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Στα παιδιά μου,
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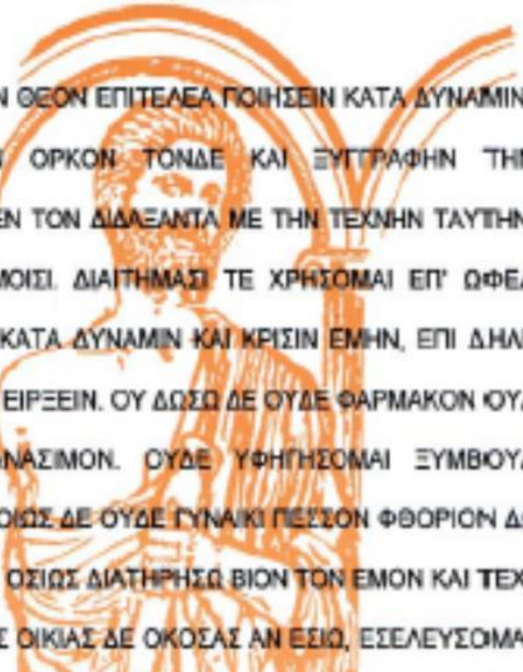

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Ευχαριστίες

«*Αν είδα μακρύτερα είναι επειδή στάθηκα στους ώμους γιγάντων*». Έχοντας αυτή την φράση του Ισαάκ Νεύτωνα στο νου, θα ήθελα να ευχαριστήσω όσες και όσους με καθοδήγησαν και με στήριξαν στην επαγγελματική μου διαδρομή, της οποίας σταθμός αποτελεί η παρούσα Διδακτορική Διατριβή.

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Το κλινικό μου έργο, στο μεγαλύτερο μέρος της μέχρι τώρα επαγγελματικής μου σταδιοδρομίας, αφορά την αξιολόγηση και αποκατάσταση των αιθουσαίων διαταραχών. Από το 2010 εώς σήμερα είμαι επιστημονικός συνεργάτης της Ά Ω.Ρ.Λ. Πανεπιστημιακής Κλινικής του Γ.Ν.Α. «Ιπποκράτειο», εφαρμόζοντας για πρώτη φορά στον Ελλαδικό χώρο την συγκεκριμένη φυσικοθεραπευτική προσέγγιση, και εξυπηρετώντας περισσότερα από χίλια (1000) άτομα με περιφερικές αιθουσαίες διαταραχές. Επιπλέον από το 2016 έως σήμερα αποτελώ μόνιμο προσωπικό των Δημοτικών Ιατρείων του Δήμου Αγίου Δημητρίου προσφέροντας φυσικοθεραπευτικές υπηρεσίες για την προαγωγή της υγείας ηλικιωμένων ατόμων και για την αποκατάσταση μυοσκελετικών παθολογιών. Επίσης για πέντε χρόνια (2011 – 2016) εργάστηκα ως ελεύθερος επαγγελματίας φυσικοθεραπευτής.

Το ερευνητικό μου έργο αφορά κυρίως την συμμετοχή του σε τέσσερα (4) Ευρωπαϊκά Χρηματοδοτούμενα Προγράμματα (ένα ΠΠ7 και τρία Horizon 2020). Το ερευνητικό πρόγραμμα EMBALANCE (2013 – 2016, FP7-ICT-2013-10, No 610454) αφορούσε την ανάπτυξη ενός υπολογιστικού συστήματος για τη διάγνωση και την αντιμετώπιση παθήσεων ισορροπίας. Το ερευνητικό πρόγραμμα HOLOBalance (2017-2021, Horizon2020, No 769574) αφορούσε την ανάπτυξη μιας πλατφόρμας επαυξημένης πραγματικότητας που αποτελείται, μεταξύ άλλων, από ολογράμματα φυσικοθεραπευτή για την αποκατάσταση διαταραχών της ισορροπίας. Το ερευνητικό πρόγραμμα Smart Bear (2019 – συνεχίζεται, Horizon2020, No 857172) αφορά την ανάπτυξη μιας ενιαίας πλατφόρμας συλλογής καταγραφής και επεξεργασίας δεδομένων σε άτομα με τουλάχιστον δύο από τις παρακάτω παθήσεις (βαρηκοΐα, διαταραχές ισορροπίας, καρδιαγγειακά προβλήματα, ήπια άνοια ή ήπια κατάθλιψη), με στόχο την ενίσχυση της αυτοδιαχείρισης. Το ερευνητικό πρόγραμμα TeleRehab (2022 – συνεχίζεται, Horizon2020, No 101057747) αφορά την ανάπτυξη μιας πλατφόρμας για την βελτιστοποίηση της εξ αποστάσεως προσωποποιημένης παρέμβασης, μέσω θεραπευτικών ασκήσεων, σε ένα περιβάλλον επαυξημένης πραγματικότητας. Επιπλέον, έχω συμμετάσχει στην συγγραφή επιστημονικών άρθρων που έχουν δημοσιευθεί σε επιστημονικά περιοδικά με αξιολογητές (h-index:4, την περίοδο συγγραφής της παρούσας Διδακτορικής Διατριβής).

Το διδακτικό μου έργο αφορά διαλέξεις σε προπτυχιακό μάθημα επιλογής της Ιατρικής Σχολής του ΕΚΠΑ, στο Π.Μ.Σ. στην Ακοολογία – Νευροωτολογία του ΕΚΠΑ, στο Π.Μ.Σ. «Προηγμένη Φυσικοθεραπεία − Advanced Physiotherapy» του Τμήματος Φυσικοθεραπείας του Πανεπιστημίου Στερεάς Ελλάδας, του Π.Μ.Σ. «Θεραπευτική Άσκηση» του Τμήματος Φυσικοθεραπείας του Πανεπιστημίου Πατρών και στα μετεκπαιδευτικά προγράμματα που διοργανώνονται στο Γ.Ν.Α. «Ιπποκράτειο» και «Ελπίς». Επίσης έχω προσκληθεί για διάλεξη από τη Σχολή Αρχιτεκτόνων Μηχανικών του Εθνικού Μετσόβιου Πανεπιστημίου (Ε.Μ.Π.) και το Ερευνητικό Πανεπιστημιακό Ινστιτούτο Συστημάτων Επικοινωνιών και Υπολογιστών (ΕΠΙΣΕΥ). Επιπλέον, έχω συστηματική παρουσία ως προσκεκλημένος ομιλητής σε όλα τα συνέδρια της Πανελλήνια Εταιρεία Ωτορινολαρυγγολογίας Χειρουργικής Κεφαλής και Τραχήλου από το 2016 και έπειτα και παρουσία με εισηγήσεις και ελεύθερες ανακοινώσεις στα συνέδρια του Πανελληνίου Συλλόγου Φυσικοθεραπευτών. Έχω υπάρξει εκπαιδευτής (2013-2016) σε σεμινάρια ανανηπτών στη «Βασική υποστήριξη ζωής και αυτόματος εξωτερικός απινιδισμός». Το διδακτικό μου έργο συμπληρώνεται με μια διάλεξη για τις σωματοαισθητικές εμβοές στην ομάδα εργασίας του TINNET (2016, COST

Action BM1306) και μια διάλεξη στο Queen Square Dizzy Course (2022) που διοργάνωσε το National Hospital for Neurology and Neurosurgery του Λονδίνου.

Πρόλογος

Τα ωτολιθικά όργανα και οι ακουστικές ακρολοφίες τοποθετημένα εντός των δύο ανθρωπίνων ώτων, αποτελούν το πιο εκλεπτυσμένο περιφερικό σύστημα ελέγχου της ανθρώπινης κίνησης ελέγχοντας βασικά αντανακλαστικά και συνεισφέροντας σε πολύπλοκες γνωσιακές λειτουργίες. Το σύστημα αυτό ορίζεται ως αιθουσαίο. Οποιαδήποτε προσβολή του έχει ως αποτέλεσμα αιφνίδια είσοδο συμπτωμάτων, με χαρακτηριστικότερο τον ίλιγγο, και διαταράσσει μια σειρά από ανθρώπινες λειτουργίες εγκαθιστώντας, κατά περίπτωση, συμπτώματα όπως ζάλη, αστάθεια, δυσανεξία στις κινήσεις, διαταραχές πλοήγησης στο χώρο, μειωμένη οπτικοχωριακή ικανότητα έως και διαταραχές προσωπικότητας.

Η διαδικασία που ακολουθεί ο ανθρώπινος εγκέφαλος για να αντιστρέψει αυτή την διαταραχή της ομοιόστασης που ακολουθεί κάθε αιθουσαία προσβολή ονομάζεται αιθουσαία αντιρρόπηση. Η περιγραφή της σε μοριακό, κυτταρικό και νευρωνικό επίπεδο περιγράφεται στο Πρώτο Κεφάλαιο της παρούσας Διδακτορικής Διατριβής. Τα τελευταία επιστημονικά δεδομένα υποστηρίζουν ότι η διαδικασία αντιρρόπησης πιθανότατα να μην επιτυγχάνεται χωρίς κόστος, το οποίο πιθανώς να αφορά την γνωστική ικανότητα του ανθρώπινου οργανισμού να εκτελέσει δύο η περισσότερους στόχους.

Το Δεύτερο Κεφάλαιο παρουσιάζει μια συγχρονική μελέτη σε άτομα με περιφερικές αιθουσαίες διαταραχές εντοπίζοντας συσχετίσεις ανάμεσά στην λειτουργική τους βάδιση και παραμέτρους της γνωστικής λειτουργίας τους καθώς και την πιθανή προγνωστική αξία της υποκειμενικής αντίληψης των συμπτωμάτων μιας περιφερικής αιθουσαίας βλάβης, της ηλικίας και της ικανότητας εγρήγορσης, στις διακυμάνσεις της λειτουργικής βάδισης και τον πιθανό κίνδυνο πτώσης.

Η κίνηση και ειδικά η θεραπευτική άσκηση, μια ειδικά σχεδιασμένη φυσική δραστηριότητα με συγκεκριμένο θεραπευτικό στόχο και υπό την επίβλεψη ενός επαγγελματία υγείας – στην περίπτωση μας ενός Φυσικοθεραπευτή, αποτελεί την ασφαλέστερη και αποτελεσματικότερη θεραπεία εκλογής για τις μη-αντιρροπούμενες περιφερικές αιθουσαίες διαταραχές. Στο Τρίτο Κεφάλαιο παρουσιάζονται συνοπτικά οι μέθοδοι καταγραφής και αναφοράς της ανθρώπινης δυσλειτουργίας εξαιτίας μιας περιφερικής αιθουσαίας παθολογίας. Επίσης παρουσιάζονται τα υπάρχοντα ισχυρά ερευνητικά δεδομένα για την αποτελεσματικότητα της θεραπευτικής άσκησης ανά παθολογία και οι ισχυρές συστάσεις των κλινικών οδηγιών για τις όποιες από τις παθολογίες που μας απασχολούν, έχουν δημοσιευθεί. Τέλος αναφέρονται οι μελλοντικές προοπτικές στην αποκατάσταση οι οποίες περιλαμβάνουν, μεταξύ άλλων, την εφαρμογή ενός θεραπευτικού πρωτοκόλλου σε συνθήκες μικτής πραγματικότητας η οποία φαίνεται να προσφέρει ένα επιπλέον κλινικό όφελος.

Με αφορμή την τελευταία παρατήρηση, στο Τέταρτο Κεφάλαιο παρουσιάζεται μια πιλοτική μελέτη διερεύνησης της επίδρασης ενός εξειδικευμένου και οικονομικού εξοπλισμού, ο οποίος είναι αναγκαίος για την δημιουργία συνθηκών επαυξημένης πραγματικότητας, στην απόδοση θεραπευτικών ασκήσεων που συμπεριλαμβάνονται συχνότατα στα πρωτόκολλα θεραπευτικής άσκησης για την αποκατάσταση των περιφερικών αιθουσαίων διαταραχών. Στο Πέμπτο Κεφάλαιο συνοψίζονται τα συμπεράσματα ολόκληρης της διατριβής.

Σύμφωνα με την μέχρι τώρα γνώση μας η, Ά Πανεπιστημιακή Ω.Ρ.Λ. Κλινική του Γ.Ν.Α. «Ιπποκράτειο» είναι η πρώτη κλινική στον ελλαδικό χώρο που ένταξε οργανωμένα την θεραπευτική άσκηση ως υπηρεσία στα άτομα με μη-αντιρροπούμενες περιφερικές αιθουσαίες διαταραχές. Και οι δύο μελέτες που περιλαμβάνονται είναι πρωτότυπες και προσφέρουν στην επιστημονική κοινότητα ενδείξεις για την προγνωστική αξία παραμέτρων στην λειτουργική βάδιση ατόμων με περιφερικές αιθουσαίες διαταραχές καθώς και ενδείξεις για την τροποποίηση της απόδοσης της θεραπευτικής άσκησης κατά την εφαρμογή της με την χρήση εξοπλισμού επαυξημένης πραγματικότητας. Το σύνολο της Διδακτορικής Διατριβής παρουσιάζεται στην αγγλική γλώσσα σε μια προσπάθεια εξωστρέφειας του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών.

Foreword

The otolithic organs and the semicircular canals, located in the inner ear, constitute the most sophisticated system of the human movement control, controlling basic reflexes and contributing to complex cognitive functions. This system is called vestibular and its dysfunction is experienced usually as vertigo, as well as dizziness, instability, intolerance to movement, impaired cognitive function and even personality disorders.

The natural process that the human brain follows to reverse vestibular dysfunction is called vestibular compensation and its description at the molecular, cellular, and neuronal level is described in Chapter One of this Ph.D. thesis. Modern evidence suggests that a successful compensatory process is likely to be achieved at a cost, which is placed on the cognitive capacity of the human brain to perform simultaneously two or more tasks.

Thus, Chapter Two addresses a cross-sectional study in individuals with peripheral vestibular disorders by identifying correlations between their functional gait and parameters of cognitive function as well as the potential predictive value of subjective perception of symptoms of a peripheral vestibular lesion, age and vigilance in functional gait and risk of falls.

Movement and especially therapeutic exercise, a specifically designed physical activity with a specific therapeutic goal and under the supervision of a health professional - in our case by a physiotherapist, is the safest and most effective treatment for peripheral vestibular disorders. Chapter Three presents the methods of recording and reporting dysfunction due to peripheral vestibular pathology, the strong research evidence for the effectiveness of therapeutic exercise, the strong recommendations of clinical guidelines and the future prospective in rehabilitation which include the implementation of a therapeutic protocol in mixed reality conditions which appears to offer an extra clinical benefit.

