions and the body sway (LNG, SA). If there was an effect of eye position, *post-hoc* Bonferroni multiple-comparisons testing was conducted to test for the effect of eye position. The statistical significance level was

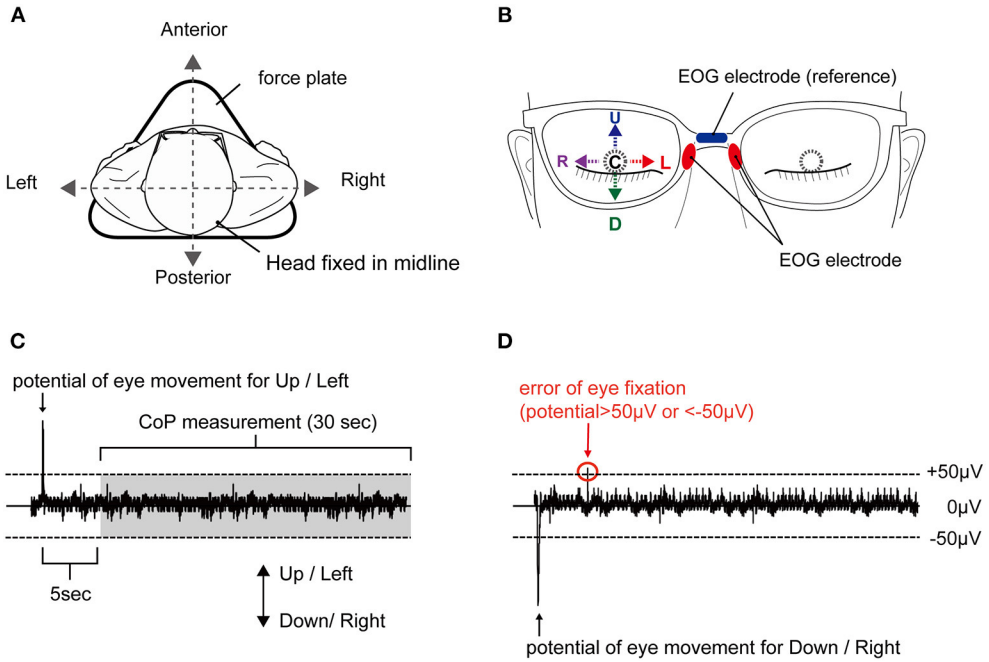

FIGURE 1 | Experimental setup and typical EOG waveform. **(A)** Body sway was measured in a static standing position on a force plate, with no head movement. **(B)** Eye positions corresponding to E-Up (U), E-Down (D), E-Right (R), E-Left (L), and E-Center (C). **(C)** Appropriate waveform and **(D)** inappropriate waveform. A plus sign reflects a shift to the anterior, and a minus sign reflects a shift to the posterior. The waveform is considered inappropriate with an EOG of ±50 μV or higher in a direction different from the target direction. EOG, electrooculography.

TABLE 1 | Results of CoP sway measurements.

	E-Center	E-Up	E-Down	E-Right	E-Left
LNG (cm)	44.2 ± 2.9	43.1 ± 2.6	43.6 ± 2.5	43.2 ± 3.3	44.1 ± 3.3
SA (cm^2)	2.6 ± 0.2	2.2 ± 0.2	2.6 ± 0.2	2.3 ± 0.2	2.4 ± 0.2
Mean AP direction (cm)	0.0 ± 0.2	−0.6 ± 0.2	0.7 ± 0.1	−0.6 ± 0.2	−0.6 ± 0.3
Mean ML direction (cm)	−0.0 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.5 ± 0.1	−0.2 ± 0.2

Data are presented as mean ± standard error of the mean. CoP, center of pressure; LNG, total trajectory length; SA, sway area; Mean AP, mean of the CoP position in the anteroposterior direction; mean ML direction, mean of the CoP position in the mediolateral direction.

set to <5%. The statistical analysis software, IBM SPSS Statistics for Windows, ver. 20 (IBM Corp., Armonk, NY), was used.

RESULTS

The one-way ANOVA revealed that the main effect on LNG was not significantly different [$F_{(4, 34)} = 0.03$, $p = 0.998$, effect size (η^2) = 0.001]. The LNG in each eye position was as follows: E-Center, 44.2 ± 2.9 cm (mean ± standard error of the mean); E-Up, 43.1 ± 2.6 cm; E-Down; 43.6 ± 2.5 cm; E-Right, 43.2 ± 3.3 cm; and E-Left, (44.1 ± 3.3 cm), with no significant difference in any position (**Table 1**; **Figure 2A**). The results of *post-hoc* testing between each group are summarized in **Table 2**.

The one-way ANOVA revealed that the main effect of SA was not significantly different [$F_{(4, 34)} = 0.764$, $p = 0.550$, effect size (η^2) = 0.02]. The SA in each eye position was as follows: E-Center, 2.6 ± 0.2 cm^2; E-Up, 2.2 ± 0.2 cm^2; E-Down, 2.6 ± 0.2 cm^2; E-Right, 2.3 ± 0.2 cm^2; and E-Left, 2.4 ± 0.2 cm^2, with no significant difference in any position (**Table 1**; **Figure 2B**). The results of *post-hoc* testing between each group are summarized in **Table 2**.

The one-way ANOVA revealed that the main effect of the mean CoP position in the AP direction was significantly different [$F_{(4, 34)} = 7.267$, $p = 0.001$, effect size (η^2) = 0.16]. The mean CoP position in the AP direction in each eye position was as follows: E-Center, was 0.0 ± 0.2 cm; E-Up, −0.6 ± 0.2 cm; E-Down, 0.7 ± 0.1 cm; E-Right; −0.6 ± 0.2 cm; and E-Left, (−0.6 ± 0.3 cm). The mean CoP shifted significantly posteriorly in the E-Up, E-Left, and E-Right eye positions, and anteriorly in the E-Down eye position. A plus sign reflects an anterior shift, and a minus sign reflects a posterior shift (**Table 1**; **Figure 2C**). The results of *post-hoc* testing between each group are summarized in **Table 2**.

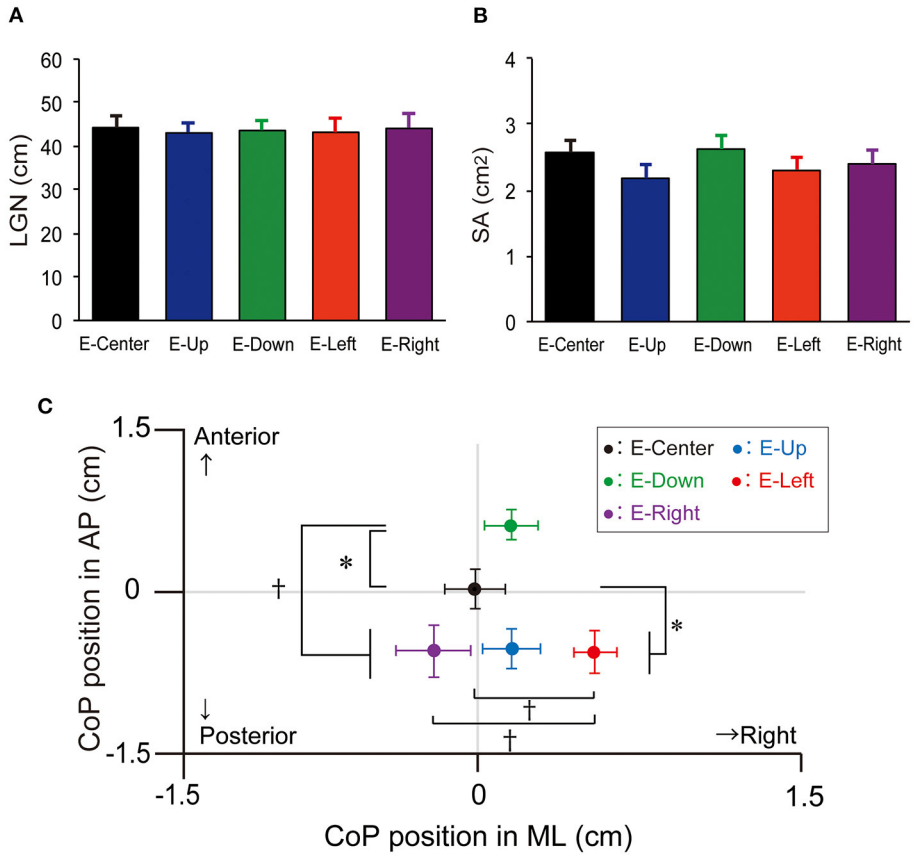

FIGURE 2 | LNG, SA, and mean position of the CoP. **(A)** LNG and **(B)** SA with the E-Up, E-Down, E-Right, E-Right, and E-Center eye positions. The vertical bars reflect the mean LNG and SA. The error bars indicate the standard error of the mean. **(C)** The mean CoP position in the ML and AP directions. The solid circles indicate the mean CoP position. The error bars indicate the standard error of the mean. $^{*}p < 0.05$, $^{\dagger}p < 0.01$. LNG, total trajectory length; SA, sway area; CoP, center of pressure; ML, mediolateral; AP, anteroposterior.

The one-way ANOVA revealed that the main effect of the mean CoP position in the ML direction was significantly different [$F_{(4, 34)} = 3.714$, $p = 0.006$, effect size (η^2) = 0.08]. The mean CoP position in the ML direction was −0.0 ± 0.1 cm for E-Center, 0.2 ± 0.1 cm for E-Up, 0.2 ± 0.1 cm for E-Down, 0.5 ± 0.1 cm for E-Right, and −0.2 ± 0.2 cm for E-Left. The mean CoP shifted significantly to the right in the E-Right position, and to the left in the E-Left position. A plus sign reflects a shift to the right, and a minus sign reflects a shift to the left (**Table 1**; **Figure 2C**). The results of *post-hoc* testing between each group are summarized in **Table 2**.

DISCUSSION

We hypothesized that the body sway would be affected by the extraocular muscle proprioception due to eye position, even in the absence of visual references. The results showed that none of the eye positions had a significant effect on LNG or SA. However, eye fixation in the E-Down position shifted the CoP anteriorly, while those in the E-Right, E-Left, and E-Up positions shifted it posteriorly. The CoP was shifted to the left only with eye fixation in the E-Left position, but to the right in the E-Up, E-Down, and E-Right positions. As a result, eye position without visual information does not increase LNG or SA but seems to shift CoP as a form of postural control.

LNG and SA did not differ significantly for any eye position. LNG assesses the length of the CoP trajectory in terms of distance, while SA evaluates the size of the CoP area, indicating that both parameters reflect the degree of body sway during upright standing. A previous study demonstrated that the fixation of gaze to a target on the right or left side may increase body sway under open-eye conditions (5). The change in optical flow in the peripheral visual field increases CoP displacement during upright standing (3). Therefore, changes in visual reference may reflect a possible mechanism to increase body sway accompanied by gazing, and the lack of change in visual reference may underpin the lack of an effect of eye position on LNG and SA in this study. Further, changing the eye position in the absence of visual information may not increase the range of CoP swing. Several possible mechanisms underlie the shift in the CoP depending on eye position in the absence of visual information. The first is eye and body coordination for gazing, as the CoP shifts for

TABLE 2 | Results of *post-hoc* testing.

Eye position			*p*-value			
			LNG	**SA**	**AP**	**ML**
E-Center	vs.	E-Up	>0.99	>0.99	0.046	>0.99
		E-Down	>0.99	>0.99	0.023	>0.99
		E-Right	>0.99	>0.99	0.032	0.068
		E-Left	>0.99	>0.99	0.036	0.034
E-Up	vs.	E-Down	>0.99	>0.99	<0.001	>0.99
		E-Right	>0.99	>0.99	>0.99	0.607
		E-Left	>0.99	>0.99	>0.99	0.743
E-Down	vs.	E-Right	>0.99	>0.99	<0.001	0.574
		E-Left	>0.99	>0.99	<0.001	0.783
E-Right	vs.	E-Left	>0.99	>0.99	>0.99	0.003

p-values were calculated with Bonferroni correction. LNG, total trajectory length; SA, sway area; Mean AP, mean of the CoP position in the anteroposterior direction; mean ML direction, mean of the CoP position in the mediolateral direction.

the upper limb, lower limb, trunk, and head in anticipatory and compensatory directions to decrease body sway accompanied by limb movement (20) and to decrease retinal slip under open-eye conditions (21). When gazing at the foot while standing, the neck and trunk are bent to enable the process. In contrast, when looking up above the head, the neck and trunk are extended for gazing. In this study, the participants were asked not to move and to stand upright during the examination, but non-voluntary body movements may have occurred with different eye positions even though the eyes were closed. Therefore, the significant shift in the CoP to the anterior and posterior directions may reflect a coordinating movement of the body associated with non-voluntary gazing. Another possible mechanism, sensory feedback, is important for motor control. It reflects afferent sensory feedback from the extraocular muscles, as there was no visual feedback with the eyes closed during the examinations in this study. Only closing the eyes increases the CoP sway but does not shift the CoP in a specific direction (22). From the results of our study, it is interesting to note from our results that the CoP did not shift with the eyes in the E-Center position, but that all conditions except E-Left shifted the CoP to the right. Furthermore, only E-Down shifted the CoP anteriorly, while E-Up, E-Right, and E-Left shifted the CoP posteriorly. In other words, the eye position may induce a shift in the CoP in the direction of contraction of the external eye muscle. There is an interrelationship such that extraocular muscle proprioception affects the perception of body space and exterior space (23). Pettorossi et al. (24) stated that eye position contributes to movement perception, which our study supports. The factor that causes these CoPs to shift to the right is considered to be the influence of the dominant foot side since the asymmetry of the dominance of the lower limb affects upright postural control (25). In all participants, the dominant foot (17), defined as the side naturally used to kick a ball, was the right lower limb. The dependency of postural control with eye shift on the dominant lower limb may increase in response to the restriction of visual information. Based on this finding, we can hypothesize that the motor command to the lower limb, trunk, or head may be generated in conjunction with the eye position command even when the eyes are closed. In addition, this motor command accompanied by that for the eyes is quite robust and may not be sufficiently canceled by simply closing the eyes. Further, changing the eye position for dynamic gazing (18) or postural control (2) may be useful when the eyes are closed. Further experiments are warranted to verify these hypotheses.