Based on the latter observation, Chapter Four presents a pilot study investigating the effect of a specialized and low-cost equipment necessary to create augmented reality conditions on the performance of therapeutic exercises that are frequently included in therapeutic protocols for the rehabilitation of peripheral vestibular disorders. Chapter Five summarizes the conclusions of the thesis.

The 1st Department of Otorhinolaryngology, Head and Neck Surgery, National and Kapodistrian University of Athens based in Hippocrateion General Hospital is the first clinic in Greece to integrate therapeutic exercise as a service for people with peripheral vestibular disorders. Both clinical studies included in this Ph.D. thesis are original and offer to the scientific community evidence for the predictive value of parameters in the functional gait of people with peripheral vestibular disorders and evidence for modifying the performance of therapeutic exercise during its implementation using augmented reality equipment.

1. Vestibular Compensation

The vestibular system is a fully sophisticated system for the control of human movement, providing sensory inputs that refer to either low-level reflexes or high-level cortical processing, and concerns the stability of the visual image on the retina, the angular and linear acceleration of the head, the stabilization of the head in space, the representation of the body and its segments (body schema), the perception of the vertical, the perception of whole-body motion at space, the visual-spatial ability and spatial representation, the executive function, the navigation, the production of cognitive maps, and ultimately in the production of emotions.

The recent modeling of the vestibular hair cell synapse, which is rapidly depolarized based on the large open probabilities of the potassium conductance of type I hair cells [1], will allows to understand and to further investigate the contribution of the vestibular inputs not only the well-known vestibular pathologies that otologist community is dealing with, but also a large spectrum of entities where our knowledge is limited such as spatial neglect after stroke[2], vestibular agnosia[3], idiopathic scoliosis[4], laterality judgment in pain[5], even decision making for elite players to return to their play[6].

Nevertheless, in this chapter we will not be consumed in an anatomical and neurophysiological analysis of the system, neither will we go into detail about the pathophysiology of the vestibular lesions or its contribution to other entities. This valuable information can be extracted from excellent books [7, 8] or will be part of future research. We will maintain our interest in the electrophysiological process that follows a disturbance of homeostasis as it arises after a peripheral damage to the vestibular system, at the level of synapses in the vestibular sensory organ, at the level of the vestibular nucleus and in superior cortical networks, a process known as **vestibular compensation**.

A vestibular dysfunction, which in our case is mainly, if not exclusively, studied in cases of vestibular neuritis, leads to canal paresis in different mammalian species including humans. Immediately after vestibular damage, changes occur at the molecular and cellular level in the sensory organs and the vestibular nucleus and within days to weeks at a variety of neural networks responsible for vestibular processing. These changes are striking in a series of clinical signs and symptoms, which occur either by the effect of gravity or by the effect of movement, and which we will try to present along the way.

After a unilateral vestibular damage, there is a decrease in neuronal discharge of the vestibular afferent nerve fibers at rest on the side of lesion, which leads to an imbalance between the vestibular systems and practically to the appearance of spontaneous nystagmus and the false sensation of movement (vertigo). At the cellular level, this imbalance leads rapidly to the activation of plasticity mechanisms even from the level of the sensory epithelia and Scarpa's ganglion in order to restore normal operation [9].

Following an excitotoxic vestibular damage in young rodents (simulating an ischemic episode in humans), an astonishing nerve growth towards sensory epithelia is recorded, creating new synaptic contacts (bouton and calyx) only 5 days after the damage[3]. The same results occurred in synapses of older rodents but to a lesser extent[3]. Configuring this process seems that swelling of afferent terminals reported hours after the damage, in rat models, is followed by fiber retraction and resorption of terminals[4]. Following that damage, an increased expression of synaptophysin (on afferent terminals) and synapsin (on efferent terminals) 7 and 12 hours after the damage respectively, correspond to synaptogenesis of the vestibule similar to the perinatal process [10].

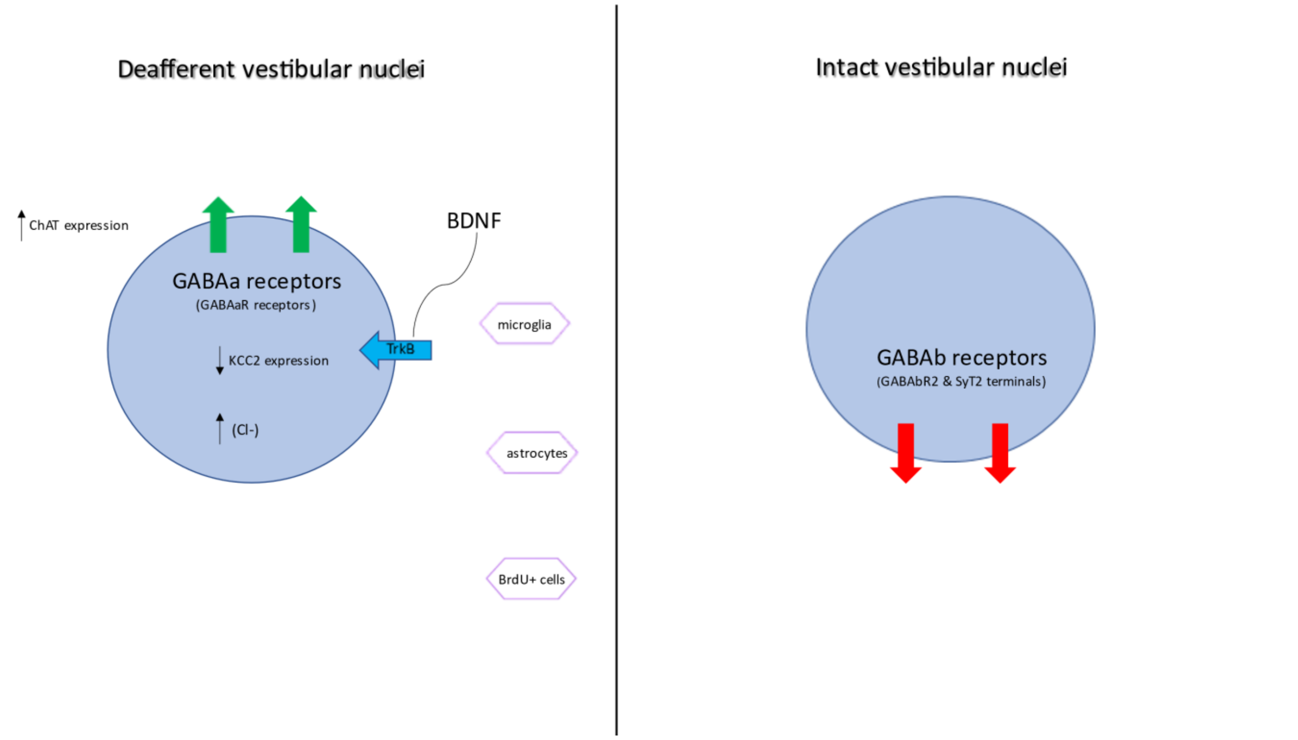

Figure 1: Action of GABA receptors during vestibular compensation in the vestibular nuclei. In the deafferent nuclei the upregulation of GABAAR receptors is a result of an increase of the Brain-derived Neurotrophic Factor (BDNF), produced by microglia and astrocytes, creating a beneficial environment for cell proliferation, survival and regeneration (BrdU+ cells). Downregulation of KCC2 is leading to an increase in Cl- in the cell and eventually an increase in its outflow. Neurons excitability in the deafferent vestibular nuclei is the main key for vestibular compensation and upregulation of ChAT enzyme confirms the hypothesis. On the contrary, downregulation in GABAbR2 and SyT2 terminals (GABAb receptors) in the intact side, also affect compensation process. BrdU+ cells: newborn cells, ChAT:

Choline Acetyl Transfase, KKC2: cation-chloride contrasporter, TrkB: tyrosine kinase B receptor, SyT2: synaptotagmin2. Graph adapted by Dutheil et al., 2016 and Shao et al., 2012.

At the vestibular nuclei (VN) level, it is known that γ-Aminobutyric acid (GABA) plays a crucial role in head acceleration excitability, taking action mostly in $GABA_A$ and $GABA_B$ receptors [11]. Evidence suggests that in unilateral pathological conditions, $GABA_A$ receptors are depolarizing during recovery in the deafferent side promoting the increase of astrocytes, microglia and newborn cells (BrdU+ cells) and eventually recovery under the action of Brain Derived Neurotrophic Factor (BDNF) which is upregulated in the first 72 hours of an injury in adult male cats [12]. The release of BDNF factor leads to an increase in action on its receptor (tyrosine kinase B-TrKB receptor) and a down-regulation in expression of cation-chloride contrasporter (KCC2), triggering neurons excitability due to the accumulated amount of cloride outflow the cell [12]. ChaT (Choline Acetyl Transfase) protein expression is also upregulated during the first 72 hours, leading consequently to an upregulation of cholinergic neurons only on the lesioned side. For $GABA_B$ receptors in rats, their down-regulation in the lesioned side up to 24 hours after an injury seems to promote recovery of spike discharge [13]. Interestingly, in the intact VN, evidence suggests that up-regulation in the presynaptic $GABA_B$ receptors in the intact side mediates inhibition of neurotransmitters in specialized terminals $GABA_BR2$ and synaptotagmin2)[8,14].

We can identify that the intrinsic excitability of vestibular nucleus (VN), mainly in the medial VN, corresponds to enhance discharge rate in vestibular neurons which is actually the key to the restoration of homeostasis after vestibular damage. A recently published meta-analysis demonstrates a statistically significant increase in the spontaneous discharge rates at rest in the medial VN on animal models with an average magnitude of 4 spikes/sec higher than before injury [15].

We have briefly discussed above the recovery of static symptoms (symptoms provoked when the subject is stationary) after a unilateral vestibular damage, which occur during the first hours to days following injury. Experiments on animal models demonstrated a modulation in gene expression, a regulation of proteins and neurotransmitters, and an excitability of neurons. From a clinical perspective, this corresponds to the recovery of spontaneous nystagmus and unsteadiness seen in the first days after vestibular damage. Movement in space reveals dynamic impairments correlating to the vestibular system and the asymmetries in vestibular neural projections in low-level reflexes and higher-level neural circuits. These dynamic symptoms (symptoms provoked as the subject navigates into the environment) are compensated to a lesser extent [16,17] but most importantly are remaining underdiagnosed by most of the non-expertise clinicians. This is a consequence of the lack of a full definition of the compensation process which involves higher neural organization, which is also consistent with the whole human behavior. In the next few paragraphs, we are trying to elucidate this complex function of the Central Nervous System (CNS) which refers to adaptation, sensory and behavioral substitution of sensory inputs in several brain areas. This does not mean that the mechanisms we described above do not play a role in long-term functional recovery, referring mostly to neurogenesis occurring on the brainstem's vestibular nuclei (VN), but how this process moves to a macroscopic level including not only reflexes by also bigger and long-range neural circuits.

Vestibular Ocular Reflex (VOR) remains the most investigated low-level reflex of the vestibular system not only in animal models but also in humans. Eye movements combined with the head's linear and angular acceleration, taking place during daily human routines, manage to stabilize targets onto the retina, based on a 3-neuron arc reflex [18]. After damage, VOR is decreased not only in terms of gain but also in time constants[13,19] resulting in a retinal slip of image. This mismatch between stimulus (vestibular-visual) is followed by an adjustment in neural activity and intrinsic properties of vestibular nuclei (VN) under the control of the flocculo-nodular portion of the cerebellum [20]. Modulation of type I hair cells and type B vestibular signals, manage to recover reflex capacity in the short term [21]. Training, provides sustained error signals into the retinal, enhance the VN's excitability, and allows control from the cerebellum[14]. The generation of covert catch-up saccades, recorded during video head-impulse test in some patients after unilateral vestibular peripheral pathology, is clinically related to the adaptation of the reflex in high acceleration [22].

Re-weighting of sensory inputs by substitution is another mechanism of brain reorganization. Visual and proprioceptive inputs could remodel neural circuits and the reported increased visual cortical activity provides evidence [23] on that, but could also produce functional deficits always with respect to the environment, as in cases of Postural Perceptual Positional Dizziness (PPPD). In PPPD patients, down-regulation in the vestibular specific cortical area (middle Insular Vestibular Cortex) is accompanied by increased activity in visual cortical areas [24]. In peripheral vestibular lesions [25] a hypermetabolism is reported in ipsilateral multisensory areas (posterior insula, thalamus, anterior cingulate gyrus, hippocampus). Contrary, in central vestibular disorders [23], affecting vestibular nuclei (VN), contralateral brainstem-cerebellar circuits are mainly involved such as medulla, cerebellar peduncles, and hemispheres. Long-term restoration due to sensory substitution, in central vestibular lesions include a decreased metabolism in contralateral cerebellar areas and an increased activity in the visual parieto-occipital area [23]. Structural changes in cortical and subcortical areas are presented in numerous neuroimaging studies. For **unilateral vestibular disorders** (neuritis) in the acute and sub-acute phase persons who compensate well, report changes in resting state activity in the contralateral intraparietal sulcus indicating changes in areas responsible for multisensory integration and spatial orientation, leading to behavioral substitution[20,26] . On the other hand, in chronic unilateral vestibular disorders, neuronal abnormalities in activity and connectivity could be identified in extent neural circuits, including supplementary motor area, right middle occipital gyrus, bilateral superior parietal lobe, left medial superior frontal gyrus, left orbital cingulate gurys, visual and auditory networks, indicating that spatial perception and sensory integration are brain functions affecting the most by the delay of the compensation process [27, 28]. For bilateral vestibulopathy, down-regulation of neural connectivity in rest is reported in the posterior insula and parietal operculum but higher in the posterior cerebellum, as well as significant hippocampal atrophy corresponding to behavioral deficits [29].

One must not forget that compensation is also influenced by the arousal system. Any deviation from homeostasis produces an adaptive stress response in which the hypothalamic-pituitary-adrenal (HPA) axis is activated via the paraventricular nucleus, synthesizing corticotropin-releasing factor (CRF) and arginine vasopressin (AVP), releasing adrenocorticotrophic hormone (ACTH) and consequently glucocorticoids [17]. Glucocorticoids antagonists could slow the compensation process and the long-term activation of the HPA axis could not only down-regulate resting activity of lesioned side VN but also keep levels of brain-histamine high affecting rebalancing of neural circuits [17]. This interconnection of the vestibular system with the extent limbic system's circuits regulate autonomic responses and modify emotions and could enhance stress factors [30]. Stress could be beneficial in the adaptive process but a history of previous stress factors during lifespan could inhibit compensation in dynamic conditions.

All the above evidence refers to dynamic symptoms' restoration, which if it fails or delays, responds not only to a variety of symptoms such as dizziness, blurry vision, unsteadiness, motion discomfort, and fear of movement but also in cognitive impairments, emotion regulation and personality changes in persons with peripheral vestibulopathy. Even if vestibulo-perceptual ability (*in which direction am I moving?*) seems to be fixed, in compensated patients diagnosed with vestibular neuritis, under the influence of a higher cortical network, in contrast to the asymmetry of VOR which remains over time and it is well documented [31], specific cognitive functions (visuospatial ability, mental manipulation, short term memory, path integration) which rely on vestibular inputs, are affected even from the acute phase [32] and continue to be impaired in chronic conditions even if the damage is mild [33]. Persons with Benign Paroxysmal Positional Vertigo (BPPV) cognitive function (mental rotation) is affected, highlighting the direct influence of vestibular processing on perception abilities [34]. Variations in personality traits (depersonalization and derealization) are also documented in peripheral vestibular disorders, enlightening the most awkward of symptoms described during history taking in a neuro-otologic clinic but also the importance of vestibular projections in temporo-parietal junction processing self-motion and self-location abilities [35]. Interestingly, a loss of self- motion sensation is described in patients with acute traumatic brain injury in which BPPV is observed[30]. This loss is accompanied by instability and is described by the term **vestibular agnosia** [3].

The partial or total loss of vestibular function bilaterally, often described as **Bilateral Vestibular Dysfunction** (BVD), is less common than unilateral pathologies with no well-defined causes. Ototoxicity, autoimmune disorders, traumatic brain injury, several ear pathologies (Meneire's disease, vestibular schwannoma, labyrinthitis) neurodegenerative disorders, genetic abnormalities and several syndromes are some of the etiologies of BVD [36]. The main diagnostic criterion is the bilaterally partial or complete absent of Vestibular Ocular reflex (gain <0.4) and the leading symptoms is the unsteadiness which is worsened during head movements, the dark and the uneven surfaces and the induced oscillopsia during locomotion [37]. The compensation process in BVD in also not well documented. Cats with bilateral labyrinthectomy exhibited rapid improvement in their postural control at the first ten days of the lesion, nevertheless notably postural impairments were recorded [38]. It is obvious that eye movements related to vestibular function are permanently diminished, even if exposure to moving visual stimuli could be retained them in a small degree [39]. Surprisingly, in animals with bilateral loss of vestibular inputs, spontaneous responses of vestibular nucleus neurons to vertical tilt rotations were reported seven days after the damage [40]. An explanation of the above observations is the effect that somatosensory and visceral inputs have on vestibular nuclei, which substitute for the lost vestibular stimuli [41]. Diminished spatial memory is one of the most profound disabilities recorded in bilaterally deafferented animals which does not improve with time [42]. In humans, as we have already mentioned, spatial abilities are significantly affected and they are strongly correlated with a decrease of the grey matter in the hippocampus [29,43]. In addition to visuospatial handicap, people with BVD reports deficits on memory, attention and executive function [44].

Static Deficits	Dynamic Deficits	Cognitive Impairment
Spontaneous nystagmus – Oscillopsia	Dizziness - Blurred vision - Lightheadedness - Motion Discomfort	Increased Reaction Time – Rapid Visual processing – Working memory
Vertigo	Unsteadiness - Disorientation - Difficulty walking on uneven surfaces	Visual-spatial ability – Executive function – Dual task execution
Nausea – Vomiting	Falls - Tendency to Fall - Fear of falling	Disruptions in Navigation – Perception – Egocentric/allocentric reference of frame
Excessive stress	Difficulties in transportation / at work – Inhibit social interaction	Depersonalization/Derealization

Table 1: Spectrum of deficits described by persons with peripheral vestibular damage reflecting the plethora of neural structures affected in several different brain regions. Compensation mechanisms, as time passes by, try to balance the mentioned abnormalities. Do they manage it successfully and simultaneously for all?

But is there any cost for successful compensation? In a recently published paper [45], a consortium of European researchers supports the scientific hypothesis, based on the finite of the brain's cognitive capacity, in which when cognitive resources are used for a successful postural control there will be a limitation in the resources used for other cognitive tasks. This model (Kahneman's Capacity Model of Attention) is supported by preliminary evidence from a pilot study [46] in which patients in different compensatory levels (n=12 well compensated; n=3 not well compensated) demonstrate differences in the reaction time while simultaneously performing a postural task. Furthermore, recent studies in animals upon VOR are revealing that compensation and adaptation processes share overlapping neural circuits (at least by 50%) but there is definitely a decrease in terms of VOR gain after an injury [20]. It should be examined whether these anticipatory actions of the CNS after damage, inevitably inhibit some other specific functions relying on vestibular processing and if so, which are the factors for prioritizing one ability over the other.

In the current thesis, cognitive function in persons with peripheral vestibular disorders is investigated and results are presented with respect to a) correlations between functional gait and cognitive parameters as measured by the commonest and widely used functional outcome measures, and b) significant prognostic factors of functional gait variability and high risk of falling.

2. Can Vigilance Predict the Status of Safe Functional Gait and Risk of Falls in Patients with Peripheral Vestibular Disorders? A Cross-Sectional Study.

2.1. Abstract

Objectives: Peripheral vestibular disorders except from reflexes dysfunction correspond also to cognitive decline. The objectives of this cross-sectional study were to a) identify correlations among variables of functional gait, cognitive function, and perceived dizziness and b) explore variables that could be used as prognostic factors of functional gait in people with peripheral vestibular deficits.

Methods: We recruited 151 people with peripheral vestibular deficits. The participants presented with moderate disability in terms of the Dizziness Handicap Inventory questionnaire (mean: 48.71, 95% confidence interval: 45.90 – 51.52), deficits in the Functional Gait Assessment test (mean: 22.78, 95% confidence interval: 22.12 – 23.44) and indication of mild cognitive impairment based on Montreal Cognitive Assessment tool (mean: 25.13, 95% confidence interval: 24.68 – 25.59).

Results: Statistically significant correlations were found among functional gait and gender, age, educational level, perceived level of disability and the total score of the Montreal Cognitive Assessment tool. Several components of the cognitive screening test (executive function, vigilance, language skills, verbal fluency) also correlated statistically significant with functional gait. Linear regression models revealed that age, perceived level of disability and vigilance significantly predicted functional gait variability (R^2=0.338; p<0.001) as well as high risk of falling, as indicated by a score on Functional Gait Assessment test <22/30 (R^2=0.362; p<0.001).

Conclusions: Cognitive impairments affect functional gait in people with peripheral vestibular disorders. Thus, the integration of cognitive functional assessment must be considered as a prerequisite for functional assessment and designing rehabilitation programs that will include dual task training.

Keywords: attention, balance, cognition, gait, vestibular

Abbreviations:

ATM: Alternating Trail Making

BVH: Bilateral Vestibular Hypofunction

CANTAB: Cambridge Neuropsychological Test Automated Battery

DHI: Dizziness Handicap Inventory

FGA: Functional Gait Assessment

MoCA: Montreal Cognitive Assessment

PUVD: Peripheral Unilateral Vestibular Hypofunction,

rBPPV: recurrent Benign Paroxysmal Positional Vertigo

VM: Vestibular Migraine

2.2. Introduction

The clinical management of patients with peripheral vestibular disorders is generally considered a challenge in primary healthcare. In addition to the symptoms related to the vestibulo-ocular and vestibulo-spinal reflexes, the potential effect of the vestibular system dysfunction on cognition has recently emerged, especially with regards to visual-spatial ability [47], cognitive processing [48] and executive function [49].

Patients with peripheral vestibular disorders have 8-fold increased odds of experiencing severe concentration difficulties and 4-fold increased odds of being socially inactive due to memory difficulties [50]. Their stress levels are also higher than expected since there are indications that overlapping neural networks are affected[5,51]. Peripheral vestibular disorders may also lead to cognitive deficits even in individuals who appear to be well compensated[6,52], while the side of the lesion and symptoms duration do not seem to be important [53]. In addition, there growing evidence that the vestibular stimulus detecting head acceleration, contributes to the sense of self [35], the representation of self-consciousness[54,55] and the perception of self-motion[56,57]. Similarly, gait abnormalities are more common in people with mild cognitive impairment [58] and various types of dementia [59,60] at a significant level, while elderly with cognitive impairment are at high risk of falls [61]. In patients with cognitive deficits, crucial equilibrium parameters are affected, such as reaction time and increased postural sway, which are considered to increase the risk of recurrent falls [62]. The socioeconomic impact of falls is well documented [63,64] and is currently one of the priorities in planning healthcare policies [65,66].

Several methods have been proposed for the evaluation of cognitive function. The Montreal Cognitive Assessment tool (MoCA) [67] is one of the most widely used tools for screening cognitive deficits. It examines several cognitive variables, such as executive function, visual-spatial ability, memory, attention, abstraction and orientation. Recently, the MoCA tool has been used in several trials investigating the contribution of the vestibular system to cognitive function. Two of these studies presented the positive effect of vestibular training in cognitive function, as measured by the MoCA tool, in people with cognitive impairment[68,69]. The third study revealed the correlations between cognitive variables measured by the MoCA tool and symptoms of dizziness and instability in patients with chronic peripheral vestibulopathy . In that study, severe symptoms of dizziness and poorer executive function makes patients to sway more during standing balance tests and have lower step length and gait speed during gait[70]. However, in those studies, the sample size was too small for drawing robust conclusions. To the best our knowledge, it is as yet known which of the categories of MoCA tool are correlated with gait instability, a factor leading to an increased risk of falls, present in populations with vestibular pathologies.

The overall aim of the study was the correlation of cognitive function using MOCA, and gait, as measured by Functional Gait Assessment test. The objectives of this study were: a) to identify possible correlations between MoCA's categories and functional gait assessment in patients with peripheral vestibular deficits, and b) the identification of possible prognostic value of demographics, cognitive function, and perceived dizziness in gait disturbances in people with peripheral vestibular dysfunctions.

2.3. Methods

We used the MoCA questionnaire to examine the correlation between functional gait and cognitive function parameters in the study population. The study received approval by the Hippocration Hospital's Ethics Committee (Registered #2657). All recruited participants were initially referred for vestibular rehabilitation to the neuro-otologic clinic of the Hospital Department of Otorhinolaryngology, Head and Neck Surgery, between 1/1/2020 and 31/06/2022. They were informed by clinical experts about the scope of the study and signed a detailed consent form. The inclusion criteria were: i) a diagnosis of a sub-acute or chronic peripheral vestibular dysfunction described as ongoing unsteadiness for more than two months, a score on the Functional Gait Assessment (FGA) test and Dizziness Handicap Inventory (DHI) questionnaire, ii) age (18 - 80 years old) and iii) fluent Greek speakers. Patients with the diagnosis of central vestibular disorder, apart from vestibular migraine were excluded.

The participants were referred for vestibular rehabilitation after a thorough examination which included a detailed history, a clinical neuro-otologic examination, audiometry testing and electronystagmography during which a peripheral vestibular disorder was confirmed. During their baseline physiotherapy assessment, the severity of symptoms was evaluated based on the DHI questionnaire [71] functional gait was assessed on FGA [72], and cognitive function based on the MoCA questionnaire. The first two assessment tools were reported by a senior specialist physiotherapist experienced in vestibular disorders, while the MoCA tool was performed by a certified psychologist.

The DHI questionnaire was developed to quantify the impact and severity of dizziness on participants daily activities. In its final form [73], it consists of twenty-five questions, divided in three subscales, with values ranging from zero to 100. The higher the score, the greater the disability [74].

The FGA test included ten progressively demanding gait tasks with each task was scored from zero to three, with zero indicating maximum impairment [75]. A score less than 22/30 indicated a high risk of falls with excellent sensitivity [72] whereas in the Greek population, it shows a moderately negative correlation with the DHI[26].

The MoCA is a neuropsychological tool for detecting mild cognitive impairment [76]. It consists of 11 domains including 30 questions with the maximum possible score of 30. For less than 12 years of educational training, one point is added to the final score. Several cognitive categories were assessed including visual-spatial ability, executive function, memory and attention, delayed recall and orientation. The cut-off point for the detection of mild cognitive impairment was <26/30 [77] or above. This test seems to prevail as a neuropsychological tool over other similar methods [78].

2.4. Statistical Analysis

Descriptive analysis was performed, reporting demographic data, self-perceived handicap, functional gait and cognitive function. Pearson correlation r was used to explore bivariate correlations. Logistic regression models were constructed to predict functional gait assessment scores based on values of cognitive function, perceived dizziness and participants demographics. The statistical analyses were performed on SPSS software, version 28 for Windows.

2.5. Results

In total, 151 participants were voluntarily enrolled in the study who met the inclusion criteria. There were 103 women and 48 men, with the average age of 55.78 (min:22, max:79). Most patients had a non-compensated unilateral peripheral vestibular hypofunction (UPVH; n = 78), followed by patients with vestibular migraine (VM; n = 27), recurrent episodes of benign paroxysmal positional vertigo (BPPV; n=25), and Meniere's syndrome (n = 21). The median duration of symptoms was six months (min: 2, max: 360 months). Mean years of education was 14.06. The participants presented with moderate disability in terms of subjective perception of dizziness (mean DHI score: 48.71; 95% CI:45.90-51.52), deficits in functional gait (mean FGA score: 22,78; 95% CI:22.12–23.44) and signs of mild cognitive impairment according to their MoCA score (mean score: 25.13; 95% CI:24.68–25.59). The participants characteristics are presented in Table 2. Indications for mild cognitive impairment, based on the MoCA tool (score <26/30) had 78 (51.65%) of the participants. This subgroup also had moderate dizziness (DHI mean:50.64, 95%CI:46.49-54.78) and indications of high risk of falls (FGA mean: 21.65 5%CI:20.75-22.55). The descriptive analysis of the MoCA scores has been presented in Table 3 for each of the subcategories. It is worth pointing out that 104 participants (68.87%) failed the cube representation task in the MoCA test.

Statistically significant correlations were found between functional gait, as measured by FGA, and gender (r = 0.208; p=0.01), age (r = -0.485; p < 0.001), educational level (r = 0.266; p=0.001), self-perceived handicap as measured by DHI (r = - 0.2; p = 0.01) and total MoCA score (r = 0.3; p< 0.001). Statistically significant correlations were also noted between FGA sore and several of MoCA’s items, as presented in Table 4.