The clinical implication of this study is that the direction of the eyes affects the body sway even without visual information such as that from the external environment. This relationship is an important finding in balance evaluation and training for people with ocular motility disorders due to various diseases.

There are several limitations to this study. First, the subjects were instructed by the examiner to fix their eyes in the direction indicated as much as possible without moving their heads. Therefore, it is not clear whether the subjects moved their eyes to their maximum capacity and whether the head was completely motionless. Second, all CoPs were shifted to the right except when the eyes were directed to the right. This was thought to be caused by the shift to the side of the dominant foot, but future experiments including participants with left-footedness are needed to verify this hypothesis. Finally, the maximum range of the eye position was not controlled because it was set arbitrarily by the subjects.

In conclusion, we found that change in eye position in the absence of visual references can induce deviation in the CoP depending on the eye position, with the direction possibly influenced by foot-dominance bias. The results of this study showed that eye positions affect body movements even without visual information such as that from the external environment and that there is a relationship between the eye positions and the body sway.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shijonawate Gakuen University, Faculty of Rehabilitation Research Ethics Committee (Approval No. 18-10). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YT: conceptualization, funding acquisition, methodology, resources, software, supervision, validation, writing—original draft, and data curation. YT and AM: formal analysis, visualization, and writing—review and editing. Both authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.835450/full#supplementary-material

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A New Sensitive Test Using Virtual Reality and Foam to Probe Postural Control in Vestibular Patients: The Unilateral Schwannoma Model

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Vestibular schwannomas (VS) are benign tumors of the vestibular nerve that may trigger hearing loss, tinnitus, rotatory vertigo, and dizziness in patients. Vestibular and auditory tests can determine the precise degree of impairment of the auditory nerve, and superior and inferior vestibular nerves. However, balance is often poorly quantified in patients with untreated vestibular schwannoma, for whom validated standardized assessments of balance are often lacking. Balance can be quantified with the EquiTest. However, this device was developed a long time ago and is expensive, specific, and not sensitive enough to detect early deficits because it assesses balance principally in the sagittal plane on a firm platform. In this study, we assessed postural performances in a well-defined group of VS patients. We used the Dizziness Handicap Inventory (DHI) and a customized device consisting of a smartphone, a mask delivering a fixed or moving visual scene, and foam rubber. Patients were tested in four successive sessions of 25 s each: eyes open (EO), eyes closed (EC), fixed visual scene (VR0), and visual moving scenes (VR1) delivered by the HTC VIVE mask. Postural oscillations were quantified with sensors from an android smartphone (Galaxy S9) fixed to the back. The results obtained were compared to those obtained with the EquiTest. Vestibulo-ocular deficits were also quantified with the caloric test and vHIT. The function of the utricle and saccule were assessed with ocular and cervical vestibular-evoked myogenic potentials (o-VEMPs and c-VEMPs), respectively. We found that falls and abnormal postural oscillations were frequently detected in the VS patients with the VR/Foam device. We detected no correlation between falls or abnormal postural movements and horizontal canal deficit or age. In conclusion, this new method provides a simpler, quicker, and cheaper method for quantifying balance. It will be very helpful for (1) determining balance deficits in VS patients; (2) optimizing the optimal therapy indications (active follow-up, surgery, or gamma therapy) and follow-up of VS patients before and after treatment; (3) developing new rehabilitation methods based on balance training in extreme conditions with disturbed visual and proprioceptive inputs.

Keywords: video head impulse test, vertigo, hearing loss, visual moving scenes, vestibular nerve, vestibular-evoked myogenic potentials, EquiTest, calorics

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INTRODUCTION

Vestibular schwannomas (VS) are benign tumors that develop from the Schwann cells surrounding the vestibular nerve. They can cause nerve VIII dysfunction by blocking nerve vascularization or by compressing the auditory and vestibular nerve fibers (1). These benign, slow-growing brain tumors affect the quality of life of patients (2). Tumor growth can lead to hearing loss, tinnitus, and imbalance, and further size increases can lead to brainstem compression (3). The estimated annual incidence of these tumors ranges from 1 to 2 per 100,000 inhabitants, according to the French National Authority for Health (HAS). A review (4) revealed that most patients complained of dizziness before and after surgery. Evaluations of balance performance in patients with VS are an important part of clinical evaluations to determine the appropriate treatment such as surgery, gamma therapy or functional follow-up, and MRI (every 6 months or annually) according to tumor size and volume [stages I–IV from Koos classification (5)]. Assessments of the severity of balance impairment are potentially useful for identifying patients likely to benefit from vestibular rehabilitation and for adapting vestibular rehabilitation strategies to the needs of the patient (4). Several methods have already been developed for testing balance: the Romberg test (6), the EquiTest (7), and the Wii Balance Board (WBB) (8). Five years ago, we developed an application called BalanceRite, for quantifying WBB time series data on an iPhone or iPod Touch (9). We were also able to modify two sensory inputs involved in balance: visual inputs *via* virtual reality (VR) and proprioceptive inputs, by attaching foam rubber to the WBB. Using the WBB, we were able to measure postural stability during a visual or visual and proprioceptive (foam attached to the board) perturbation (9).

In this study, we developed a new method, not involving the WBB, for quantifying postural oscillations in patients subjected to visual and proprioceptive disturbances. This quantification was achieved with accelerometers from an Android smartphone (Galaxy S9) used as a sensor and placed on the lumbar vertebrae during the recordings on foam rubber. VS patients and controls were tested in four sets of conditions: eyes open (EO), eyes closed (EC), fixed visual scene (VR0), and moving visual scene (VR1) delivered *via* the mask. We also assessed the balance of the VS patients with the EquiTest. We characterized nerve VIII dysfunction, audiometric and vestibular function with caloric tests, vHIT, and cervical and ocular VEMPS (c- and o-VEMPs).

We had three aims: (1) To analyze the effects of VS on the vestibular system through caloric, vHIT, and VEMP assessments; (2) to study the effect of VS on balance performance with the DHI and our new device VR/Foam (foam + VR + smartphone); and (3) to demonstrate the advantages of VR/Foam over the EquiTest for assessing balance.

Soon, we hope to be able to determine postural performance for individual VS and try to develop new methods of vestibular rehabilitation. In addition, the vestibular tests combined with the VR/Foam should help the surgeon choose the best treatment (active follow-up of VS, Gamma Knife therapy, surgery). Indeed, GK may induce dizziness.

TABLE 1 | The three categories of variables used to assess the functional deficit following a unilateral VS clinical signs (patients characteristics) gave multimodal informative data; auditory and vestibular unimodal tests allowed the appreciation of the dysfunction of either the auditory and or of the vestibular function; postural control which were by essence multimodal and which combined EquiTest and VR/Foam tests.

Class of tests	Data	Uni or multimodal
Patients characteristics	Age, BMI, VS Stage, DHI	Multimodal
Auditory and Vestibular tests	Hearing loss, Calorics, vHIT, c-and o-VEMPS	Unimodal
Postural control	EquiTest, VR/Foam	Multimodal

METHODS

In this study, we aimed to compare three categories of tests in the same patients to assess the functional deficit following a unilateral VS. They are summarized in **Table 1**. The first category of test encompassed the clinical signs (patients characteristics): age, body mass index (BMI), the VS stage according to Koss classification (5), and the dizziness Handicap Inventory (DHI). In essence, they are multimodal to the extent they mixed questionnaires, radiological signs, and morphologic variables. The second category of variables probed specifically the auditory and vestibular functions and therefore can be considered as unimodal tests. The audition was tested with standard tonal and vocal audiometry; the Horizontal semi-circular canal function was investigated with the caloric and vHIT tests, the otoliths function with c-VEMP and o-VEMP (see below and **Table 1**). Finally, the gold standard EquiTest and the newly designed VR/Foam test probed postural control in patients. Both tests are multimodal to the extent they probe how patients combined vestibular, visual, and proprioceptive information to overcome their vestibular deficit.

This retrospective study included a group of controls ($n = 46$) and a group of patients with unilateral vestibular schwannoma ($n = 63$). The protocol was approved by the local Ethics Committee following the requirements of the Helsinki Declaration. All subjects included in the study gave written and informed consent.

The Healthy Controls

There were 30 female and 16 male controls, aged 16–90 years (mean age: 58 ± 17.9). None of the individuals complained of either dizziness or vertigo. Controls were only selected for this study if they had a dizziness score on the DHI < 20. The subjects were asked to provide their height and weight for the calculation of BMI. The healthy controls had normal results in vestibular and hearing tests (vHIT, audiogram). They were able to balance easily for 25 s on the VR/Foam in all four sets of test conditions and had normal scores in all EquiTest conditions, including conditions 5 and 6.

Unilateral VS Group

The VS group consisted of 43 female and 20 male patients ($n = 63$). The VS was on the left side in 31 patients, and the right side in

32 patients. The patients were aged 20–86 years (mean age: 58.2 ± 15.5 years). DHI scores were >30 in 41.3% of the VS patients. All patients were diagnosed by brain MRI. Only patients with a brain MRI diagnosis of VS stage I, II, III, or IV according to the Koos classification were included in the VS group. BMI was calculated for each patient.

The DHI questionnaire developed by Jacobson and Newman (10) was used to assess the handicap suffered by the patients in terms of dizziness and unsteadiness. All subjects completed the DHI on a customized computer table, to provide a detailed evaluation of the degree of handicap due to balance or vertigo problems.

Audiometric Tests

Tympanometry and stapedial reflex assessments were carefully performed, to exclude patients with conductive (even slight) hearing loss, to prevent the misinterpretation of air-conducted sound (ACS) o-VEMPs. The mean pure-tone threshold (PTA) for tones at 500 Hz, 1 kHz, and 2 kHz was used as an indicator of hearing loss.

Vestibular Tests

vHIT: Horizontal and Vertical Canal Tests

The function of the horizontal semicircular canals at high frequencies of stimulations was assessed with horizontal vHIT from ICS Impulse (Otometrics/Natus, Denmark) as previously described for the head impulse paradigm (HIMP) (11). Subjects were instructed to focus on a fixed point on a wall at their eye level. The wall was 90 cm away. For each testing session, the clinician applied ∼20 brief, rapid, horizontal head turns (head impulses) to each side, always starting from the center but of unpredictable timing and direction, with a minimal overshoot at the end of the head impulse. The amplitude of head rotation was ∼10–15°, and the peak head velocity of the impulse was 180–220 deg/s, with angular accelerations of ∼4,000–8,000 deg/s^2 (9). Eye velocity and head velocity were recorded for each head turn. Gain is the usual measurement of the vestibulo-ocular reflex (VOR) slow phase in the HIMP paradigm: it represents the ratio of the eye and head areas under the curve during HIMP. Covert saccades were removed if they modified the gain of the horizontal vestibulo-ocular reflex (H-VOR). Gain values <0.8 are characteristic of a unilateral vestibular lesion (12).

Caloric Testing: Horizontal Canal Test

The function of the horizontal semicircular canals at low frequencies of stimulations was assessed with the caloric tests. They were performed with closed-loop sequential bithermal irrigation with water at 30 and 44 °C and video-nystagmography. The percent canal paresis (CP) was calculated with Jongkees' formula: CP = 100 * [(UW + UC) – (AW+AC)] / (UW + UC + AW + AC), where UW, UC, AW, and AC are the velocities of the induced ocular nystagmus obtained on the unaffected and affected sides, with warm and cold water, respectively. A value of CP >25% was considered to indicate an abnormal decrease on the affected side.

Otolith Function: Cervical and Ocular VEMPs

The function of the otolith system was assessed with the cervical and ocular VEMPs. Vestibular-evoked myogenic potentials were recorded with a Nicolet Viking 4 apparatus (Nicolet Biomedical Inc., Madison, WI, United States) with a four-channel averaging capacity, as previously described (13, 14).