A multiple linear regression model was used to test if age, perceived symptoms of dizziness and vigilance significantly predicted functional gait. Functional gait in the participants was found equal to 29.087 – 0.14 (age) – 0.05 (DHI) + 4.149 (Vigilance). The overall regression was statistically significant [$R^2 = 0.338$, F (3) = 24.722, p <0.001]. It was found that age (β = - 0.14; 95% CI: -0.178 to -0.102; p < 0.001), DHI (β = -0.05; 95% CI: -0.082 - -0,024; p < 0.001) and vigilance (β = 4.149; 95% CI:1.780 – 6.517; p <0.001) significantly predicted functional gait.

Furthermore, binary logistic regression was also used, revealing that age, self-perceived handicap, as measured by DHI, and vigilance were significant predictors of high risk of falls, as indicated by a score on FGA <22/30, (x^2=45,020 df=3 <0.001), All three predictors explained 36,2% of variance in the cut-off point of FGA and correctly classified an overall 74.5% of the cases (56% at high risk of falling and 83.8% not at high risk of falling). Increasing age and scores in DHI questionnaire were associated with an increased likehood of having a FGA score >22/30. Surprisingly, succeeding in the vigilance subcategory of MoCA test was associated with 6.2 more times for participants to have a FGA score >22/30.

2.6. Discussion

This study aimed to assess and correlate functional gait with cognitive deficits and level of disability of people with peripheral vestibular disorders using common and easy-to-use outcome measures. The rationale for this study was to explore which of the cognitive domains, as examined by the MoCA tool, can be related to functional gait and whether prognostic models of functional gait could include some of these domains. It is known that executive function, which can be assessed by the MoCA, is correlated with the risk of falls [79,80]. It is also known that measures that enhance an individual's cognitive reserve, are associated with executive function[81,82]. Our study, provide evidence of statistically significant correlations between functional gait and demographic data (gender, age, educational level), perceived level of disability and total score of MoCA test. Statistically significant correlations are also seen between certain MoCA's subcategories (such as executive function, conceptualization, vigilance, language skills and verbal fluency) and functional gait. We also provide evidence that age, perceived level of disability and speed of response in letter A tapping test (vigilance) are statistically significant predictors of variability of functional gait in total and as an indication of risk of falling. Nevertheless, correlations were mild to moderate, and the models predicted 33,8% of the variance in FGA and 36,2% of score variability if a cut-off point for increased risk of falls is implemented.

Cognitive reserve is a concept proposed to explain identified discrepancies between the extent of mental and cognitive dysfunction, and relevant manifestations[83,84]. The theory of cognitive reserve attempts to explain how people with similar pathology may experience different range and severity of symptoms [85,86]. According to this hypothesis, certain individuals apply a set of pre-existing cognitive skills and compensatory mechanisms, by activating different neural circuits to perform a specific task.

This may decrease symptoms and may delay the onset of clinical signs of cognitive decline [85]. Executive function enables different cognitive abilities such as attention [87], working memory, inhibition, shifting and fluency [88] which correspond to adaptation throughout lifespan. This ability is crucial for safe decision making with respect to equilibrium and thus decline in executive function and attention increase the odds of falling, even years before the event. The relationship between cognitive reserve and executive function remains strong during advanced ages [89].

Both cognitive decline and vestibular dysfunction correlate with age [80]. Recent research endorses a direct rather than secondary correlation between cognition and postural control[62,90]. Short-term decline in visual-spatial skills is affected by vestibular dysfunction[4] regardless of sleep and comorbid mental disorders [91] and compensation [46], explaining dysfunctions in specific anatomical structures and neural circuits in the hippocampal area [43]. Difficulty in retrieving words is also described as a deficiency in people who have received vestibylotoxic treatment with gentamycin [92]. Moreover, vestibular information is necessary for orientation, especially when attention is required [93]. Postural control depends upon attentional demands [48], as in a dual task condition. Attention is related to walking especially when cognitive demands are increasing [94]. Vestibular dysfunction appears to lead to concentration deficits[4] although the results so far are not robust [95]. Correlations were observed in our study between functional gait and MoCA's components of sustained attention, language skills and verbal fluency support all the above evidence. Functional gait also correlated with educational level. A recent study reveals that lower education is associated with greater gait speed decline [96]. The educational level is considered as one of the most important socio-economic factors for the risk of falls [97]. A recent review indicates that more years of educational training are associated with better performance in cognitive assessments, memory and executive functions [98]. Evidence correlating functional gait and vestibular deficits are well documented [47, 99, 100], thus well-structured measures, such as FGA, are included in clinical guidelines [101.]

It is well known that postural control is adapted to daily cognitive tasks and gives priority to either the balance [102, 103] or cognitive loads [104] depending on the condition. In the elderly, increased cognitive loads may lead to reduced postural stability, especially in those at risk of falls [105,106]. Falls are highly associated with cognitive deficits and differences in gait parameters predetermining different mechanisms that lead to falls between healthy individuals and those with mild cognitive impairment [107,108]. In the present study, correlations between functional gait and age, level of disability and sustained attention have been observed. Based on our results, future studies could investigate the hypothesis in which people with reduced ability to sustain attention, fail to prioritize postural control upon cognitive tasks, especially in rapidly changing dynamic conditions such as locomotion, thus increasing the risk of falls.

Even though statistically significant differences occurred amongst gait, cognition, levels of disability and age, the clinical importance of results remains to be confirmed. Screening of cognitive function must be integrated in functional assessment procedure of people with vestibular disorders. This can provide clinicians with important information upon cognitive functions related to vestibular function, which can affect management and prescription of therapeutic exercises (type, volume, intensity of dual-task exercises, optimal time for integration into a rehabilitation protocol). In our study sample, 51.65% of participants with a mean age of 60 years, had indications of mild cognitive impairment (MoCA <26/30). We cannot not conclude whether these indications of cognitive decline were mainly due to vestibular pathology. We can emphasize the fact that degeneration of vestibular system practically starts at the age of 50 years old and affects signal processing in neural circuits to which vestibular inputs are projected [109]. However, based on our results, MoCA test may not be the optimal solution for people with peripheral vestibular pathologies. The MoCA overall score is poorly correlated with FGA, a dynamic test which is strongly recommended as an outcome measure in vestibular[61] and neurological assessment [110]. Only one feature of MoCA's test (vigilance) is included as significant predictor of FGA's score variance and linear models fail to largely explain such a complex phenomenon as postural instability, which requires multiple sensory integration. Moreover, adjusting the MoCA score to the individual's educational level may negatively affect the sensitivity in this population as is already indicated [111], while the overall MOCA score may be affected by education and nationality [112]. In any case, MoCA tool may be suboptimal to draw reliable conclusions [113], since it is used for screening mild cognitive decline and is not designed to establish a clinical diagnosis. Therefore, more sensitive and standardized tools, such as Cambridge neuropsychological test automated battery (CANTAB) [114] may provide more reliable clinical information but cost could be prohibitive for everyday clinical practice. The development of measures that realistically assess locomotion, involving cognitive tasks representing real human thinking and "actual" cognitive reserve remains a challenge. The newly introduced by the WHO concept of intrinsic capacity (IC) aims to connect person's functional abilities, including five subdomains, vitality, locomotor, visual, hearing, psychological and cognitive capacity [115]. So far, published data are not adequate for clinical implementation however the existence of a common variable that probably determines a person's overall health status could be established soon. Personality characteristics (age, sex, education and wealth) seems to affect ability for daily activities and independent living via the IC model [116]. This factor will contribute significantly towards a more holistic approach and could be implemented in population of interest. Nevertheless, we propose a closer collaboration between cognitive neuroscientists and clinicians in the future, towards a targeted monitoring of cognitive deficits in vestibular pathologies, leading to optimization of health services. Until then, using MoCA tool as part of functional assessment in vestibular disorders is the best available solution.

2.7. Conclusion

In this study, we assessed aspects of cognition, self-perceived handicap and functional gait of people with peripheral vestibular disorders and investigated their correlations. We also proposed prognostic models on how functional gait, could be affected by age, perceived level of disability and vigilance. We also hypothesized that sustained attention, could prioritize cognitive tasks against dynamic postural control, thus affecting functional gait variability and the risk of falls. Inclusion of a cognitive screening test in baseline assessment of people with symptoms of vestibular dysfunction could be considered beneficial, although may not be a strong predictor of gait disturbances. Hence, the way this factor could be considered during functional assessment and in the development of a rehabilitation program remains a challenge, especially in prescribing of dual and/or multiple task. Development of more sensitive neuropsychological tools will lead to better understanding of the link between cognition and equilibrium under more realistic conditions and will offer more effective and targeted therapies.

2.8. Tables

Participants Characteristics	Value
Gender n(%)	
Male	48 (31.5%)
Female	103 (68.5%)
Age (years) mean;95%CI	55.78; 53.48-58.07
Education (years) mean;95%CI	14.06; 13.43-14.70
Duration of symptoms (months) median	6
Diagnosis n(%)	
PUVH	78 (51.7%)
VM	27 (17.9%)
rBPPV	25 (16.6%)
Meniere's disease	21 (13.8%)
DHI mean;95%CI	48.71; 45.90-51.52
FGA mean;95%CI	22.78; 22.12-23.44
MoCA mean;95%CI	25.13; 24.68-25.59

Table 2: Participants characteristics. Abbrevations: PUVD: Peripheral Unilateral Vestibular Hypofunction, VM: Vestibular Migraine, rBPPV: recurrent Benign Paroxysmal Positional Vertigo, BVH: Bilateral Vestibular Hypofunction, DHI:Dizziness Handicap Inventory, FGA:Functional Gait Assessment, MoCA: Montreal Cognitive Assessment

	Min	Max	Mean	95% Confidence Interval	
				Lower	Upper
ATM_MoCA	0.00	1.00	,7616	,6928	,8303
Cube_MoCA	0.00	1.00	,3113	,2366	,3860
Clock_Total_MoCA	1.00	3.00	2,6954	2,6063	2,7844
Visuospatial/Executive_MoCA	1.00	5.00	3,7682	3,6263	3,9102
Naming_MoCA	2.00	3.00	2,9139	2,8687	2,9592
Digit_Span_MoCA	1.00	2.00	1,8212	1,7594	1,8830
Vigilance_MoCA	0.00	1.00	,9470	,9109	,9832
Serial7_MoCA	0.00	3.00	2,6689	2,5643	2,7734
Language_MoCA	0.00	2.00	1,3046	1,1829	1,4264
Verbal_Fluency_MoCA	0.00	1.00	,5497	,4694	,6299
Abstraction_MoCA	0.00	2.00	1,6954	1,6083	1,7824
Recall_Total_MoCA	0.00	5.00	3,2252	2,9984	3,4519
Orientation_MoCA	5.00	6.00	5,9536	5,9197	5,9876

Table 3: Descriptive analysis for the score in each of MoCA's subcategory for all participants (Abbreviations: MoCA: Montreal Cognitive Assessment, ATM: Alternating Trail Making)

	ATM	Cube	CLOCK_Total	Visuospatial/Executive	Naming	Digit_Span	Vigilance	Serial7	Language	Verbal_Fluency	Abstraction	Recall_Total	Orientation
FGA	,149	,028	,168*	,188*	,014	,102	,233**	,148	,225**	,320**	,112	,059	,107
p value	,009	,739	,04	,02	,869	,216	,004	,071	,006	<,001	,138	,475	,192

Table 4: Correlations of FGA with each of MoCA's MoCA's subcategory for all participants (Abbreviations: MoCA: Montreal Cognitive Assessment, ATM: Alternating Trail Making, FGA: Functional Gait Assessment)

2.9. Supplementary Material

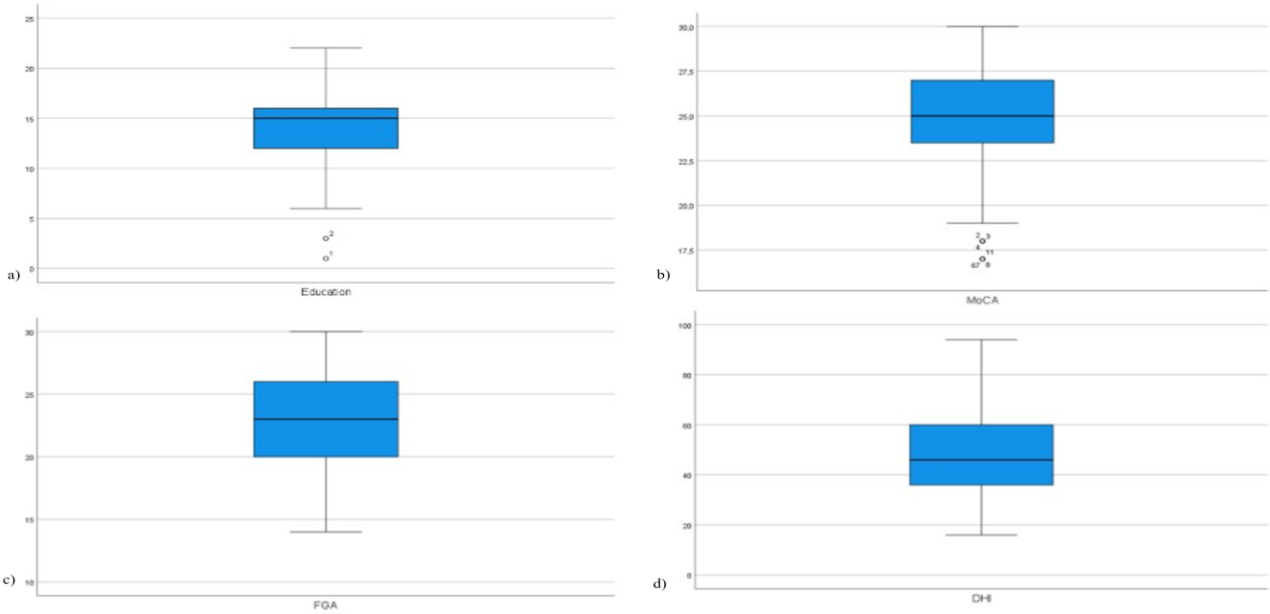

Figure 2: Boxplots of descriptive analysis for the study population. a) Education in years, b) cognitive function as measured by MoCA tool, c) functional gait as measured by FGA, d) perceived level of disability as measured by DHI. Abbreviations: DHI: Dizziness Handicap Inventory, FGA: Functional Gait Assessment, MoCA: Montreal Cognitive Assessment.