Cervical vestibular-evoked myogenic potentials (cVEMPs) assess predominantly the function of the sacculo-spinal pathways (15). They were recorded from surface electrodes above the tensed sterno-cleido-mastoideus (SCM) muscle ipsilateral to the stimulated ear in response to air-conducted (AC) short-tone burst (STB) stimuli: 500 Hz, 102 dB nHL, 128 dB SPL, rise/fall time 2 m/s, plateau time 2 m/s, presented through calibrated TDH39 headphones. The EMG activity of the SCM was monitored on a display to ensure that sufficient muscle activation was maintained (>150 μV) (13). The latencies of the first two waves (P13 and N23) of the cVEMPs were measured in m/s, and the peak-to-peak amplitude between the P13 and N23 waves was measured in univolts (μV).

Ocular vestibular-evoked myogenic potentials (oVEMP) assess predominantly the function of the utriculo-ocular pathways (16). They were recorded from surface electrodes above the inferior oblique extraocular muscle contralateral to the stimulated ear in response to AC STBs. The AC STBs (500 Hz, 110 dB nHL, 132 dB SPL, rise/fall time 2 m/s, plateau time 2 m/s) were presented through calibrated TDH39 headphones. Patients with no measurable response on either side were considered to be non-responders. We measured the maximum latencies in m/s and the peak-to-peak amplitude in μV of the first two waves (n1 and p1) if the n1-p1 peak-to-peak amplitude was <2 μV.

The percent VEMP asymmetry in patients with unilateral vestibular lesions was measured by calculating the ratio of evoked potentials (EPr) as follows (17): EPr = 100*(Al – As)/(Al + As), where Al is the largest P13-N23 or n1-p1 peak-to-peak amplitude, and As is the smallest P13-N23 or n1-p1 peak-to-peak amplitude.

Balance Test

The balance performance of the patients was tested in two ways: the newly designed VR/Foam test and the EquiTest. These two tests explore how patients compensate for a vestibular deficit by combining the remaining visual and proprioceptive information in various combinations.

Balance Quantification in the EquiTest

Balance was assessed with the sensory organization test (SOT) on the EquiTest (7, 1982). The SOT included six conditions delivered in a specific order, as follows. *Condition 1*: the subject was asked to stand upright whilst keeping his/her eyes open. *Condition 2*: the subject was asked to stand upright whilst keeping his/her eyes closed. *Condition 3*: the cabin moved adaptively in response to the subject's movements. Here, the vision was sway-referenced. *Condition 4*: the support base moved adaptively, following the subject's movements while the eyes were open: sway-referenced proprioception. *Condition 5*: as in condition 4, but with the eyes closed. *Condition 6*: the support base and the cabin moved in a synchronized manner: both vision and

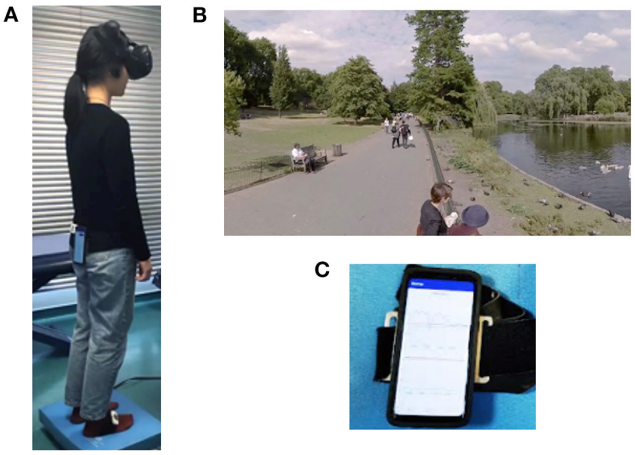

FIGURE 1 | Illustration of the device for testing balance on foam rubber with VR. The subjects wear a mask over the eyes, which delivers a static or moving visual scene. They are asked to keep their balance for 25 s, and all postural oscillations along the *X, Y*, and *Z* axes are quantified with a smartphone attached to the subject's back. **(A)** Patient standing up on the foam with the smartphone one the back and the HTC Vive mask over the eyes. **(B)** Visual scan projected into the the mask. **(C)** Smartphone allowing the quantification of the postural oscillations.

proprioception were sway-referenced. Based on the differences in body pressure center between the six different conditions, somatosensory, visual, and vestibular scores were calculated as percentages, a visual preference was estimated, and a composite score was obtained. Patients who did not fall but had a below-normal score were considered abnormal in conditions 5 and 6 of the EquiTest.

Balance Test on Foam With Moving Visual Scenes (VR/Foam)

The balance performance of the patients was tested on foam rubber using an HTC, VIVE VR masks using Unity 3D as the interface (18–20). We tested postural oscillations under the following conditions, presented sequentially and in this order: eyes open (EO), eyes closed (EC), within a stable environment (VR0), and, finally, with the VR mask delivering a moving visual scene with a small amplitude of disturbance (VR1) (**Figure 1**).

As in the EquiTest, the conditions were selected to make it increasingly difficult for the patients to keep their balance. The foam used was a blue Airex Balance Pad (Airex AG, Sins, Switzerland, 41 cm × 50 cm × 6 cm thick). Patients were placed feet 3 cm apart with their head in the center of two cameras delivering the moving visual scenes into the mask. In all test conditions, the test took 25 s to perform on the foam provided. If the patients fell in EC, VR0, or VR1 conditions, they were systematically retested in the same condition (i.e., two trials were systematically performed if the patient fell). Patients able to maintain their balance during this second trial were then allowed to move on to the next set of conditions. Patients who fell on the foam in VR1 conditions were then systematically retested in VR1 conditions, but on the ground, rather than on the foam (21). This made it possible to exclude postural phobias due to the use of visual inputs.

In this study, the VR environment was a visual scene of swans and ducks moving in a park in London (Source: "360/VR Master Series/Free Download/London Park Ducks Swans," https://vimeo.com/215985064). The scene was recorded with a 360° camera. A virtual environment was created from this scene with the cross-platform game engine Unity (Unity Technologies). We gave this virtual environment the geometric appearance of a white sphere, into which we projected the London Park Ducks Swans scene, to obtain the final 360° virtual environment. The different rotation speeds used for visual disruption were programmed in the C# language with the cross-platform Visual Studio environment (Microsoft and Mono Project).

The *y*-axis rotation was the sum of three sine waves with frequencies of 0.4, 0.1, and 0.1 Hz and phase angles of 0°, 25°, and 0°, respectively. The *z*-axis rotation was the sum of three sine waves with frequencies of 0.5, 0.2, and 0.2 Hz and phase angles of 70°, 45°, and 90°. In each case, it was possible to control the peak amplitude of the rotation (between 0° and 30°), which was arbitrary, on a VR scale between 0 and 1. We chose VR1 condition because this visual moving scene triggered no falls in normal subjects on the foam other than elderly individuals over the age of 65 years (9).

Postural oscillations were quantified with an Android smartphone (Galaxy S9) used as a sensor and held in position on the back by a belt at the level of the lumbar vertebrae. This device made it possible to measure the linear accelerations with the effect of gravity removed. **Figure 2** shows an example of such a measurement. The black sinuous and noisy curve represents the acceleration along the *x, y*, and *z*-axis (in m/s^2 = meters per second^2) measured by the Android sensors (Galaxy S9) in the phone's reference frame. The red and blue curves were plotted in MATLAB as the RMS signal envelope of this acceleration. The area between the red and blue curves was used to estimate the amplitude of the oscillations. For the comparison of measurements, we defined the quantity "A*x*, A*y*, A*z* activity" as the area divided by the duration, which provided effective acceleration values for the study (in m/s^2).

The acceleration values obtained with the sensors for the *y*-axis were higher and more directly related to postural oscillations than those for the *x*- and *z*-axes, in subjects trying to keep their balance on foam. The Shapiro–Wilk normality test showed our data to be normally distributed (non-significant *p*-values for all variables). We, therefore, used the mean acceleration values obtained for the *y*-axis with two times the standard deviation, in all four conditions, for the control group as the reference values (norms). These norms (means + 2SD) were used to define the upper limit of the normal range. The individuals in the control and VS groups were classified as normal if they were able to balance for 25 s (acceleration values strictly below the norm), abnormal (if they were able to balance for 25 s but had acceleration values greater than the norm), and fallers (if they fell within 25 s) on the foam.

Statistical Analysis

Statistical analyses were performed with the statistical software RStudio version 3.6.1. For numerical data comparisons, we used the Chi-square test to analyze the significance of differences in

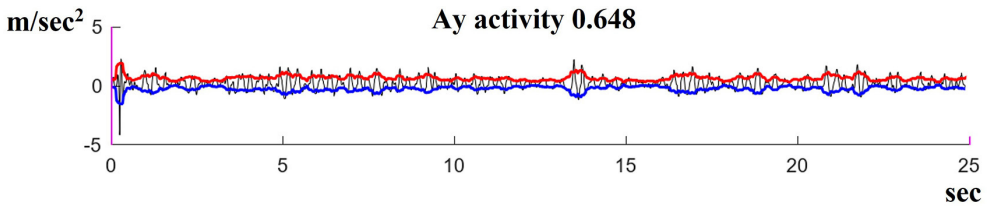

FIGURE 2 | Illustration of the method used to quantify postural oscillations measured by the Android sensor along the *X, Y,* and *Z* axes in m/s^2. A typical result in VR1 conditions is shown for a VS patient displaying high oscillations.

balance assessments between the foam test and the EquiTest platform test. The Shapiro test showed that the data were normally distributed. Differences with p below 0.05 were considered to be significant. To identify the relationship between the tests and other parameters, correlation coefficients were calculated either with Pearson if the variables were raw numerical data or Spearman-Rho if the variables were not raw numerical data only.

RESULTS

As described in the method section, in this study, we aimed to compare the same patients with three categories of tests to assess their functional deficits following a unilateral VS. They are summarized in **Table 1**. The first category of tests encompassed the clinical signs or patients' characteristics, and the second category of variables probed specifically the vestibular functions. And the gold standard EquiTest and the newly designed VR/Foam test probed postural control in patients.

The Clinical Signs

The patients' characteristics are the following: The VS patients were aged between 20 and 86 years (mean age: 58.2 ± 15.5). A total of 37 (58.7%) patients were younger than 65 years and 26 (41.3%) were older than 65 years (seniors). According to the Koos classification (5), 31 patients had VS stage I, 21 had VS stage II, 8 had VS stage III, and 3 had VS stage IV tumors. The mean BMI was 25.3 ± 4.12. The mean DHI score was 28.2 ± 24.2 and 26 of the 63 patients (41.3%) had a DHI score >30 (mean score for these patients: 51.3 ± 14.2, with a minimum score of 30 and a maximum score of 78).

The Auditory and Vestibular Function

Auditory Test

A total of 50 out of 63 (79.4%) patients had an abnormal hearing function on the VS side. The mean hearing loss was 63.24 dB ± 24.1.

Vestibular Function

Vestibular dysfunction of the horizontal canal nerve was assessed by both caloric tests and the vHIT (H).

Caloric Tests

The results of the caloric test were abnormal on the side of the lesion in 42 of the 63 patients (66.6%), with a mean deficit on the VS side of 64.7% ± 24.6 (canal paresis range: 29–100%).

Horizontal vHIT

The results of the vHIT were abnormal on the side of the lesion in 19 of the 63 patients (30.2%), with a mean gain deficit for horizontal canal function of 0.61 (range 0.3–0.77) with covert and overt saccades.

No correlation was detected between mean vHIT (H) gain on the injured side and the caloric test result (**Figure 3**). More importantly, 23 of the 63 (36.5%) patients had a normal vHIT (H) result (gain > 0.85) but abnormal caloric test results (see **Table 2** and **Figure 3** red diamonds). The patients with this dissociation had a mean caloric deficit of 50.6% ± 17.9. We identified no patients with abnormal vHIT (H) and normal canal paresis results.

We found no correlation between VS stage and vHIT (H) (correlation coefficient: - 0.159) and also VS stage and caloric test results (correlation coefficient: 0.386) (**Figure 4**).

Anterior and Posterior vHIT

Isolated posterior canal vHIT (vHIT P) was abnormal in 24/63 patients (38.1%) and isolated anterior canal vHIT (vHIT A) was abnormal in 16/63 patients (25.4%). Abnormal VOR gain for all anterior, posterior, and horizontal canals was detected in 12 of 63 patients (19%). All 12 patients also had abnormal canal paresis on caloric testing (mean canal paresis 85.3 ± 20.9%).

Three of the 23 patients with dissociated vHIT (H) (normal) and caloric (abnormal) test results (13%) had an abnormal anterior gain and seven of the 23 (30.4%) had an abnormal posterior canal gain (**Table 2**). For example, **Figure 5** illustrates the vHIT recording for patient 18 (from **Table 2**). Note the normal horizontal and anterior, but abnormal posterior VOR gain (**Figure 5**).

Otolith Saccular and Utricular Nerve Function

Hearing function was measured before VEMPs: hearing function was abnormal on the side of the VS in 50 of the 63 (79.4%) patients. Mean hearing loss was 63.2 dB ± 24.1. None of the patients had a conductive hearing loss.

The cVEMPs induced by STBs were abnormal on the side of the VS lesion (abolished or decreased) in 38 of the 63 patients (63.3%). The oVEMPs were also abnormal (abolished or

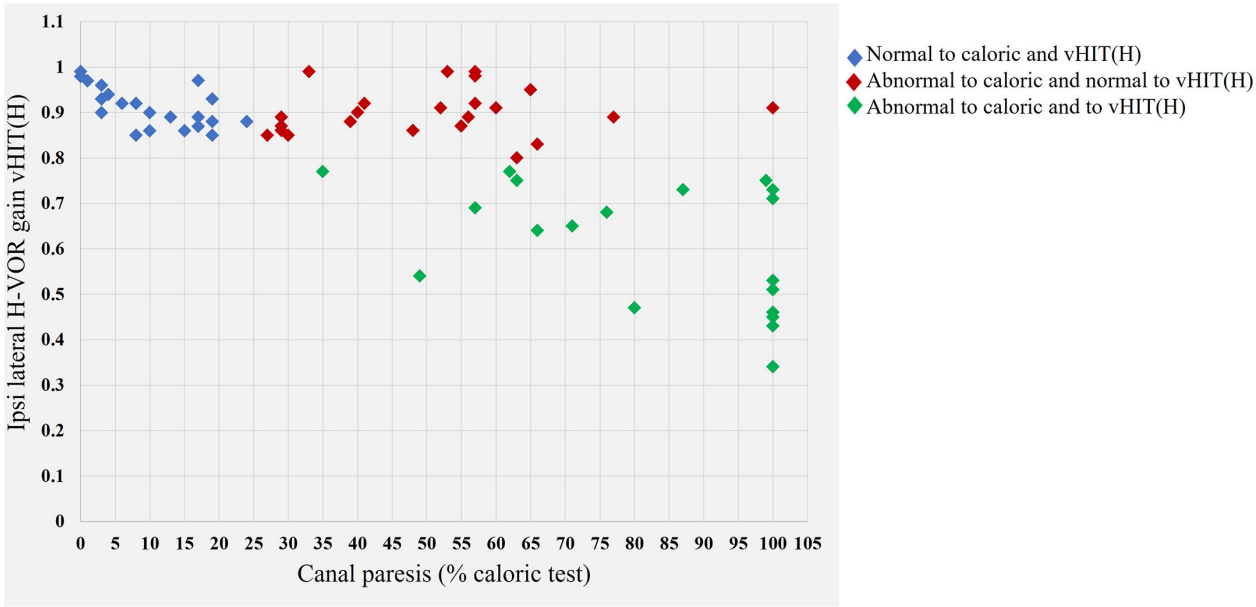

FIGURE 3 | Graph illustrating the relationship between the horizontal vestibulo-ocular gain in the vHIT test and canal paresis in the caloric test. Blue diamonds indicate the normal values for the caloric test and vHIT (H). Red diamonds indicate values for patients with a normal vHIT result but abnormal caloric test results (canal paresis >25%). A dissociation is observed between the findings for the two different tests of horizontal nerve function [normal vHIT (H)—abnormal canal paresis]. Green diamonds, abnormal results in both the caloric test and vHIT (H).

decreased) on the side of the VS lesion in 29 of 63 patients (46%). Ocular VEMPs were normal in 24 patients (38.1%) and bilaterally suppressed in 10 patients (15.9%).

Among the 63 VS patients, 76% had abnormal c- and o-VEMPS, 66% abnormal caloric, and 47% abnormal vHIT. No significant difference could be found between caloric and VEMPs ($p = 0.426$).

Postural Control

The EquiTest

All the healthy controls had normal balance in all the conditions of the EquiTest, including, in particular, conditions 5 and 6 ($n = 46$).

In the VS group, in condition 5 of the EquiTest, 18 of the 63 patients fell (28.6%), and 20 patients (31.7%) had an abnormal score but did not fall. The remaining patients had normal performances in the three trials. In condition 6 of the EquiTest, 27 of the 63 patients (42.9%) fell and 2/63 patients (3.2%) had an abnormal score but did not fall. In summary, 38 of the 63 VS patients (60.3%) fell or had an abnormal score in condition 5, and 29/63 patients (46%) fell or had an abnormal score in condition 6. The abnormal scores and frequencies of falls in EquiTest conditions 5 and 6 were highly significant, with a $p = 0.0009$. Eighteen of 63 patients (28.6%) fell in both conditions 5 and 6. All VS patients who fell in condition 5 of the EquiTest also fell in condition 6.

EO, EC, and VR Tests on Foam

For the healthy group, the mean values for AY activity in m/s^2 obtained on the foam for EO, EC VR0, and VRI are presented in **Table 3**. The mean ± SD was 0.10 ± 0.03 for EO, 0.18 ± 0.03 for EC, 0.12 ± 0.04 for VR0, and in 0.28 ± 0.06 for VR1.

The AY activity norms (mean + 2SD) were 0.17 for EO, 0.25 for EC, 0.20 for VR0, and 0.40 for VR1. No falls were detected in the healthy group, even in the two most difficult conditions: EC and VR1.

Postural oscillations were larger than normal in 13 of the 63 patients (20.6 %) for EO and 28 of the 63 patients (44.4%) for EC ($p = 0.00315$). Similarly, large oscillations were observed in 20/63 patients (31.7%) for VR0 and 7/63 patients (11%) for VR1 ($p = 0.0015$) (**Figures 6A**, **7A**).

Falls were observed in 0/63 VS patients (0%) in EO conditions and 23/63 patients (36.5%) in EC conditions which is statistically different ($p = 1.527e{-}09$). Falls were significantly more frequent in VR1 conditions 52/63 patients 82.5%, ($p = 3.863e{-}08$) than in VR0 conditions (16/63 patients, 25.4%) (**Figure 6B**). VR1 was the most destabilizing set of conditions. **Figure 7B** shows the recording of patients who fell after 6.2 s.

We found no correlation between age and the likelihood of falling (correlation coefficient: −0.035). Some patients over 65 years of age did not fall, whereas other much younger patients fell within 10 s. The time to the fall ranged from 3 to 20 s for EC, 1 to 21 s for VR0, and 1 to 17 s for VR1. A 75% of the VS patients who fell did so within 10 s in VR1 condition. Some VS patients displayed large oscillations and had abnormal AY activity values during the VR/Foam test but did not fall (**Figure 6B**).

No falls or abnormal postural oscillations were detected in patients who performed the VR1 test on the ground (a systematic VR1 test on the ground was performed for all those who fell two times during VR1 tests on foam; see Methods).

TABLE 2 | Data for the 23 of VS 63 patients presenting a dissociation between the average VOR gains of the three canals tested with the vHIT (H) and the results of the caloric test.

VS patients	Side	vHIT (H)	vHIT (P)	vHIT (A)	Canal paresis %
Patient 1	L	0.85	0.85	0.92	27
Patient 2	R	0.9	0.9	0.8	29
Patient 3	R	0.89	0.88	0.89	29
Patient 4	L	0.86	0.98	0.98	29
Patient 5	R	0.86	0.9	0.86	30
Patient 6	R	0.99	0.95	0.72	33
Patient 7	R	0.86	0.85	0.89	39
Patient 8	L	0.9	0.76	0.88	40
Patient 9	R	0.87	0.89	0.96	41
Patient 10	L	0.86	0.76	0.86	48
Patient 11	R	0.89	0.9	0.96	52
Patient 12	R	0.99	0.62	0.73	53
Patient 13	L	0.87	0.96	0.83	55
Patient 14	R	0.90	0.99	0.89	56
Patient 15	R	0.99	0.89	0.89	57
Patient 16	R	0.88	0.57	0.88	57
Patient 17	R	0.99	0.57	0.98	57
Patient 18	R	0.91	0.4	0.81	60
Patient 19	L	0.8	0.5	0.9	63
Patient 20	L	0.95	0.91	0.89	65
Patient 21	L	0.83	0.9	0.89	66
Patient 22	R	0.89	0.92	0.9	77
Patient 23	R	0.91	0.84	0.74	100

Seven of the 23 patients had a deficit for the mean gain of the posterior ROV (Patients 8, 10, 12, 16, 17, 18, 19) and 3/63 presented isolated decreases in anterior ROV gain (Patients 6, 12, 23). All 10 patients with abnormal caloric tests had normal vHIT (H) results. Side, the side on which the VS was located, left (L) or right (R); vHIT (H), mean gain of the H-ROV; vHIT (P), posterior gain; vHIT (A), anterior gain; canal paresis %, quantification of the deficit in the caloric test.

We also found no correlation between abnormal caloric test results and falls in VR/Foam conditions. There was also no correlation between cVEMPs and oVEMPs with falls in VR/Foam conditions (the correlation coefficient: 0.28). More importantly, no correlations between all these multi- and unimodal tests and the result of the VR/Foam test could be found.

EquiTest vs. VR/Foam

We found no significant difference between the percentages of patients falling in conditions 5 and 6 of the EquiTest ($p = 0.2$). By contrast, there was a highly significant difference ($p = 0.000024$) between the percentages of patients falling in EC and VR1. A highly significant difference was found between EquiTest condition 6 and the VR1 condition of balance on foam: 82.5% of the VS patients fell in VR1 conditions, whereas only 42.9% fell in condition 6 of the EquiTest ($p = 0.0003$) (**Figure 8**). No significant difference in the percentage of patients falling or in abnormal values was detected between EC on foam and condition 5 of the EquiTest ($p = 0.9$).

DISCUSSION

We show in this study, for the first time, that patients with unilateral VS frequently present balance abnormalities when placed in highly disturbed conditions (distortion of visual and proprioceptive information), regardless of their age, vestibular system function, or vestibular compensation processes.

DHI and Balance Tests

Many VS patients complain of instability and poor balance in their daily lives (4). These complaints were revealed in the results of the DHI questionnaire (22), with 41.3% of VS patients having a DHI score >30. We found no correlation between the patients' complaints and the results of the various balance tests performed. There was also no relationship between the results of the vestibular tests and the DHI score. This lack of correlation probably reflects an inability of the patients to self-assess their balance state accurately. The DHI questionnaire combines functional, physical, and emotional questions. However, it does not measure the psychological state and anxiety symptoms of the patients (fear of falling), which may also have an effect on the appreciation of balance by the patient.

VS and Vestibular Function

Caloric test results were abnormal on the side of the lesion in 67% of the VS patients. The superior vestibular nerve was, therefore, frequently affected by the schwannoma, regardless of tumor stage. In our patients, horizontal canal paresis, when present, was well compensated, as no ocular nystagmus was

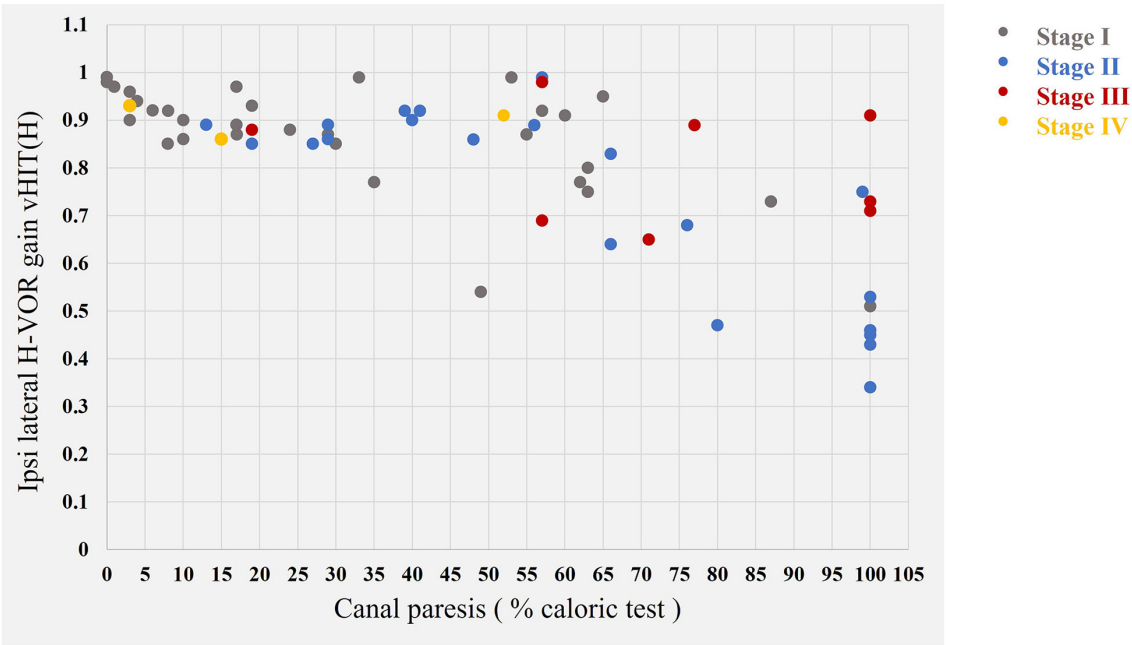

FIGURE 4 | Representation of the results obtained with the vHIT (H) and caloric tests as a function of VS stage. In gray, the 31 stage I tumors; in blue, the 21 stage II tumors; in red, the 8 stage III tumors, and, in yellow, the 3 stage IV tumors according to the Koos classification (5).