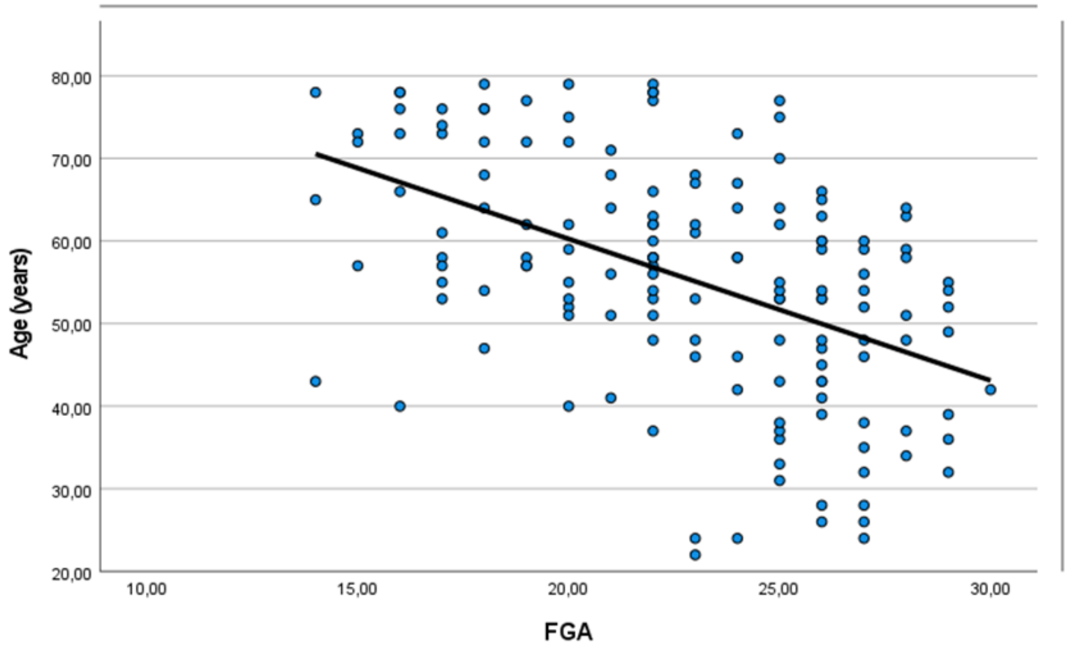

Figure 3: Partial Regression plot of FGA adjusted by age (years). Abbreviations: FGA : Functional Gait Assessment.

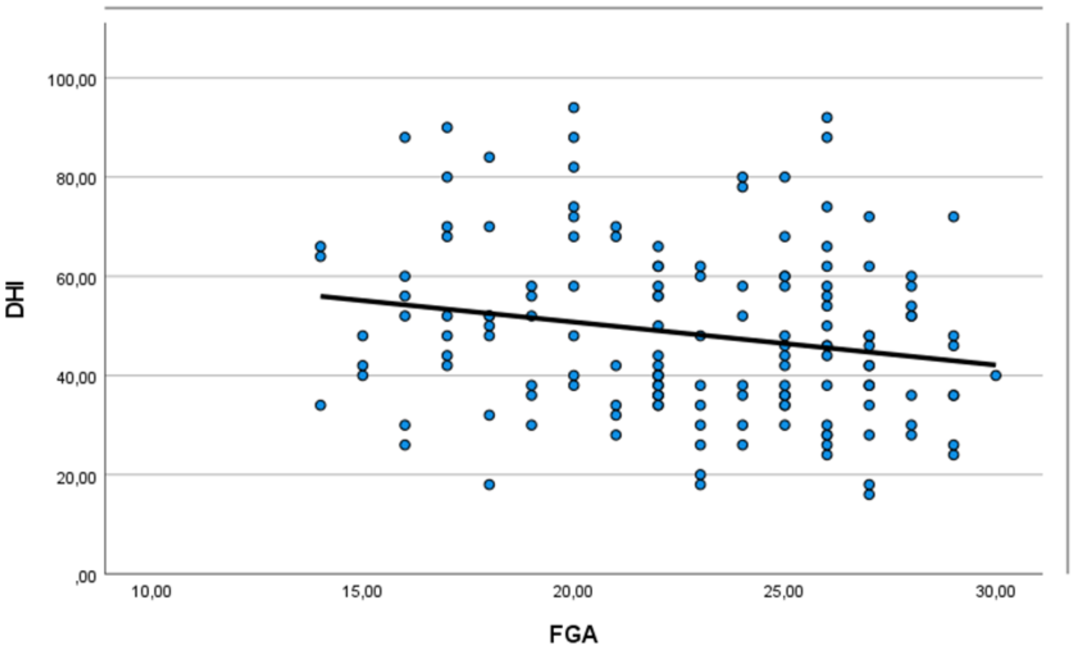

Figure 4: Partial Regression plot of FGA adjusted by DHI. Abbreviations: FGA : Functional Gait Assessment, DHI : Dizziness Handicap Inventory.

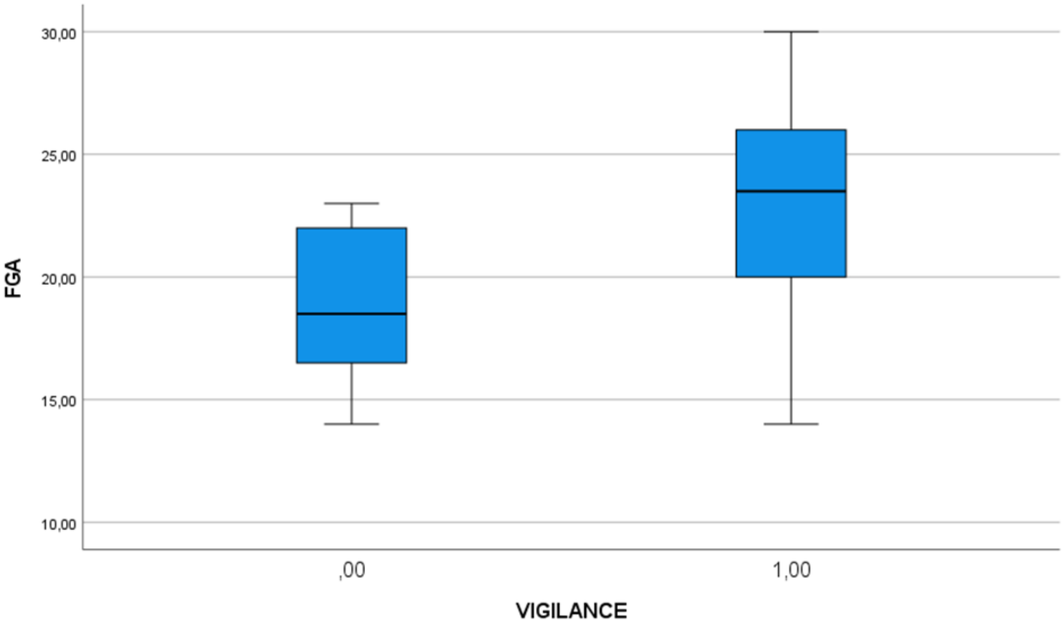

Figure 5: Boxplot of FGA adjusted by Vigilance. Abbreviation: FGA: Functional Gait Assessment.

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The data of the published study could be retrieved from the link below: osf.io/fm3gs.

3. Vestibular Rehabilitation Treatment: Evidence and Future Perspectives

As we already mentioned in the first chapter, homeostasis imbalance in the vestibular system may be due to an increase in entropy, as a consequence of age [109,117], and/or to iatrogenic factors, infections, trauma, and neurodegenerative diseases. Vestibular Compensation is the natural process that Central Nervous System mobilizes (modulation in neurons excitability and neurogenesis process in the vestibular nucleus, adaptation and substitution process in sub-cortical and cortical levels) to cope with vestibular disturbances in the acute and subacute phase. Nevertheless, as already mentioned, this process has a cost that in the most reported, recorded and studied cases in relation to dynamic symptoms such as oscillopsia, dizziness, unsteadiness, disequilibrium, gait instability, lightheadedness, motion discomfort, impaired orientation, and navigation as well as several vestibulo-cognitive functions. These symptoms are reported by people suffering from a vestibular disorder after the acute phase of the disease (approximately 14 days) affecting their ability to work, their daily activities, their social life and their overall quality of life contributing to an overall disability [118] [119] [120]. But the most severe consequence of vestibular disorders are falls which are a pandemic for people over 65 years of age.

Vestibular vertigo in the general European adult population is generally underestimated as evidence [120]indicates one-year prevalence of 5%. A survey on an entire European population [121] indicates a prevalence of 6.5%, with women and older adults <75 years old being affected the most. Moreover, falls are the second leading cause of accidental death with an additional enormous economic cost for non-fatal injuries [122]. World Health Organization has recently reported that 1 out of 3 people older than 65 years old fall each year [123]. Vestibular deficits are diagnosed in most fallers, since 80% of the adults with an unexpected fall have a history of an inner ear pathology affecting postural control [124]. Benign Paroxysmal Positional Vertigo (BPPV), Vestibular Migraine (VM), Meniere's disease, Vestibular Neuritis are the commonest of the incidences in specialized units [125, 126]. Underestimated and undiagnosed cases as well as insufficient management are reflecting upon patients attitudes [127] enlightening the main deficits of a neuro-otologic clinic which, to a certain extent is due to the insufficient training of the health professionals providing therapeutic interventions for the management of peripheral vestibular disorders [128].

The effectiveness of movement under the supervision of a health professional and within the framework of a therapeutic exercise protocol, generally called Vestibular Rehabilitation Treatment

(VRT), is very well documented as the safest and most efficient treatment in uncompensated vestibular disorders [129, 130, 131]. The scope of VRT is to accelerate the natural process of vestibular compensation [132] under the principle of re-weighting of sensory inputs [133] (**adaptation**, **habituation**, **sensory substitution**, stimulation). In the next paragraphs, we will refer to the qualitative and quantitative methods of recording and reporting the functional disability in vestibular disorders, which are the prerequisites for sufficient clinical decisions with respect to rehabilitation, we will provide the evidence about the effectiveness of VRT in each of the vestibular pathologies that a physiotherapist encounters in a neuro-otologic clinic. We will also elucidate the parameters affecting the effectiveness of the treatment and finally, mention the future perspectives and approaches.

3.1. Assessment of Vestibular Deficits

The use of reliable outcome points is mandatory for effective physiotherapy practice regardless of the pathology examined. It adds reliability to clinical practice and quantifies the severity of pathology, functional limitations as well as the effectiveness of the intervention. Cultural adaptation of the outcome measures is essential for establishing cultural equivalent. For vestibular deficits, this was well documented in two different European countries where urban differences and social cohesion modifies the impact of symptoms on the participants' quality of life [118]. In vestibular assessment, self-report questionnaires reflect better functional handicap compared with physical tests although a combination of the above will provide the most comprehensive clinical information required by the physiotherapist [134] for taking appropriate clinical decisions.

3.2. Early Beginning of Vestibular Rehabilitation Treatment

When should VRT start after a vestibular lesion? A recent animal study provides evidence that starting VRT as quickly as possible allows the development of an additional adaptive mechanism since multisensory training enhance microgliogenesis in the deafferent median vestibular nucleus [135]. In a clinical study on cats, it was observed that the delayed start of movement (up to one month from the onset of lesion) has consequences on the postural control and locomotion performance of the experimental animals [136] underlining the need for Physiotherapists to take advantage of the critical period of reorganization of the of neural circuits from the vestibular nucleus to higher cortical levels. A series of human clinical trials [137, 138, 139] confirm the above findings pointing up improvement in outcome measures regarding severity of symptoms, disability, postural control, gait and quality of life. The use of technology, even if it is low-cost, in the acute phase of vestibular neuritis reduce even the hospitalization time as the patients who didn't use it stayed in the hospital for 2.4 days[25].

3.3. Benign Paroxysmal Positional Vertigo (BPPV)

BPPV is the commonest pathology diagnosed in a neuro-otologic clinic. Two versions of clinical guidelines [140] [141] referred to VRT as an option of adjunctive therapy to canalith repositioning procedures in people with BPPV and high risk of falling, as 75% of older adults with undiagnosed BPPV fell within 3 months prior to referral. Thus, people, especially the elderly, with recurrent episodes of BPPV and balance impairment are ideal candidates for VRT.

3.4. Peripheral Vestibular Hypofunction (PVH)

Two versions of clinical guidelines for PVH have been published in the last six years, providing physiotherapists with recommendations on effectiveness of intervention *per se*, the effectiveness of different forms of VRT, dosage, supervision, decision making, factors that can modify the outcome and harm/benefit ratio [101, 142]. Strong recommendations that VRT is a safe and effective therapeutic approach in acute and subacute phases for unilateral and bilateral lesions - especially for adults over 50 years, which leads people to improve gaze stability, balance, function, quality of life and reduces falls as well as that supervision promotes adherence and improve outcome especially in people with cognitive impairment and moderate mobility disabilities are reported. In the updated version specific recommendations are made regarding optimal dosage on balance and gaze stabilization components of a rehabilitation protocol as presented in Table 5. Factors that potentially modify intervention outcomes and future perspectives will be discussed in the next paragraphs.

3.5. Meniere's Disease (MD)

In the recently published clinical guidelines for the management of MD [143], VRT plays a crucial role in improving postural control, implementing multifactorial rehabilitation exercises in unilateral and bilateral MD patients with incomplete central compensation either due to the nature of the disease or because of specific medical therapy (ablative surgical or medical therapy). Despite the limited evidence, especially for the long-term benefit of the intervention in balance impairment, experts recommend VRT as people with MD are considered at high risk of falling. In the same clinical guidelines, it is recommended not to apply VRT in acute vertigo attacks. Although the evidence on other vestibular pathologies in the acute phase do not agree with this position, the absence of data specific to MD makes experts wary, but in any case, they recommend clinicians regularly monitor symptoms, impairment, including imbalance, and course of the MD disease.

Exercise Module	**Level of Recommendation**	**Recommendations**
Balance Exercises	Weak	20min /day, 4-6 weeks for chronic UVH
	Expert opinion	2-3 balance sessions/day, 6-9 weeks for BVH
	Expert Opinion	Consider dosage in acute/subacute UVH
Gaze Stabilization Exercise	Weak	At least 12min/day in acute UVH
	Weak	3 -5 sessions/day, for at least 20min/day, 4–6 weeks chronic for UVH
	Weak	3 – 5 sessions/day, for at least 20 – 40min/day, 5–7 weeks for BVH

Table 5: Exercise dosage recommendations for Balance and Gaze stability exercises from the updated Clinical Guidelines Vestibular Rehabilitation for Peripheral Vestibular Hypofunction (ref 29).

3.6. Vestibular Migraine (VM)

There are no published clinical guidelines, and a recently published systematic review [144], including six clinical trials, cannot provide conclusive evidence regarding the efficacy of the VRT in patients with VM as the most of trials are at high risk of bias. Nevertheless, all included studies showed improvement in perceived symptoms and postural control. This lack of robust evidence on treatment (physical or pharmacological) strategies is based on the fact that the spectrum of symptoms and different types of the disease, the related comorbidities, and the several pathophysiological mechanisms of VM remain unclear, and that there are no disease-specific outcome measures for quantifying patient's quality of life[145] and consequently the effectiveness of non-pharmacological intervention.