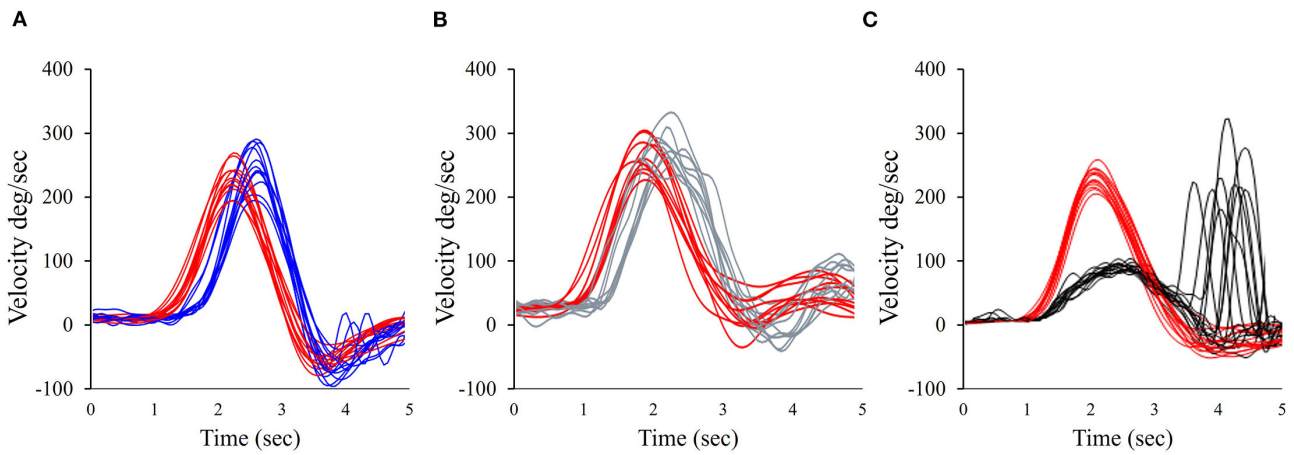

FIGURE 5 | Illustration of the vHIT for patient 18 in **Table 2**. Note the normal horizontal VOR gain; eye velocity is shown in blue, and head velocity is in red; the normal vHIT (A) eye velocity is shown in gray, with head velocity in red. This patient has an abnormal vHIT (P) for eye velocity in black and head velocity in red. **(A)** Horizontal vHIT; **(B)** Anterior vHIT; **(C)** Posterior vHIT.

detected when the patients opened their eyes in darkness while in the supine position. The growth of this benign tumor was very slow [<2.5 mm per year (23)], accounting for the effective compensation of static ocular deficits when the tumor was detected by MRI, many years after disease onset in some cases.

By contrast, abnormal vHIT (H) results were obtained for only 30.2% of the patients, consistent with a previous report (24). Caloric irrigation was shown to have a higher sensitivity than vHIT [72% *vs.* 41% (25)]. We obtained a sensitivity of 66.7% for caloric irrigation and 30.2% for vHIT. This dissociation may reflect the intrinsic differences between these two tests: the caloric test evaluates the horizontal vestibular system in the low-frequency range (0.003 Hz) (26), whereas vHIT (H) assesses the function, not only of the horizontal vestibular system, but also of the anterior and posterior vestibular system (through head impulses) up to 5 Hz (27). Furthermore, different mechanisms are at work in the stimulation of the vestibular hair cells of the horizontal ampullae in these two tests: in the caloric test, the cells are stimulated by endolymph flow due to a temperature gradient from one side of the canal to the other (28). The head impulse

induces a flow of endolymph due to the high acceleration, low amplitude, and high velocity of head impulses on either side (29). The explanation for this discrepancy remains unclear: it could be due to the caloric test preferentially evaluating tonic fibers over phasic fibers. Some neurons (tonic neurons) have been shown to display a sustained response to maintained stimuli, whereas others (phasic neurons) have a transient response to the same stimuli. A similar distinction has been applied to the primary semicircular canal (30), which establishes diverse vestibular afferences (31). Tonic vestibular primary neurons may be more sensitive to the temperature gradient in the caloric test. The vHIT should be used in addition to the caloric test, as it can be used for anterior and posterior evaluations in addition to quantifying horizontal canal nerve function.

The vHIT is a useful bedside examination of the semicircular canals, because it provides information about sensitivity to higher frequencies of the vestibular–ocular reflex (VOR) <0.002 Hz for caloric testing and up to 0.8 Hz for vHIT (32). Neurons synapsing with the type I receptors of canals have also been reported to display a preference for high frequencies, which has been interpreted as sensitivity to shaking (33).

It has also been suggested that some patients with VS also suffer from dysfunctions of the secretion and resorption of endolymphatic liquid, potentially with associated hydrops (34) due to the inflammatory process occurring around the vestibular schwannoma (35). None of our subjects displayed an abnormal vHIT result with a normal caloric test result. Similar findings have been reported for other vestibular conditions, such as vestibular neuritis and chemical labyrinthectomy. We found no correlation between VS stage and the degree of canal paresis in caloric tests. The dissociation of the results of these two tests was not, therefore, related to tumor size or volume.

These two tests [caloric and vHIT (H)] can, therefore, be considered complementary. Furthermore, vHIT results could be normal for head impulses performed in the horizontal plane but abnormal for head impulses in the sagittal plane. For example, we found posterior (30.4%) and anterior (13%) canal dysfunction (albeit less frequently) in patients with a normal horizontal vestibulo-ocular reflex gain in the vHIT (H) test and abnormal results for the caloric test.

TABLE 3 | Presentation of the mean values (means + standard deviations) obtained for each of the *X, Y,* and *Z* axes in the control group, in EO, EC, VR0, and VR1 conditions, on foam, with smartphone sensors attached to the back.

Conditions	Activity (m/s^2)	Mean	SD
Foam + EO	AX activity	0.080	0.034
	AY activity	0.103	0.034
	AZ activity	0.080	0.036
Foam + EC	AX activity	0.129	0.052
	AY activity	0.187	0.034
	AZ activity	0.134	0.054
Foam + VR0	AX activity	0.089	0.039
	AY activity	0.123	0.041
	AZ activity	0.086	0.034
Foam + VR1	AX activity	0.204	0.074
	AY activity	0.282	0.060
	AZ activity	0.200	0.090

Vestibular-Evoked Myogenic Potentials

The c- and o-evoked potentials were, therefore, also used to assess the probable vestibular deficit in these patients (13) that was not picked up by the caloric test. It is therefore essential to integrate all these vestibular otolith tests, to identify the vestibular deficits of the saccular and utricular nerves.

Assessment of the Balance of VS Patients on the VR/Foam Device

We tested the VS patients with VR/Foam and the sensors of an Android smartphone (see Methods). We aimed to improve the detection of their deficits and to obtain a precise evaluation of their balance performances before making decisions about management (active follow-up, surgery, or gamma treatment).

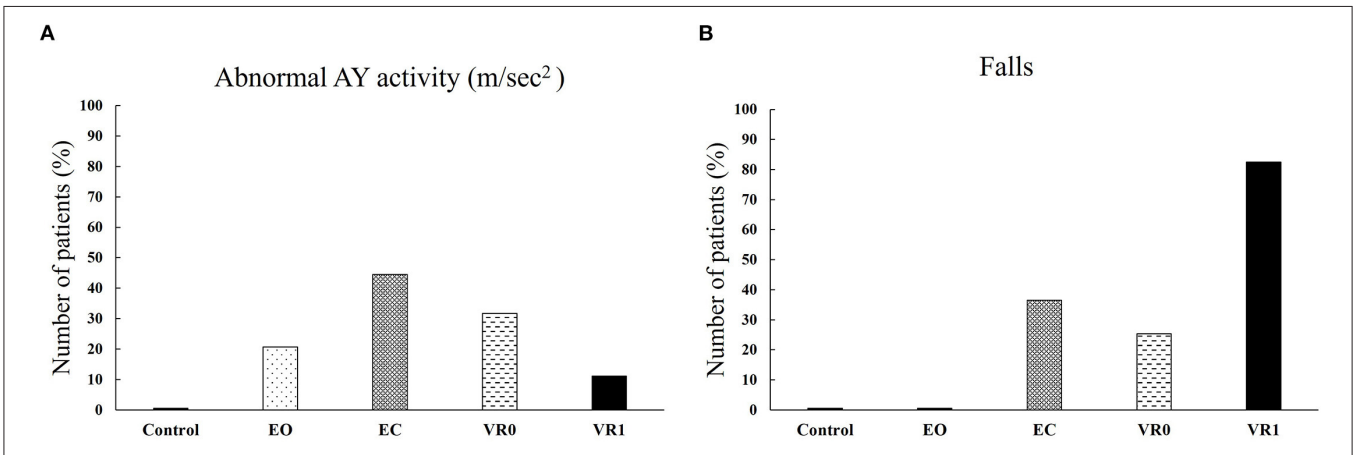

FIGURE 6 | Percentage of patients displaying abnormal postural oscillations or falling, for the control and VS groups, under EO, EC, VR0, and VR1 conditions. **(A)** Percentage of patients with abnormal AY activity in control group an VS group in the EO, EC, VR1 and VR1 conditions; **(B)** Percentage of falling in control in control group an VS group in the EO, EC, VR0 and VR0 conditions.

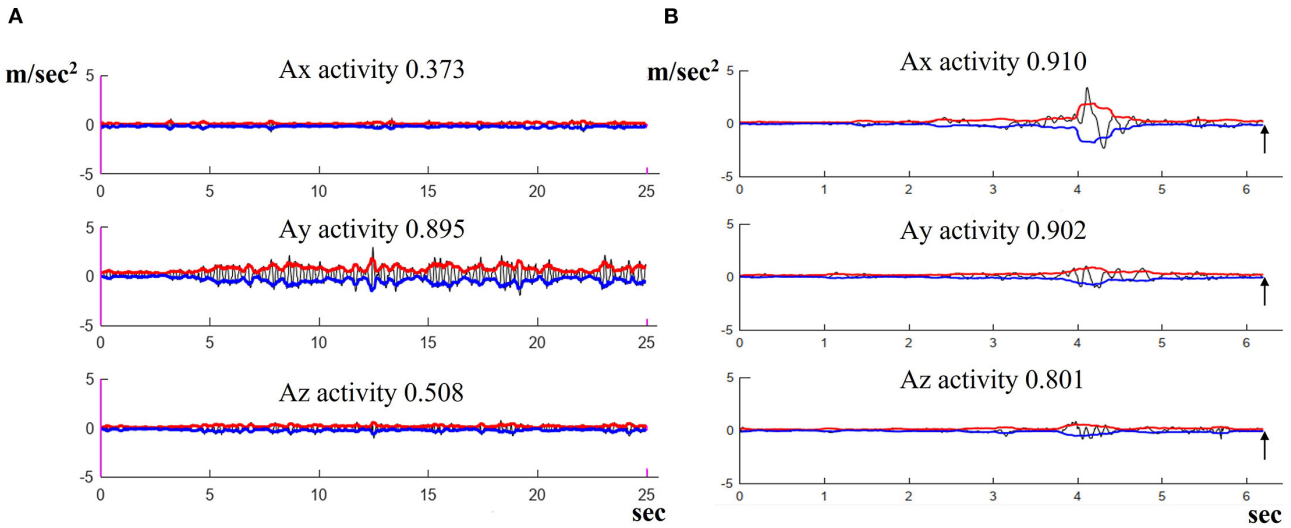

FIGURE 7 | Illustration of the oscillations of acceleration (m/s^2) along the *X, Y,* and *Z* axes, as measured with the Android sensor. **(A)** Abnormal result in VR1, not the high AY activity in m/s^2, with large oscillations. **(B)** A fall, about 6 s after the start of the recording (see arrow).

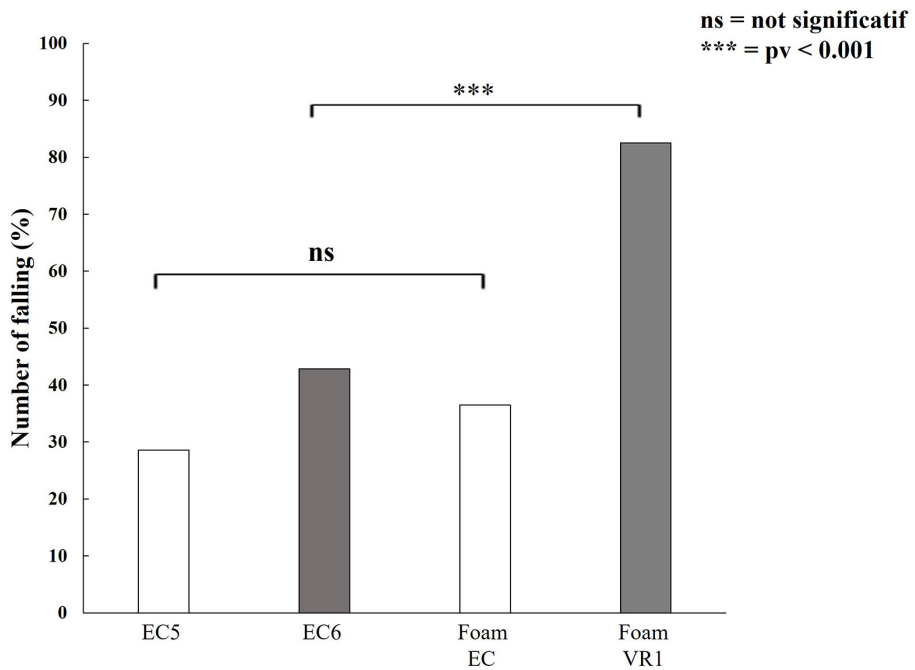

FIGURE 8 | Percentage of patients falling in the EquiTest (EC5, condition 5 and EC6, condition 6) and with our VR-foam-smartphone device. Note that VR1 is much more sensitive than EquiTest for detecting an imbalance in patients suffering from a unilateral VS.

Virtual reality proved to be a very good test for assessing the ability of the patient to maintain balance on foam under difficult and extreme conditions in which erroneous visual and proprioceptive information was supplied. This has already been shown to be the case for normal, senior, and bilateral areflexic patients (36). Furthermore, previous studies have also shown that unilateral vestibular dysfunction can lead to high sensitivity to visual stimulation (37) and a disturbance of proprioceptive inputs to the lower limbs (21).

In the VS group, the percentage of patients falling increased with the difficulty of the conditions, from EO to VR1: no falls were observed in EO but 36.6% of the VS patients fell in EC on

the foam. Falls with the eyes closed could not be attributed to age in this study as no falls in EC conditions were detected in our control group, which included senior patients. Chiarovano et al. showed that <3% of healthy subjects over the age of 70 years fall into EC conditions (9). VS patients found it more difficult to keep their balance when they received disturbed proprioceptive inputs (due to standing on foam). Only two of our 63 VS patients were in their eighties.

Falls were observed in 25.39% of the VS patients in VR0 conditions and 82.53% in VR1 conditions. Age did not affect the likelihood of falling in VR1. Chiarovano et al. showed that falls occurred in VR1 conditions for 26% of healthy subjects over the age of 70 years and 66% of those over the age of 80 years (9).

This high percentage of falls in VR1 highlights the attentional demands on the patient for the maintenance of balance for 25 s on foam. Foam is used clinically as a tool for assessing the contribution of proprioceptive information to static postural control (38). VS patients were unable to use their vestibular system properly to ignore visual inputs, as standing on foam provided them with false proprioceptive information. They tried to keep their balance, but they often fell within 10 s (see Results). In 1982; Nashner et al. suggested that the main problem of patients with vestibular deficits was their inability to integrate sensory information (39, 40). Our patients appear to be less handicapped by the loss of vestibular information than by their inappropriate responses to proprioceptive and visual information (41). In our study, even patients with normal caloric test and VEMP results fell or had abnormal results in VR1. All our VS patients with normal caloric test results (<25%) fell or had abnormal results in VR1. All these patients had a history of rotatory or positional vertigo. They had, therefore, developed a dependence on visual cues, which was evident from the abnormal results and falls observed in VR1. It has been shown that following sensory loss, for example, unilateral vestibular deafferentation, individual weighting changes with the prevailing view that visual inputs become more important which often leads to high visual dependence (42).

In patients with abnormal results for VR1, AY activity levels were higher than those for AX and AZ activity, but with these large oscillations maintained until the end of the test without falling. Our patients who fell two times in VR1 conditions on foam had no problem when they were tested in VR1 on the ground because this made it possible for them to use true proprioceptive inputs correctly. In the presence of disturbances of proprioceptive and vision inputs, these patients required symmetric vestibular inputs to maintain their balance on the foam.

VR/Foam vs. EquiTest

Condition 6 of the EquiTest is performed on firm ground support that swings exclusively in the anteroposterior plane (43). The patient's eyes are also open and receive sway-referenced vision input from the surrounding cabin. By contrast, VR1 on foam is performed with a total immersion in a virtual environment that very closely resembles reality (44). Furthermore, proprioception on foam is controlled in all the planes (anterior–posterior, inferior–superior, and lateral).

In the EquiTest, only 42.8% of patients fell in condition 6 due to their reliance on visual cues (45). VR1 conditions had a sensitivity of 93%, whereas EquiTest condition 6 had a sensitivity of 46%. Both tests had a specificity of 100% for both our groups (control and VS patients). These findings highlight the utility of our VR1 conditions (44). Abnormal results in the VR/Foam test are of particular interest because they are predictive of a high probability of falling. Such tests would therefore be useful for assessment before treatment or rehabilitation to improve the patient's balance.

VR/Foam vs. the Other Unimodal Tests

No correlations between all the vestibular tests and the result of the VR/Foam test could be found. These results can be explained in two ways:

The VR/Foam probes how patients used a combination of visual proprioceptive and vestibular information, which may explain why we did not find any correlation in any specific vestibular tests we used. The underlying assumption would be that various degrees of vestibular compensation for each patient blurred a correlation between the VR/Foam test (multimodal tests and any specific vestibular test (unimodal test).

On the other hand, this argument cannot be put forward for the EquiTest, which is also a multimodal test like the VR/Foam. The present data cannot explain why VR/Foam is more sensitive than the EquiTest. Two hypotheses can be put forward but they should be tested in future studies:

First, standing on a foam may be more difficult than standing on a firm platform which always moves along the same axis of rotation.

Second, stabilizing the visual scene with respect to the head (EquiTest) could be less disturbing than a random movement of the visual scene with respect to the head (VR/Foam).

Finally, the combination of the visual scenes combined with the random disturbances caused by the foam support could be more disturbing than the more stereotyped sensory postural and visual conflict of the EquiTest. This hypothesis should be tested in further studies.

CONCLUSIONS

Our findings demonstrate that VS affects the function of the superior and inferior vestibular nerve. Both caloric tests and vHIT should be performed to characterize the function of the horizontal canal nerve in patients suffering from VS. Finally, the test developed here, based on the use of foam, a VR mask, and smartphone sensors, is a highly sensitive and cheap method for quantifying balance. This test can detect postural performance disorders and visual dependence early, which is not always the case for EquiTest. This VR/Foam test should, therefore, help clinicians to assess and quantify balance performance. This system can also detect inappropriate vestibular compensation processes, such as visual dependence.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CV directed the research. GO and CV conceived and performed all the balance tests for patients and wrote the paper. CM performed the mathlab work for X,Y,Z postural oscillation analysis. IB helps for sway velocity calculation. GL and FT helped to test the patients suffering from unilateral vestibular schwannoma. All authors have reviewed the text and approved the final paper for submission.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Balance control impairments in Fabry disease

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Background: Fabry disease (FD) is a rare inherited lysosomal storage disorder caused by the deficiency of the enzyme alpha-galactosidase A. This deficiency leads to an accumulation of glycosphingolipids leading to progressive and multisystemic disease, including renal, cardiac, and neurological damages. FD may also have neuro-otological and visual impairments, which can generate postural control alterations, inner ear, and vision being involved in this function. This study aimed to evaluate the impact of FD on postural control.

Methods: In total, fourteen adult patients (8 men/6 women, mean age = 37.6 ± 11.4 years) and two children (mean age = 11 years) with FD and 19 healthy adults (12 men/7 women, mean age = 36.5 ± 16.9 years) and two healthy children (mean age = 10.5 years) took part in this study. Postural control was evaluated by a sensory organization test combining three visual situations (eyes open, eyes closed, and sway referenced visual surround motion) with two platform situations (stable platform and sway referenced platform motion), aiming to calculate a composite equilibrium score (CES), a high score being representative of good postural control. Somatosensory (R^{SOM}), visual (R^{VIS}), and vestibular (R^{VEST}) contributions to postural control were calculated, a low score reflecting a poor use of the indicated sensory input.

Results: The CES was lower in adult patients with FD compared with the healthy subjects ($p < 0.001$). R^{VIS} ($p = 0.001$) and R^{VEST} ($p = 0.003$) were lower in patients with FD compared with the control group, whereas no difference in R^{SOM} was observed.

Conclusion: Inner ear and visual pathologies associated with the central nervous system impairments are factors of postural control impairments. Physical activities, which can also be rehabilitative, by maintaining or increasing the weight of proprioception, may help diminish dependency on altered sensorial inputs.

KEYWORDS

Fabry disease, postural control, posturography, cochleo-vestibular disorders, rehabilitation

Introduction

Fabry disease (FD) (OMIM 301500) is an X-linked recessive inborn error of glycosphingolipid metabolism due to the deficient activity of the lysosomal enzyme alpha-galactosidase A (EC 3.2.1.22). The deficiency of alpha-galactosidase A leads to the storage of neutral glycosphingolipids, particularly, globotriaosylceramide and galactosylceramide, in many tissues and cell types (1). The accumulation of its substrate, the globotriaosylceramide (GL-3) leads to cellular dysfunction which might in turn trigger inflammation or fibrosis or both and results in a complex, and heterogeneous disease (2). The incidence of FD, is estimated between 1/35,000 and 1/476,000 births (3, 4). Both hemizygous males and heterozygous females can be affected. Phenotypic expression in heterozygous female depends on random X inactivation and male patients usually develop a more severe form of the disease with an earlier age at onset than female patients. The manifestations of FD are progressive and multisystemic. FD induces a progressive accumulation of GL-3 in the lysosomes of endothelial, perithelial, smooth–muscle cells of blood vessels, ganglion cells, and in many cell types in the heart, kidneys, eyes, and most other tissues (5, 6). Neurological (cerebrovascular and acroparesthesia), renal, cardiac, dermatological (angiokeratoma and hypohidrosis) involvements and corneal abnormality are the major clinical manifestations in patients with the classic phenotype (2). Vascular involvement contributes to the central nervous system abnormalities (7) and vascular ischemia and lipid deposition in the perineurium may cause the peripheral nerve conduction abnormalities seen in FD (8). Patients with FD suffer from sensorineural hearing loss, with both progressive hearing impairment (microvascular mechanism) and sudden deafness (macrovascular mechanism). These patients also present peripheral vestibular deficits with dizziness and vertigo. Vascular damage seems to be involved in the pathophysiologic mechanisms of cochleo-vestibular disorders (9). A correlation of neuropathic and vascular damage with hearing loss was found in men in whom residual alpha-galactosidase A activity appears to have a protective effect against hearing loss (10). Progressive vestibular loss was found in 80% of men and 77% of women when assessed with head impulse testing (11).

Postural control, which is an inner part of many ordinary activities, is a complex sensorimotor function that requires central integration of visual, vestibular, and proprioceptive/somatosensory systems. Integration of these three inputs generates a context-specific motor response, which leads to stabilization of gaze and antigravity posture (12–15). Visual and inner ear inputs, which can be affected by FD, contribute to the postural control.

Aging and a sedentary lifestyle are accompanied by a reduction in muscle mass and strength, which may be prevented or delayed by the practice of physical and sporting activities. Becoming skilled in the sporting activities helps to improve postural performance and as a consequence, reduce the number of falls (16).

To our knowledge, only one study included postural control evaluation in FD. This study, performed in eight patients, showed normal results in all the cases except for one whose postural control was abnormal with low scores in composite and vestibular component analysis (10). Our study aimed to evaluate the impact of FD on the postural control in treated and untreated patients.

Methods

Patients and controls

A case control study was conducted in the Nancy University Hospital (France) on 14 adult patients (8 men/6 women, mean age = 37.62 ± 11.43 years, ranging from 18 to 60 years) and two children (mean age = 11.01 ± 2.54 years) with FD issued from 6 families. Adult patients are those followed by the Department of Internal Medicine and Clinical Immunology and the children by the Reference Center for Inborn Errors of Metabolism, Children Hospital, University Hospital of Nancy.

A control group of 19 healthy adult volunteers (12 men and 5 women, mean age = 36.51 ± 16.99 years ranging from 21 to 72) and two children (mean age = 10.5 years ± 0.79) with no pathology took part in this study.

All the patients were included after neuro-otological examination, and the history of FD was recorded for each patient.

The history of FD was recorded for each patient and a clinical neuro-otological assessment aimed at detecting and discriminating central and vestibular signs, identifying segmental or axial deviations, and ruling out confounding associated factors. Concerning the vestibular syndrome, the consequences of a vestibular lesion were appreciated by evaluating the vestibulo-ocular pathway (presence of nystagmus) and the vestibulo-spinal pathway (which lesion can produce instability).

When abnormalities were observed at the clinical neurootological examination (including videonystagmoscopic head-shaking test and head impulse test) or if vertigo were reported, a more complete assessment was performed (caloric test, rotatory test, and skull-vibration-induced-nystagmus test), adapted to the age, the associated pathologies, and the side effects of the treatment of these pathologies.