3.7. Factors affecting intervention outcome

Several factors could affect VRT intervention outcomes and especially differences and/or changes in specific outcome measures and perceived patient's disability. Updated clinical guidelines for PVH strictly indicate that age and gender do not affect improvement from intervention and either time of onset, even if early VRT in acute vestibular disorders could lead to a substantial benefit [101]. Moderate evidence presented in the same guidelines suggests that mood and mental disorders, migraine, peripheral neuropathy, and abnormal binocular vision could probably lead to a plateau in the patient's improvement from VRT. The use of optokinetic stimulation seems to overcome this plateau since the optokinetic nystagmus activates larger brain areas compared to smooth pursuit and saccades eyes movements [146]. Repeated visual stimuli extend the frequency bandwidth in which deafferent vestibular nucleus respond [147]. Also inhibits vestibular perception and normal postural sway in young healthy adults [148]. In patients with peripheral vestibular hypofunction and visual dependency (increase of discomfort in busy visual environments) optokinetic stimulation had a better effect on dizziness, postural control and visual dependency [149]. This extra benefit to vestibular recovery is a result of the resolution of visuo-vestibular mismatch, as people decreased their reliance on visual stimuli for postural control. Regardless of the rehabilitation protocols used, supervision is a crucial factor in the intervention's outcome [150]. Even if a systematic review could not provide robust evidence in favor of supervision, data from the inclusive clinical studies show better scores in outcome measures [151]. Advances in technology allow us to monitor our participants via teleconference, sensors, and platforms.

3.8. Future Perspectives

Technology provides a major advantage in several aspects of physical rehabilitation. Clinical guidelines suggest that virtual reality, either high-tech or low-tech, provides better clinical outcomes in people with vestibular disorders, especially when accompanied by head movements. But besides strictly clinical improvement, technology provides better supervision and compliance [101]. A beyond the state-of-the-art digital platform was recently developed by a consortium of universities and companies across Europe, for personalized virtual coaching and motivation in an aging population with balance disorders. This platform (HOLOBalance) creates an augmented reality environment, where participants immerse and interact with a physiotherapist's hologram, which provides four different modules of training (balance exercises, gamified balance exercises, cognitive games, and auditory training) as well as a mobile application for monitoring the levels of physical activity. The main goal of this platform was to integrate low-cost sensors (cell phone, head mounted display, inertia measurement units, insoles, accelerometers, laptops) into a multimodal rehabilitation for increasing distance monitoring, as the platform was installed in participants' houses, enjoyment and adherence but also for enhancing long term behavioral changes in the elderly. Clinical protocol for the feasibility and acceptability of the platform has been already published [152]. In the next chapter, we will demonstrate data from a clinical study investigating the effect of low-cost equipment (Head Mounted Display) on several performance variables used to present therapeutic exercises in the HOLOBalance platform.

4. Head Mounted Display Affects Vestibular Rehabilitation Exercises Performance.

4.1. Abstract

Objectives: Vestibular rehabilitation clinical guidelines document the additional benefit offered by the **Mixed Reality** environments in the reduction of symptoms and the improvement of balance in peripheral vestibular hypofunction. The HOLOBalance platform offers vestibular rehabilitation exercises, in an **Augmented Reality** (AR) environment, projecting them using a low-cost Head Mounted Display. The effect of the AR equipment on performance in three of the commonest vestibular rehabilitation exercises is investigated in this pilot study.

Methods: Twenty-five (25) healthy adults (12/25 women) participated, executing the predetermined exercises with or without wearing the AR equipment.

Results: Statistically significant difference was seen only in the frequency of head movements in the yaw plane during the performance of a vestibular adaptation exercise by healthy adults (decrease of 0.97 Hz; 95% CI = (0.56, 1.39), $p < 0.001$ on the head movement wearing the equipment). In terms of difficulty in exercise execution, the use of the equipment led to statistically significant differences in the vestibular-oculomotor adaptation exercise in the pitch plane (OR = 3.64, 95% CI (-0.22, 7.50), p = 0.049), and in the standing exercise (OR = 28.28. 95% CI (23.6, 32.96), p = 0.0001).

Conclusion: The use of AR equipment in vestibular rehabilitation protocols should be adapted to the clinicians' needs.

Keywords: Augmented Reality, Exercise, Head Mounted Display, Rehabilitation, Vestibular

Abbreviations

AR: Augmented Reality

VRT: Vestibular Rehabilitation Treatment

HMD: Head Mounted Display

DHI: Dizziness Handicap Inventory

VOR: Vestibular Ocular Reflex

vHIT: Video Head Impulse Test

RoMotion: Range of Motion

IMU: Inertia Measurement Units

Hz: Hertz

CoP: Centre of Pressure

4.2. Introduction

As we have already mentioned, peripheral vestibular disorders are common among adults, since their prevalence is as high as 8.4%, with the older population and women predominating [50]. In the First Chapter we discussed in detail the natural process of the Central Nervous System which is starting immediately after peripheral vestibular damage, by activating intrinsic plasticity mechanisms at a molecular and cellular level on the sensory organs and the vestibular nucleus as well as on a variety of neural networks responsible for vestibular processing [9,26], leading to the functional recovery of the vestibular system after a period of time[136]. Moreover, we mentioned that Vestibular Rehabilitation Treatment (VRT) has been evaluated as the optimal treatment for people with uncompensated symptoms of dizziness and imbalance due to peripheral vestibular disorders [130,132,142]. Its main objectives include the promotion of vestibular compensation and re-weighting of sensory inputs (reliable sensory inputs gain "weight" during postural control, suppressing the possible sensory mismatch [153, 154]), leading to reduced symptom intensity and duration as well as the risk of falls [130, 132, 142]. Systematic reviews [130,132] provide moderate to strong evidence supporting the effectiveness of this intervention and recent clinical guidelines [142] provide clinicians with a high degree of evidence-based recommendations for home-based treatment. The effectiveness of vestibular rehabilitation seems to be affected by age, physical inactivity, visual deficits, medication as well as psychological factors [155, 156]. This reflects to necessary modifications of the intervention protocol based on patients' profile without deviating from its basic principles [157].

Supervision of VRT programs may have an additional positive effect compared to that of the exercises toward clinical improvement, however, the relevant evidence remains weak [151]. Hence, without the appropriate guidance and feedback from a specialized physiotherapist, patients often do not follow the instructions correctly, which results in inadequate improvement and symptom prolongation [158]. Indeed, time exclusivity, positive feedback, motivation, test-retest in standardized measures, proper clinical reasoning, and opportunity for real-time correction of exercise performance are beneficial for performance and adherence[15]. Supervision promotes compliance and clinical improvement. Conversely, lack of supervision increases the dropout rate from the program [142, 159].

Rehabilitation in mixed reality environments with the use of high-end technology is a novel therapeutic option with promising results. Immersive reality vestibular rehabilitation has been used in people suffering from vestibular disorders with reported benefits on perceived handicap and minimum side effects [160, 161]. The use of augmented reality and holograms in a beyond-the-state-of-the-art, multi-modal platform has recently become available, offering a holistic solution with respect to motivation, monitoring, and supervision for people with vestibular disorders and/or the risk of falling [152]. Recently, the HOLOBalance platform has been equipped with a real-time motion capture system for assessing the balance exercises, included in its flowchart, providing accuracy for assessing the frequency of head rotations and head's range of motion (RoMotion) in yaw and pitch plane, posture assessment and gait analysis [162].

The Head Mounted Display (HMD) is the mandatory equipment for successful immersion in simulated environments and is commonly used in mixed reality applications[163] for medical training and education[164,165], as well as in interventions including those for balance disorders [166,167]. Recent technological advantages introduced to the medical market a series of low-cost and reliable HMD solutions allowing easier and more accurate application in rehabilitation with the implementation of a head device and a mobile phone. However, the effect of using such a low-cost HMD on the performance of vestibular rehabilitation exercises remains unclear, even though there have been studies reporting successful transfer of improved motor skills to real-life or other type environments after HMD facilitated virtual reality based training [168,169].

This pilot study aims to investigate the effect of a low-cost HMD on the performance of therapeutic exercises specifically designed for the improvement of perceived handicap and disequilibrium in the context of Vestibular Rehabilitation.

4.3. Methods

4.3.1. Population

This is a pilot study of healthy adults (n=25; 12 women) aged from 18 – 50 years old, recruited in the tertiary neuro-otologic clinic of 1st Department of Otorhinolaryngology, Head and Neck Surgery, at Hippocration Hospital, Athens, Greece. Approval obtained by the Ethics Committee of the Hippocration Athens Hospital was obtained (39444/16-3-2021). The age threshold was set to avoid any age-related degeneration of the peripheral vestibular system. The sample size was in line with similar clinical trials [148].

Participants were informed about the study through a leaflet and verbal communication by the researchers. Inclusion criteria for the study were a) absence of a history of a peripheral, central, or mixed vestibular disorder, b) absence of perceived symptoms related to vestibular pathology spectrum c) normal Dizziness Handicap Inventory [71] questionnaire score (DHI < 6), d) normal values for the Vestibular Ocular Reflex (VOR) gain in video-Head Impulse (v-HIT) tested in the horizontal plane, (EyeSeeCam v.1.3, gain between 0.8 and 1.2) e) no history of a severe musculoskeletal injury and f) absence of a history of any systematic rheumatic disease or any cardiovascular disease. Lack of the ability to understand the Greek language for the proper and full completion of the study's outcome measures were considered exclusion criteria.

4.3.2. Procedure

Before the baseline assessment, the participants were informed, via an informative leaflet and by the researchers, about the study and a consent form was signed. A short clinical interview was then conducted and demographic information (gender, age, educational level, body mass index) physical activity levels, history of any visual disorders, and any musculoskeletal symptoms were recorded. Subjects completed the DHI and had the VOR tested in a yaw plane with the EyeSeeCam v.1.3. The total DHI questionnaire score and horizontal VOR gain on the left and right were also recorded. After a fifteen-minute's break the subject was transferred to a dedicated room where the augmented reality platform was set up. Three different exercises were performed, two in a sitting position related to VOR adaptation 's principle and one in standing related to sensory substitution's principle. In the sitting position, participants had to focus on a target at eye level, moving their head horizontally (VOR adaptation exercise in the yaw plane) or vertically (VOR adaptation exercise in the pitch plane), respectively, and in the standing position, participants had to stand with their eyes closed and feet close together on a foam (standing exercise). These exercises are the most used in a prescribed vestibular rehabilitation protocol and were fully described, configured, and included in the exercise flowchart implemented on the HOLOBalance platform [152 162]. The HOLOBalance platform was created to integrate evidence-based multisensory rehabilitation exercises into an augmented reality (AR) environment. Among the plethora of functional balance training exercises, their gamified variations, and motor-cognitive exercises, the three exercises mentioned above were also included. Details of the clinical protocol investigating the feasibility and acceptability of the system have already been published [162]. Prior to the experiment a demonstration of all the exercises (*pre-test phase*) was held and the participants were asked to perform them, and an agreement was made between clinicians and participants upon execution to avoid any errors due to limited understanding. A steady armless chair was used for the sitting exercises and a foam pad (Airex Balance Pad, 16" x 20" x 2.5") for the standing position exercise. The monitoring system of the platform consisted of two Inertia Measurement Units (IMU) sensors (MBinetLab MMR-METAMOTIONR), placed on the head and pelvis of the participants respectively. The IMU on the head recorded frequency, in Hertz (Hz), and RoMotion, in degrees, of the head's movement either on the yaw or pitch plane. The IMU on the pelvis recorded anteroposterior (frontal plane) and mediolateral (sagittal plane) sway of Centre of Pressure (CoP) displacement, measured on degrees. Data were stored in an edge computer anonymously and extracted via the HOLOBalance interface. The order of the executed exercises remained the same in all cases, but every participant performed the exercises in two different randomly selected conditions. Randomization was exported by a computed generated sequence. Two different experimental conditions were tested, before and after wearing the low-cost equipment used to create an AR environment. *Before* is referring to the implementation of an IMU with velcro on the head of the participant with no extra weight of the HMD and the mobile phone, and *After* to the implementation of the head's IMU via the HMD (Docooler AR Headset Box Glasses 3D Holographic Hologram Display Holographic Projector for Smart Phones) with the adjustment of a mobile phone (Google Pixel 3) used for the creation of AR environments which was switched-off, which means that no AR environment was projected. The duration of each exercise was one minute. Between each one of the exercises, there was one minute rest time. Between the pre-test phase and the actual experiment and between experimental conditions the participants had a fifteen minute break. Oral pre-recorder instructions of the exercises were provided by an avatar projected in a 2x2x2 meter box, placed behind the participants so they were able to clearly hear the instructions but not see the avatar. At the end of each exercise in both conditions, participants were asked to rate on a Likert scale (1-7) "*how difficult it was to perform the exercise*". In Figure 6 the low-cost equipment of the HOLOBalance platform is provided.

Figure 6: Low-cost equipment of the HOLOBalance platform. Inertia measurement unit, mobile phone, head mounted display. Cumulative weight: 583 gr.

4.3.3. Statistical analysis

A three-level linear mixed effect model was used to reflect the multilevel structure of the data (repeated measurements of levels of Exercises, before and after wearing the equipment, within the same subject). Age, Sex, Body Mass Index, and the interaction between wearing the Equipment and different Exercises were modeled as fixed factors. Random effects were modeled by a random intercept of Frequency within Subject to account for individual differences in the outcome measure for each subject, before wearing the equipment, and a random intercept for Exercise, to account for differences in the outcome measures in each exercise, before wearing the equipment. A random slope of the effect of wearing the Equipment within Subjects was also fitted to account for differences in the magnitude of the effect of its effect for each individual. Odds ratios for the effect of the equipment on the difficulty of performing exercises between conditions were also calculated.

Linear mixed models were fitted by the restricted maximum likelihood method and t-tests using Satterthwaite's method [170] [171]. Model selection was based on backward stepwise regression. Deviations from homoscedasticity or normality were verified by visual inspection of residual plots. Analysis of variance (ANOVA) tables (using the Kenward–Rogers method for estimating degrees of freedom), marginal means, and significance testing of their differences were calculated via the lmerTest package [172].