This work has been conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and conducted in soundproof rooms for balance control recordings (Agence Régionale de Santé de Lorraine agreement for research). All the participants gave their informed consent prior to the clinical

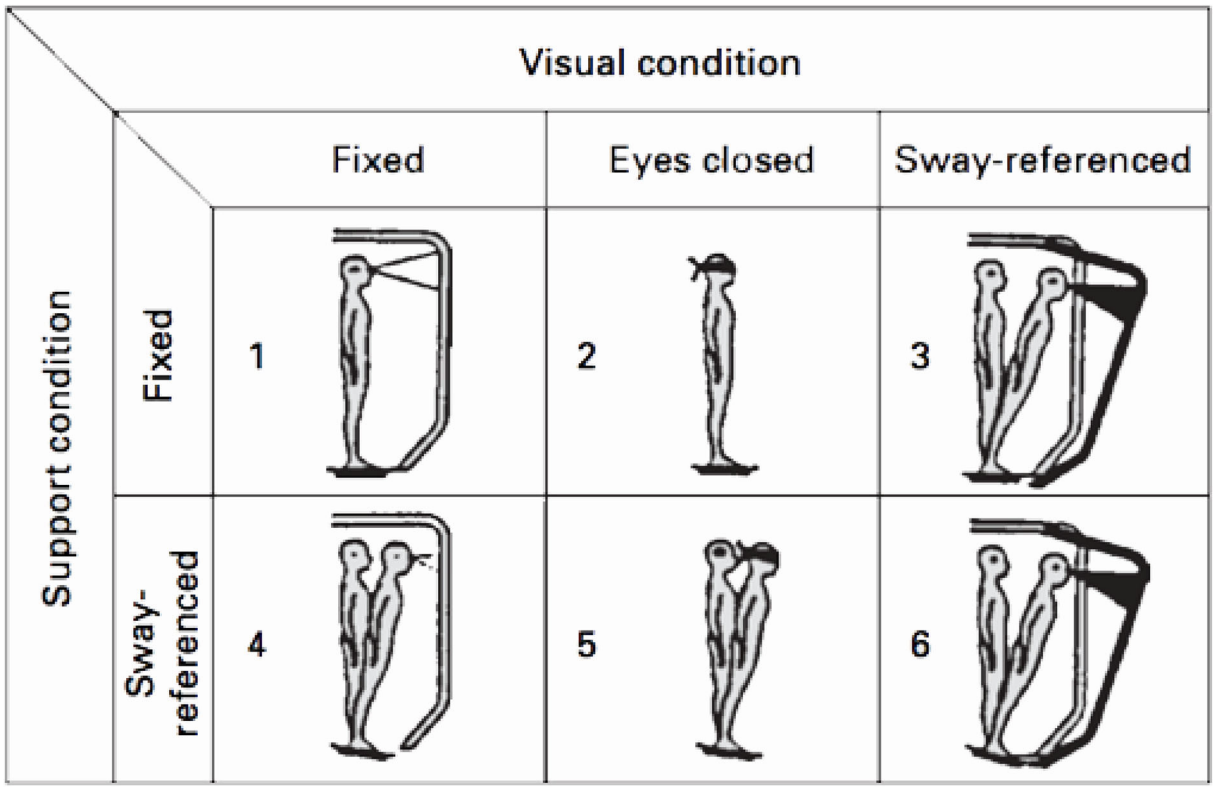

FIGURE 1
The six conditions of the SOT (EquiTest, NeuroCom International Inc., Clackamas, OR, USA). Conditions 1–3 were performed on a fixed platform with eyes open, eyes closed and vision sway-referenced. Conditions 4–6 were performed on a sway-referenced platform (somatosensory input inaccurate) with eyes open, eyes closed and vision sway-referenced (visual input inaccurate).

TABLE 1 Sensory organization test.

Conditions	Situation	Sensory consequences
Condition 1 (C1)	Eyes open, fixed support	-
Condition 2 (C2)	Eyes closed, fixed support	Vision absent
Condition 3 (C3)	SR surround, fixed support	Altered vision
Condition 4 (C4)	Eyes open, SR support	Altered proprioception
Condition 5 (C5)	Eyes closed, SR support	Vision absent, altered proprioception
Condition 6 (C6)	SR surround, SR support	Altered vision and proprioception
Ratios		**Significance**
Somatosensory (R^{SOM})	C2/C1	Question: does sway increase when visual cues are removed? Low scores: poor use of somatosensory references
Visual (R^{VIS})	C4/C1	Question: does sway increase when somatosensory cues inaccurate? Low scores: poor use of visual references
Vestibular (R^{VEST})	C5/C1	Question: does sway increase when visual cues are removed and somatosensory cues are inaccurate? Low scores: poor use of vestibular cues or vestibular cues unavailable

Determination of the six conditions and significance of sensory ratios (17–19).
The composite equilibrium score (CES) was calculated by adding the average scores from conditions C1 + C2 + 3 x C3 + 3 x C4+ 3 x C5+ 3 x C6 / 14.
SR, sway-referenced.

evaluation. For children, the parents and the participant gave their consent to participate.

Posturographic analysis

The Sensory Organization Test (SOT) was performed on an EquiTest computerized dynamic posturography platform (Neurocom, Clackamas, OR, USA). For the test, the subjects were requested to stand upright and barefoot on the platform, remaining as stable as possible, breathing normally, and with their arms at their sides, and were instructed to look straight ahead at a picture located on the visual surround. The SOT evaluates the patient's ability to make effective use of visual, vestibular, and somatosensory inputs separately and to suppress sensory information that is inappropriate. To give inadequate information, somatosensory and visual cues are disrupted by using a technique commonly referred to as sway-referenced. This technique involves tilting the support surface and/or the visual surround to directly follow the anterior–posterior sways of the subject's center of gravity (CoG) (17) (Figure 1). The SOT comprised six conditions (Table 1). The first two conditions provide a basic measurement of the subject's stability. The support is fixed and the subject's eyes are open (condition 1) or closed (condition 2). In condition 3, the support surface remains fixed while the subject stands, eyes open, within a sway-referenced visual surround. For conditions 4–6, somatosensory information is systematically disrupted (sway-referenced) and vision is fixed (condition 4), absent (condition 5), and sway-referenced (condition 6), respectively. In conditions 3 and 4, a sensory conflict is induced, but relatively easy to solve according to a ratio between the number of disrupted information and the number of reliable information (one disrupted cue for two reliable cues). The sensory conflict is more difficult to solve in conditions 5 (one disrupted cue for one reliable cue and vision being absent) and 6 (two disrupted cues for one reliable cue). For each condition, the subject maintains an upright stance during three 20 s trials with as little sway as possible and without moving the feet. When the subject required the assistance of the harness or took a step, the test was rated a fall. An Equilibrium Score (ES) was calculated by comparing the patient's anterior–posterior sway during each 20 s SOT trial to the maximal theoretical sway limits of stability. The theoretical limit of stability is based on the individual's height and size of the base of support (8.5° anteriorly and 4.0° posteriorly).

A composite equilibrium score (CES) was calculated by adding the average scores from conditions 1 and 2 and the ES from each trial of sensory conditions 3, 4, 5, and 6, and finally dividing that sum by the total number of trials (Table 1).

Lower sways lead to a higher CES, indicating a better balance control performance (a score of 100 represents no sway, while 0 indicates sway that exceeds the limit of stability, resulting in a fall).

Statistics

Results between the two adult groups are presented as mean ± SD. Comparison of qualitative variables used the Fisher's exact test while that of quantitative variables was performed using the non-parametric Mann Whitney *U*-test. Multivariate analysis used a multiple logistic regression model. A *p*-value lower than 0.05 was considered as significant.

Results

No significant differences were observed between the two groups for age, height, weight, BMI, and sex. Acroparesthesia were present in 64.3% (9 patients), 57% of them (8 patients) suffered from dizziness (accompanied by orthostatic hypotension for 28.6% [3 patients, one of them related to side effects of antihypertensive treatment (severe HCM)], 42.9% of them suffered of tinnitus (6 patients), 85.7% have a hearing loss (57% have a slight hearing loss (8/14 patients), 28.6% have a moderate hearing loss (4/14 patients), and 7.1% have an unilateral sudden hearing loss (1/14 patient); 64.3% of adult patients (9/14) were treated by enzyme replacement therapy (ERT) (Table 2). In the adult patients, 7/8 men and 5/6 women had hearing loss.

No genotype–phenotype correlation was found for hearing/balance disorders.

Posturography analysis

In adults, patients with FD showed significantly lower composite equilibrium score (CES) (73.1 ± 8.7 vs. 83.8 ± 5.3 ($p < 0.001$), visual ratio (R^{VIS}) (0.831 ± 0.087 vs. 0.932 ± 0.047; $p = 0.001$) and vestibular ratio (R^{VEST}) (0.534 ± 0.282 vs. 0.750 ± 0.097; $p = 0.003$) compared with the control group whereas no difference of somatosensory ratio (R^{SOM}) ($p = 0.182$) were observed (Figure 2, Table 3). In the adult patients, postural control was impaired in 3/8 men and 5/8 women.

Enzyme replacement therapy did not influence postural measures. However, patients with postural control instability (4 patients) presented more frequently impaired CES ($p < 0.001$), R^{SOM} ($p < 0.02$), and R^{VEST} ($p < 0.001$) than the other patients and were more frequently women than men ($p < 0.005$). In the multivariate analysis, altered R^{VEST} remained the sole independent factor explaining abnormal postural control in patients with FD.

TABLE 2 Fabry disease patients characteristics.

Part 1: Clinical characteristics

Patients	No	Age range (y)	Same family members	Hearing loss	Tinnitus	Vertigo/ Dizziness	Vision	Somesthesia	CNS	Gaze stabilization	Postural control	Organ failure
Family 1	1	15–19	2, 3, 4	Slight	+		Myopia	Acroparesthesia		Bilateral end-point nystagmus		
	2	20–24	1, 3, 4	Slight			Astigmatism	Acroparesthesia				
	3	25–29	1, 2, 4	Normal		+	CV, astigmatism, hypermetropia	Acroparesthesia		Bilateral end-point nystagmus		
	4	45–49	1, 2, 3	Moderate		+ orthostatic hypotension	Astigmatism, myopia		Cephalalgia (visual)	Vergence deficit		
Family 2	5	25–29		Slight				Acroparesthesia		Vergence deficit		
	6	30–34	7	Normal			Hypermetropia	Acroparesthesia	MRI periventricular hypersignals			Nephrotic syndrom
	7	60–64	6	Moderate	+	+ orthostatic hypotension				Bilateral end-point nystagmus		Severe HCM
Family 3	8	10–14	9, 10, 11, 12	Slight							Instability	
	9	5–9	8, 10, 11, 12	Normal								
	10	35–39	8, 9, 11, 12	Unilateral sudden hearing loss	+			Acroparesthesia	MRI periventricular hypersignals	Vergence deficit, saccadic ocular pursuit		HCM
	11	35–39	8, 9, 10, 12	Slight	+	+		Acroparesthesia	Pituitary adenoma		Instability	
	12	40–44	8, 9, 10, 11	Slight	+	+ orthostatic hypotension		Acroparesthesia			Instability	Mild HCM
Family 4	13	35–39	14	Slight		+ (VVS, epilepsia)	Astigmatism, myopia		MRI periventricular hypersignals	Bilateral end-point nystagmus, vergence deficit	Instability	
	14	40–44	13	Slight		+			Migraine, darkness phobia		Instability	

(Continued)

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TABLE 2 (Continued)

Part 1: Clinical characteristics

Patients	No	Age range (y)	Same family members	Hearing loss	Tinnitus	Vertigo/ Dizziness	Vision	Somesthesia	CNS	Gaze stabilization	Postural control	Organ failure
Family 5	15	50–54		Moderate	+	+	CV, astigmatism, hypermetropia	Acroparesthesia		saccadic ocular pursuit		Moderate HCM
Family 6	16	40–44		Moderate			CV, astigmatism, hypermetropia		MRI periventricular hypersignals			ESRD

Part 2: Genetic mutations and treatments

Families	No	Age range (y)	Mutation	Nucleotide aberration	Megalastat sensible	ERT	Treatment duration (y)	Other treatments
1	1	15–19	IVS4-2 A>T	c.640-2A>T	–	AA	3	
	2	20–24	IVS4-2 A>T	c.640-2A>T	–	AA	3	
	3	25–29	IVS4-2 A>T	c.640-2A>T	–	AA	0.5	
	4	45–49	IVS4-2 A>T	c.640-2A>T	–	-	0	Anti AHT
2	5	25–29	p.A143T	c.427G > A	+	-	0	
	6	30–34	p.A143T	c.427G>A	+	AB	3	
	7	60–65	p.A143T	c.427G>A	+	AB	0.5	Anti vertiginous
3	8	10–14	p.M42R	c.125 T>G	+	-	0	
	9	5–9	p.M42R	c.125 T>G	+	-	0	
	10	35–39	p.M42R	c.125 T>G	+	AA	1	Anti AHT
	11	35–39	p.M42R	c.125 T>G	+	-	0	Vestibular Rehabilitation, anti vertiginous
	12	40–44	p.M42R	c.125 T>G	+	AA	1	
4	13	35–39	p.P205S	c.613 C>T	+	-	0	Antiepileptic
	14	40–44	p.P205S	c.613 C>T	+	-	0	Balance Rehabilitation
5	15	50–54	del 50 pb Ex7	del 50 pb Ex7	–	AA	5	
6	16	40–44	-	–	-	AA	4	

Anti AHT, anti-arterial hypertension; HCM, hypertrophic cardiomyopathy; CV, cornea verticillata; ESRD, End-stage renal disease; VVS, vasovagal syndrome; ERT, Enzyme replacement therapy; AA, AB, agalsidase alfa, beta; MRI, Magnetic Resonance imaging.

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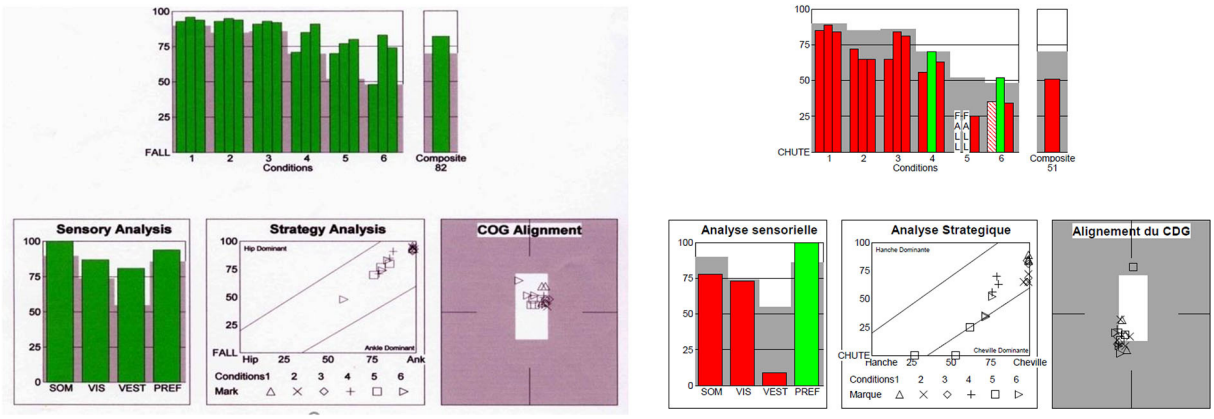

FIGURE 2
Sensory organization test. On the left: normal values of the Composite score (82) and of R^{SOM}, R^{VIS}, R^{VEST}. Strategy analysis: ankle dominant, Center of gravity (COG) alignment: normal. On the right: Fabry disease patient (patient No 14): low Composite score (51), low values of R^{SOM} and R^{VEST}. Strategy: ankle and hip dominant strategies and falls according to the condition. Center of gravity shifted to the backward position.

Postural control analysis was also performed on the other two younger patients with FD, one age range 10–14 y and one age range 5–9 y. Postural control was lower in the oldest child compared with the two healthy children while no difference was observed in the youngest one compared with the healthy children.

Vestibular examination

Vertigo and/or R^{VEST} abnormalities were noted in patients 3, 4, 7, 8, 11, 12, 13, 14, and 15.

There were no abnormalities on complementary examinations in patients 3 and 7. The interpretation was disturbed in patient 4 by a strabismus. In patient 13, the results were disturbed by the side effects of the antiepileptic treatment. Unilateral vestibular areflexia was observed in patients 8 and 12 and bilateral vestibular hyporeflexia in patient 14, and areflexia in patient 11. In patient 15, eye pursuit was saccadic.

Discussion

This study showed that balance control performance was lower in adult patients with FD patients compared with the healthy subjects. Inner ear and visual pathologies associated with the central nervous system impairments are the main factors of postural control impairments in these patients whereas no difference was observed between the two groups in the use of somesthetic input.

Fabry disease frequently leads to the inner ear dysfunctions, such as sensorineural hearing loss, sudden deafness, tinnitus, and dizziness or vertigo (20). Hearing loss in FD is due to the accumulation of GL-3 in the inner ear (21). In the mouse the loss of a-galactosidase A activity is genetically or biochemically buffered and not sufficient *per se* to cause an appreciable degree of hearing impairment (22). Although the alpha-galactosidase A deficient mice showed no clear hearing loss, GL-3 accumulation was demonstrated in the cochlea (21). The data demonstrate that in the mouse the loss of α-galactosidase A activity is genetically or biochemically buffered and not sufficient *per se* to cause an appreciable degree of hearing impairment.

Histopathologic evidence of glycosphingolipid accumulation in vascular endothelial and ganglion cells, and also atrophy of the stria and spiral ligament, might explain the otoneurologic symptoms (23).

To date, it is not known if ERT can reduce or prevent the cerebrovascular complications and hearing loss associated with FD, and it is unclear whether vertigo and tinnitus can be improved with ERT. It has been hypothesized that since migalastat is able to cross the blood–brain barrier, it might contribute in reducing the occurrence of cerebrovascular events (24).

Progressive sensorineural hearing loss can be stabilized, but not reversed (with or without treatment), but frequency of sudden hearing loss decreases during ERT compared with the frequencies observed in untreated patients (25). ERT does not appear to be a recognized therapy for sudden hearing loss. Therapeutic goals for hearing loss include stabilization of hearing loss, the possible use of hearing aids or cochlear implants to improve both hearing and patient quality of life (26).

No age effect was observed in the adult patients and one of both children (age range 10–14 y) with low posturographic performances do not present other clinical signs than postural instability.

Genotype–phenotype correlation remains controversial in FD and there is no specific data about hearing/balance disorders in term of genotype–phenotype correlation. In FD, more than

TABLE 3 Posturographic and vestibular results in the Fabry disease patient group.

Patients	Vertigo	Composite score (CES)	Vestibular ratio (RVEST)	Visual ratio (RVIS)	Somatosensory ratio (RSOM)	Posturographic pattern	Vestibular examination
1		77	0.71	0.79	0.99	RVIS slightly ↘	-
2		78	0.62	0.83	1.01	Normal	-
3	+	81	0.70	0.93	0.97	Normal	Nothing to notice
4	+	74	0.65	0.70	1.00	RVIS ↘	Interpretation disturbed by strabismus
5		82	0.68	0.89	0.99	Normal	-
6		85	0.83	0.98	0.96	Normal	-
7	+	83	0.72	0.95	0.98	Normal	Nothing to notice (orthostatic hypotension)
8		51	0.00	0.68	0.86	RVEST ↘RVIS ↘CES ↘	Left vestibular areflexia
9		72	0.59	0.84	0.99	Normal	-
10		76	0.65	0.77	0.96	RVIS ↘	-
11	+	66	0.00	0.88	0.85	CES ↘RVEST ↘	Bilateral vestibular areflexia
12	+	49	0.00	0.77	0.85	RVEST ↘RVIS ↘CES ↘	Left vestibular areflexia
13	+	67	0.52	0.75	0.94	CES ↘RVEST ↘RVIS ↘	Interpretation disturbed by epilepsy treatment and vergence deficit
14	+	51	0.10	0.73	0.78	CES ↘RVEST ↘RSOM ↘	Bilateral vestibular hyporeflexia
15	+	72	0.58	0.79	0.96	RVEST ↘RVIS slightly ↘	Vestibular central pathology Saccadic ocular pursuit
16		83	0.72	0.87	0.98	Normal	-

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1,000 variants have been described and this high number underly the phenotype heterogeneity observed in this disease. Most of variants are "private" and confined to individual pedigrees with possible variability in phenotypic expression due to phenotype-modifying factors: i.e., genetic background, epigenetics, and environmental conditions (27, 28). One recent paper described the genotype–phenotype correlation in term of event-free but not in function of each possible clinical event, and in particular, there is no specific data about hearing/balance disorders in these patients (29). Moreover, in women patients, the phenotype depends of the genotype but also (and mainly) of the X-chromosome inactivation (30).

Patients with FD respond inappropriately to conflicting or inaccurate sensorial inputs. Vestibular alteration may explain a lower inner ear contribution in postural control (R^{VEST}) with lower values in postural control (CES) in patients with FD compared with the healthy subjects.

Concerning the 4 patients with vestibular hypo or areflexia, all 4 had a slight hearing loss (16 to 20 dB). The combination of vertigo and hearing loss may point to the inner ear as the origin of the disorder because of anatomic proximity of the vestibular and cochlear structures, whereas a lack of correlation between vestibular and cochlear disorders may suggest different pathophysiological mechanisms for these two structures.

Among the four patients with the vestibular disorders, two were unilateral and two were bilateral and symmetrical. Slow progressive vestibular damage, through the development of vestibular compensation mechanisms involving effective use of alternative sensory inputs, may allow the patient to experience few symptoms.

Vergence disorders and saccadic ocular pursuit contribute also to a lower postural control. Strabismus may interfere with pursuit and visual fixation and be accompanied by ophthalmic nystagmus. This oculomotor disturbance may suggest central vestibular damage. Because of the vestibuloplegic effect (antiepileptics) or the induction of nystagmus or abnormal eye movements (antiepileptics and anti-inflammatory drugs) of some of the prescribed drugs, vestibulo-ocular reflex analyses were difficult to interpret. Dizziness could be induced by inner ear toxicity (bilateral toxicity) or by the central damage.

Corneal abnormalities (cornea verticillata), neither responsible for changes in visual acuity nor causing complaints, did not decrease the weight of visual input in postural control. None of the patients with FD in our study had a visual dependency or preference.

Acroparesthesia did not cause a decrease in somesthetic afference weight.

The presence of both a decrease in visual and vestibular afference may reflect a central integration defect.

Usher syndrome, an autosomal recessive disorder, is characterized by congenital hearing loss combined with retinitis pigmentosa, and in some cases, vestibular areflexia, leading to postural disability, that may have similar posturographic results to those of the FD (31).

In patients with FD, recovery in treated patients, i.e., *a priori* the most severe forms, would be in favor of damage to peripheral structures and a potentially curative action of the treatment. In our study, in adults, the composite score (CES) was better in treated patients than in untreated patients (76 vs. 69), as were R^{SOM} (0.96 vs. 0.92), R^{VIS} (0.86 vs. 0.79), and R^{VEST} (0.61 vs. 0.43), the results favoring peripheral involvement not being significant, however, due to the small size of the population.

Since the patients had comparable characteristics to the controls (in particular, age, sex, and body mass index), it was considered that if the patients showed statistically lower values than the control group, this could probably be due to their pathology. Nevertheless, based only on the average of the CES, patients with FD have values of balance (measured by dynamic posturography) close to the norms of the device, although worse than healthy individuals of the same age.

Enzyme replacement therapy treatment does not cross the blood–brain barrier and, therefore, cannot have any positive effect on the central component of the disorder.

The efficacy of the treatment would be more in favor of an effect of ERT on microvascular involvement of FD. This improvement in microvascularization could stabilize the inner ear functioning, which would require long-term follow-up to be confirmed.

This study has several limitations. The limited sample size of the population and in particular of the children should be highlighted, which limits in particular the study of the difference in symptomatology between men and women and of the impact of the type of treatment on balance and hearing. The postural control will need to be considered in the evaluation of current and future treatments for FD, whether migalastat or gene therapy. According to Palla et al., age correlated with auditory and vestibular impairments (11). The evaluation of the type of balance control recovery of vestibular disorders (i.e., recovery by compensation involving effective use of alternative sensory inputs or recovery by restoration) could require a longitudinal follow-up by vestibular and posturographic investigations, in situations of sensory conflict.

We emphasize the importance of multisensory evaluation in these patients to guide development of personalized visuo-vestibular rehabilitation techniques.

Otherwise, as we age, balance control becomes more and more dependent on vision, while this input becomes increasingly less performant. Training allows sportsmen to acquire new balance control abilities, which may differ according to the discipline practiced. Physical activity may help diminish this visual dependency by maintaining or increasing weight of proprioceptive input (32).

Physical activity practice (e.g., tai-chi, yoga) or physiotherapy can be useful to prevent balance control impairments. The beneficial effect of this training may then be transferred to daily activities.

Conclusion

These data suggest that understanding of specific balance control impairments in FD could contribute to propose better balance-oriented rehabilitation programs with the particular attempt of preventing falls. The multisensory evaluation of postural control helps determine the adapted modalities of visuo-vestibular rehabilitation and to evaluate in a quantifiable way its effect to improve postural stability and quality of life.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials. Requests may be directed to the following clinicians (MD): RJ: R.JAUSSAUD@chru-nancy.fr, JD-K: j.deibener@chru-nancy.fr, FF: f.feillet@chru-nancy.fr, and PP: philippe.perrin@univ-lorraine.fr. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the patients/participants or patients/participants' legal guardian/next of kin.

Author contributions

LP-C realized posturography recordings. PK, FF, RJ, and JD-K carried out the internal medicine assessment and therapeutic management of the FD. PP managed the neuro-otological assessments. All authors contribute to the study concept and design, and contribute to the writing of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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