4.4. Results

4.4.1. Model selection

The basic structural equation of the final model [Outcome measures]tij = β_0 + β_1 [Equipment]$_{tij}$ + β_2 [Exercise]$_{tij}$ + β_3 [Equipment]$_{tij}$ x [Exercise]$_{tij}$ + +$u_{0i|j}$ + ε_{tij} where, u_{0i} is the random intercept for Exercise nested into Subjects (capturing individual differences of the outcome measures of each exercise for each subject) within subjects, before wearing the equipment), ε_{tij} is the residual (unexplained) error.

Age, Sex, and Body Mass Index were selected as fixed effects in some models, but their coefficient estimates were not significant. Random effects did not significantly contribute to the performance of the model for the standing exercise, and a standard fixed effect model was used. The baseline assessment's data are presented in Table 6. All values correspond to the normal range for adults.

4.4.2. Head movement variables in VOR adaptation exercises

There was a statistically significant decrease of 0.97 Hz in VOR frequency in the yaw plane *After* compared to *Before* ([(0.56, 1.39) (t (48) = 6.42, 95% CI = (0.56, 1.39), $p < 0.001$) (Table 2). No statistically significant differences were observed in the range of motion in the yaw plane, and neither of the head movement variables in the pitch plane (Table 7).

4.4.3. Standing exercise

No statistical differences were observed for the two experimental conditions in any of the say parameters in the standing substitution exercise (Table 8).

4.4.4. Difficulty in exercise execution

Concerning difficulty in execution, there was a significant increase in the difficulty of performing the exercises *After* compared to *Before* in both the VOR adaptation exercise in the pitch plane (OR = 3.64, 95% CI (-0.22, 7.50), p = 0.049) and in the standing exercise (OR = 28.28. 95% CI (23.6, 32.96), p = 0.0001). No statistical difference was observed in performing the VOR adaptation exercise in the yaw plane (OR = 1.90, 95% CI (-1.66, 5.46), p = 0.266) (Figure 7).

4.5. Discussion

We conducted a pilot study to evaluate the effectiveness of low-cost HMD equipment used in an augmented reality environment upon the performance of three of the commonest therapeutic vestibular exercises which are integrated into the flowchart of the HoloBalance platform [152,162] and are commonly prescribed in balance rehabilitation protocols [173,174,175]. Statistically significant differences in the frequency of head movement were found for the VOR adaptation exercise performed in the yaw plane *After* with respect to *Before* (Figure 8). However, no statistically significant differences were found regarding RoMotion between the two conditions. With the use of the low-cost HMD, the frequency of movement is decreased by 0.97 Hz ($p<0.001$) on average. For the rest of the exercises, no statistically significant differences were observed neither for frequency of head movement and RoMotion nor for sway.

Reduction of rotation frequency during therapeutic movements in the yaw plane may be a consequence of the cumulative weight of the HMD (actual weight: 399 gr) and the mobile phone (actual weight: 184 gr), as well as of the ergonomic construction of the HMD, possibly causing a forward shift of the axis of motion, which is normally placed mainly on the central portion of the dens at 1st – 2nd cervical vertebrae level for rotation[176]. Furthermore, the perceived difficulty in performance- was reported to be 3.6 times higher in the adaptation exercise in the pitch plane and 28 times higher for the standing exercise in *After* compared to *Before*. This perceived difficulty may reflect the additional required activation of muscle synergies of back and neck extensors muscles, to counteract gravity and the extra placed weight of the HMD. This is a factor that clinicians should consider as a potential new external barrier that may influence adherence to a physical rehabilitation intervention.

The VOR adaptation exercise performed in the yaw plane is one of the most studied exercises in vestibular rehabilitation [177]. It aims to trigger a visual-vestibular mismatch for the retina slip signal error to promote the re-weighting of stimulus in the central vestibular neural circuits. The adaptation mechanism, which is activated, is frequency-specific [177]. Thus, magnifying improvement in clinical outcomes, a high-velocity head movement is essential [178]. Recently updated rehabilitation clinical guidelines provide moderate evidence for the prescription of such gaze stabilization exercises [101]. The VOR is thought to be the most important vestibular reflex which operates over the head velocities of up to 8 Hz required for normal activities [179]. VOR adaptation is thus important for symptomatic recovery after vestibular failure, and vestibular handicap reduction is inversely proportional to the reorganization of the compensatory saccades that the VOR adaptation exercise provides [180]. In our study, a mean difference of 0.97 Hz ($p<0.001$) for head rotation in the yaw plane was observed. This result could probably reflect some clinical consequences that experts should take into consideration with respect to exercise frequency, dosage, and progression. Clinicians should be aware that in head movements in the yaw plane, the frequency will probably be reduced compared to the one recommended. Clinical decision making upon dosage and progression in VOR adaptation exercise in the yaw plane should also take into consideration perceived symptoms and frustration level on top of metrics, at least until a fully ergonomic HMD is adapted or constructed accordingly and validated for this scope. The HMD used in the present study was chosen over other products, during the procurement process, because of its low cost, the offered field of view, and the ability to provide an adequately realistic visual experience and interaction with the rest technical components in the mixed reality environment.

The use of special equipment, required for the creation of an augmented reality environment, seems to make it 3.6 and 28 times more difficult to perform the exercise in the pitch plane the standing position respectively. This difficulty can have a short-term impact on the performance of daily exercise sessions, which lasts about 20 minutes based on clinical guidelines [101]. We hypothesize that the evoked muscle fatigue will cause some level of discomfort towards the use of the equipment and incorrect execution of exercises. Nevertheless, oscillations during standing substitution exercise are far from approaching the limits of stability. Thus, although the additional weight of the equipment makes the execution of two of the three exercises examined more difficult, it does not seem to affect the performance of the exercise individually, nor to create conditions reaching the limits of stability. However, we hypothesize that it will create difficulties in implementing a full therapeutic exercise protocol in an augmented reality environment with the use of existing low-cost equipment and so clinicians should take this into account when prescribing vestibular rehabilitation exercises, adopting longer breaks between exercises or modifying the dosage (fewer exercises / more times daily). Findings in no way imply that the general safety instructions given during the performance of balance exercises should not be considered and thoroughly monitored. Future electromyography on activated muscles recordings will confirm or reject the above hypotheses.

It is not expected that the equipment alone, as patients acquiring motor skills in an augmented environment, will significantly influence effectiveness. Evidence of performance in highly immersive environments is at least promising [163,164], hence examples for rehabilitation in mixed reality environments are extremely limited [181]. Improvement of technological solutions soon will provide the necessary equipment for transferring motor learning principles[182] into augmented reality and enhancing personalized intervention. However, the overall outcome should be weighted as additional motivation and commitment provided by augmented reality platforms should be considered as variables which have led to an increase in completion rate exceeding 50% in the HoloBalance proof of concept study (unpublished data). Nevertheless, it must be emphasized that the existence of metrics, concerning the execution of vestibular rehabilitation exercises, objectifies any clinical decision and is expected to improve the clinical intervention of Vestibular Rehabilitation Treatment *per se,* either with or without the use of technology.

Limitations

Our pilot study was necessary for resolving safety and performance issues before implementation of the HOLOBalance platform to people with balance disorders, as accurately described in the feasibility protocol [152]. Investigating the effect of this specific equipment on the performance of the exercises in pathological populations will provide answers to the clinical questions presented above (exercise frequency, dosage, and progression, adherence). It is obvious that by changing the equipment any exercise performance will be modified, in an unpredictable way. Thus, we recommend that such pilot studies precede the actual clinical studies so that researchers understand the possible effect of the equipment used in mixed reality environments upon exercise parameters.

4.6. Conclusion

This study compared the performance of healthy adults in Vestibular Rehabilitation Treatment exercises with and without the use of equipment necessary for the projection of an augmented reality-based avatar guiding and correcting the performance of the exercises. A statistically significant difference was obtained in the frequency of head movements but not in the range of motion in the yaw plane during the performance of a vestibular adaptation exercise by healthy adults. No statistically significant differences were found for variables in the vestibular adaptation exercise in the pitch plane as well as in one of the most demanding of the standing exercises, usually prescribed by physiotherapists. The optimal equipment must be designed and tested in healthy adults, before any integration into augmented reality environments.

4.7. Tables

	Mean	Median	Std. Deviation	Minimum	Maximum
Age (years)	34.36	34	5.80	24	46
BMI	24.64	22	5.99	17	39
Education (years)	17.8	18	2.92	12	24
DHI	1.52	0.0	2.25	0.0	6
VOR_R	0.99	1	0.10	0.80	1.17
VOR_L	0.99	1	0.09	0.80	1.20

Table 6: Characteristics of the study's population. (BMI: Body Mass Index, DHI: Dizziness Handicap Inventory, VOR_R: Vestibular Ocular Reflex_Right horizontal semicircular canal, VOR_L: Vestibular Ocular Reflex_Left horizontal semicercular canal.

	VOR adaptation exercise performed in yaw plane		VOR adaptation exercise performed in pitch plane	
	RoMotion	Frequency	RoMotion	Frequency
Before	47.65 (41.83, 53.47)	2.56 (2.26, 2.86)	42.21. (36.38, 48.03)	1.66 (1.35, 1.97)
After	51.63 (45.81, 57.45)	1.59 (1.28, 1.90)	37.72 (31.90, 43.54)	1.55 (1.24, 1.86)
Difference (p value)	3.98 (-4.22, 12.18) (p = 0.19)	**0.97 (0.56, 1.39) p <0.001**	-4.49 (-12.69, 3.71) (p = 0.14)	-0.11 (-0.53, 0.31) P = 0.47

Table 7: Marginal mean values with 95% confidence intervals and their differences for RoM and frequency of head movements for VOR adaptation exercise performed in yaw plane and pitch plane respectively. (RoMotion: Range of Motion; VOR: Vestibular Ocular Reflex; Before: Inertia Measurement Unit sensor with a velcro on the head; After: Inertia Measurement Unit sensor on the Head Mounted Display with a switched-off mobile phone on).

	Anteroposterior and mediolateral sway in the standing exercise on foam (marginal means with 95% CI)	
	AP sway	ML sway
Before	0.07 (-0.50, 0.63)	0.06 (-0.41, 0.53)
After	-0.20 (-0.76, 0.36)	0.27 (-0.19, 0.74)
Difference p value	0.26 (-0.48, 1.00) p = 0.50	0.21 (-0.45, 0.87) p = 0.52

Table 8: Marginal mean values with 95% Confidence Intervals and their differences for anteroposterior and mediolateral and sway in the standing exercise on foam (ML: mediolateral; AP: anteroposterior; Before: Inertia Measurement Unit sensor with a velcro on the head; After: Inertia Measurement Unit sensor on the Head Mounted Display with a switched-off mobile phone on; CI: Confidence Intervals).

4.8. Figures

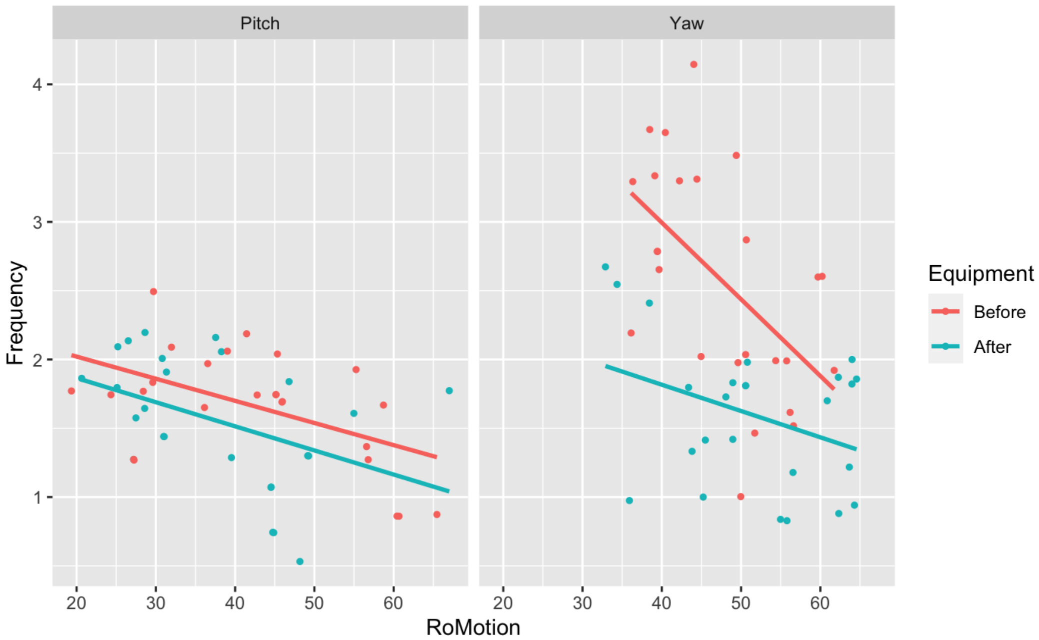

Figure 7: A scatterplot and linear gitted regression lines for RoMotion and frequency of head movements are presented for the VOR adaptation exercise performed in the pitch and yaw planes. (Before: Inertia Measurement Unit sensor with velcro on the head; After: Inertia Measurement Unit sensor on the Head Mounted Display with a switched-off mobile phone on; RoMotion: Range of Motion, VOR: Vestibular Ocular Reflex).

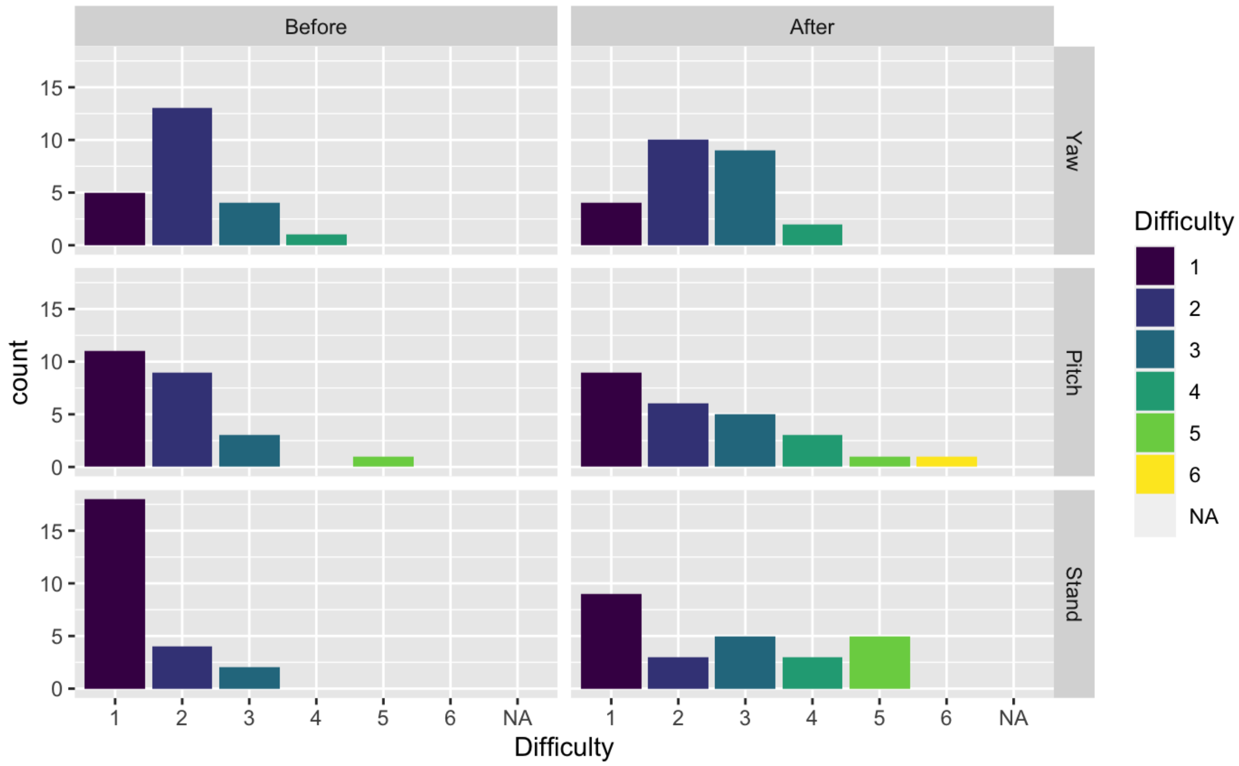

Figure 8: Histograms reporting the perceived difficulty of performing the exercises on a Likert scale between conditions (before and after wearing the equipment) for the VOR adaptation exercise in the yaw and pitch plane and in the standing position. (NA: Not answered; no reported answer for the 7th point of the Likert scale, VOR: Vestibular Ocular Reflex).

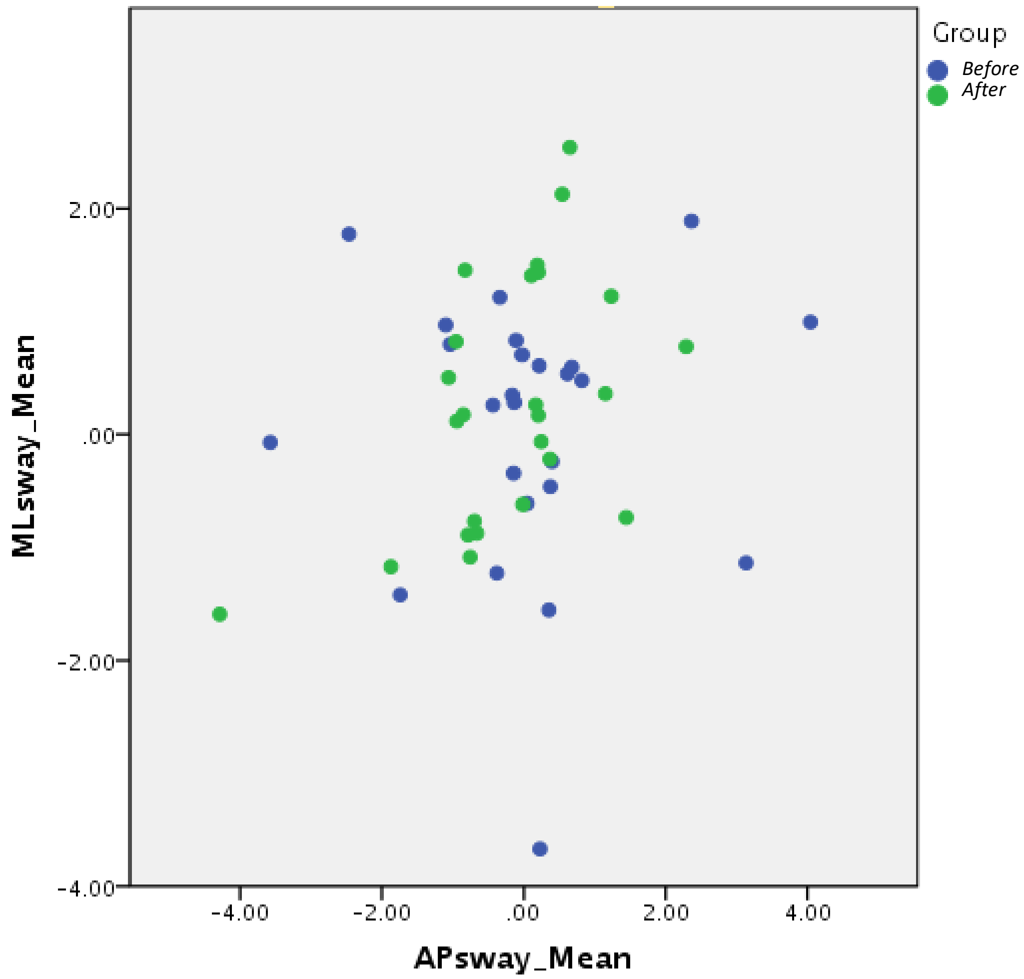

Figure 9: Scatterplot for average ML and AP mediolateral and average anteroposterior sway for the standing exercise. (ML: Mediolateral, AP: Anteroposterior).

4.9. Supplementary Material

The raw data of the pilot study *Head Mounted Display Affects Vestibular Rehabilitation Exercises Performance* could be retrieved from the link below: osf.io/fm3gs

The study has been accepted for publication in the Journal of Frailty, Sarcopenia and Falls.

Thesis Conclusions

The function of the vestibular system is crucial for the movement of the human body and its interaction with the environment. Damage to it, whether unilateral or bilateral, is a major hit to the maintenance of the body's equilibrium. For this reason, the Central Nervous System (CNS) takes over to counteract this disturbance of homeostasis through the process of vestibular compensation. In the first days after injury, changes in the expression of specific genes leading to the release of factors, such as brain-derived neurotrophic factor (BDNF), creating an attractive environment for enhancing the production of proteins and neurotransmitters in order to increase the excitability of neuronal cell at the level of the vestibular nuclei. As the days go by, and the human body starts moving into space, the deficits of the compensation process begin to become apparent, as the disturbance in the firing rate of vestibular afferent nerve fibers affects a number of reflexes (vestibulo-ocular reflex), the overall postural control as well as complex cognitive processes, such as visuospatial ability, forcing some of the patients to disability. Recent data make researchers hypothesize that a successful compensation procedure always comes at a cost due to the brain’s finite cognitive capacity in which when cognitive resources are used for a successful postural control there will be a limitation in the resources used for other cognitive tasks.

In our cross-sectional study of 151 subjects with peripheral vestibular disorders we investigated the possible correlations between cognitive function, functional gait and perceived level of disability, using the most popular clinical tools, the Montreal Cognitive Assessment tool (MoCA), the Functional Gait Assessment (FGA) and the Dizziness Handicap Inventory (DHI) questionnaire. We also investigated whether any of the above variables, including demographics, could have a predictive value on the functional gait variability. We found that age, perceived level of disability (DHI) and vigilance (a MoCA parameter) could predict the variance of the FGA test score by 33.8% (R^2=0.338; $p<0.001$) and the risk of falling as defined by an FGA test score<22/30 (R^2=0.362; $p<0.001$). The ability to maintain attention may play a role in prioritizing cognitive functions over postural control, precisely because there is a cost to compensation, thus increasing instability and risk of falls in people with peripheral vestibular disorders. From clinical perspective, the use of the MoCA tool is considered essential for the detection of cognitive impairment in people with peripheral vestibular disorders although its correlation with the FGA gait test is weak (0.30; $p<0.001$). Therefore, the development of more sensitive cognitive tools is necessary.

Movement, and in our case therapeutic exercise, seems to accelerate the process of vestibular compensation, promoting microgliogenesis at the level of the vestibular nuclei. Clinical research is sufficient to consider vestibular rehabilitation as the safest and most effective treatment of choice for non-reversible peripheral vestibular disorders. Its early beginning also seems to bring better clinical results. The factors that could affect the outcome of vestibular rehabilitation are mental disorders, migraine, peripheral polyneuropathy, and visual disorders. The application of optokinetic stimulation seems to be able to overcome these barriers, especially in cases of visual dependency. In any case, supervision by a health professional is essential for the success of the rehabilitation program and nowadays technology offers the tools to do so. Moreover, the use of virtual reality combined with head movements also offers an additional clinical benefit.

Technology provides an advantage to rehabilitation in terms of supervision, adherence, and motivation. A beyond the state-of-the-art digital platform was recently developed for personalized virtual coaching and motivation in an aging population with balance disorders. This platform (HOLOBalance) creates an augmented reality environment providing balance exercises and cognitive games using low-cost sensors. A pilot study investigated the effect of low-cost equipment (Head Mounted Display - HMD) on performance variables (frequency, range of motion, centre of pressure displacement, difficulty in execution) in therapeutic exercises specifically designed in the context of Vestibular Rehabilitation Treatment. Results revealed a decrease in the frequency (0.97 Hz; $p < 0.001$) on the execution of vestibular-ocular adaptation exercise in the yaw plane when the healthy adults were wearing the HMD. Also a difficulty in exercise execution was recorded when participants were using the HMD in the vestibular-oculomotor adaptation exercise in the pitch plane (OR = 3.64; $p = 0.049$), and in the standing exercise (OR = 28.28; $p < 0.001$). For these reasons, augmented reality technology equipment should also be tested for clinical utility before being applied to the clinical population of interest.

Συνολικά Συμπεράσματα

Η λειτουργία του αιθουσαίου συστήματος είναι καίρια για την κίνηση του ανθρώπινου οργανισμού και την αλληλεπιδρασή του με το περιβάλλον. Μια βλάβη του, μονόπλευρη είτε ετερόπλευρη, αποτελεί σημαντικό πλήγμα στην διατήρηση της ισορροπίας του οργανισμού. Γι’ αυτό το λόγο το Κεντρικό Νευρικό Σύστημα (ΚΝΣ) αναλαμβάνει να αντιρροπήσει αυτή την διαταραχή της ομοιόστασης μεσω της διαδικασίας της αιθουσαίας αντιρρόπησης. Ήδη από τις πρώτες μέρες μετά τη βλάβη παρατηρούνται αλλαγές στην έκφραση συγκεκριμένων γονιδιών που οδηγούν στην έκλυση παραγόντων, όπως είναι ο εγκεφαλικός νευροτροφικός παράγοντας (BDNF), οι οποίοι δημιουργούν ένα ελκυστικό περιβάλλον για την ενίσχυση της παραγωγής πρωτεινών και νευροδιαβιβαστών με στόχο την ενίσχυση του ρυθμού εκπόλωσης των νευρωνικών κυττάρων στο επίπεδο των αιθουσαίων πυρήνων. Με την κίνηση του οργανισμούς τον χώρο αρχίζουν να διακρίνονται τα ελλείμματα αυτής της διαδικασίας αντιρρόπησης καθώς η διαταραχή στον ρυθμό πυροδότησης των αιθουσαίων νευρωνικών κυττάρων επηρεάζει μια σειρά από αντανακλαστικά (αιθουσο-οπτικο αντανακλαστικό), τον συνολικό ισορροπιστικό έλεγχο του οργανισμού και πολύπλοκες γνωσιακές διαδικασίες όπως την οπτικοχωριακή ικανότητα οδηγώντας κάποιους από τους ασθενείς στην αναπηρία. Πρόσφατα δεδομένα οδηγούν τους ερευνητές να υποθέσουν ότι μια πετυχημένη διαδικασία αντιρρόπησης έχει πάντα ένα κόστος εξαιτίας της πεπερασμένης γνωσιακής ικανότητας του ΚΝΣ που εξαναγκάζει τον εγκέφαλο να χρησιμοποιήσει εφεδρικούς γνωσιακούς πόρους για να ανταπεξέλθει στο έλλειμμα του ισορροπιστικού ελέγχου.

Στην συγχρονική μελέτη που πραγματοποιήσαμε σε 151 άτομα με μονόπλευρες περιφερικές αιθουσαίες διαταραχές διερευνήσαμε τις πιθανές συσχετίσεις ανάμεσα στην γνωσιακή λειτουργία, την λειτουργική βάδιση και την βαρύτητα της αντίληψης των συμπτωμάτων με την χρήση των δημοφιλέστερων κλινικών εργαλείων, της γνωσιακής εκτίμησης κατά Montreal (MoCA), της δοκιμασίας λειτουργικής βάδισης (FGA) και του ερωτηματολογίου καταγραφής του μειονεκτήματος της ζάλης (DHI). Επίσης μελετήσαμε κατά πόσο κάποια από τις παραπάνω μεταβλητές, συμπεριλαμβανομένων και των δημογραφικών στοιχείων, θα μπορούσαν να έχουν μια προγνωστική αξία στην διακύμανση της βαθμολογίας της δοκιμασίας FGA στον συγκεκριμένο πληθυσμό. Διαπιστώσαμε ότι η ηλικία, η βαρύτητα της υποκειμενικής αντίληψης των συμπτωμάτων (DHI) και η εγρήγορση (παράμετρος της MoCA) μπορούν να προβλέψουν την διακύμανση της βαθμολογίας της δοκιμασίας FGA κατά 33.8% (R^2=0.338;p<0.001) αλλά και τον κίνδυνό πτώσης όπως αυτός ορίζεται από μια βαθμολογία της δοκιμασίας FGA<22/30 (R^2=0.362;P<0.001). Η ικανότητα για διατήρηση της εγρήγορσης ίσως παίζει ρόλο στην προτεραιοποίηση των γνωσιακών λειτουργιών επί του ισορροπιστικού ελέγχου, ακριβώς γιατί υπάρχει το κόστος της αντιρρόπησης, και έτσι να αυξάνεται η αστάθεια και ο κίνδυνος πτώσης στον συγκεκριμένο πληθυσμό. Κλινικά, η χρήση του εργαλείου MoCA κρίνεται απαραίτητη για την ανίχνευση των γνωσιακών διαταραχών σε άτομα με περιφερικές αιθουσαίες διαταραχές αν και η συσχέτισή του με την δοκιμασία βάδισης FGA είναι ασθενής. Επομένως η δημιουργία πιο ευαίσθητων εργαλείων είναι απαραίτητη.

Η κίνηση, και στην δική μας περίπτωση η θεραπευτική άσκηση, φαίνεται να επιταχύνει την διαδικασία της αιθουσαίας αντιρρόπησης, προωθώντας την μικρογλοιογένεση στο επίπεδο των αιθουσαίων πυρήνων. Η αρθρογραφία είναι επαρκέστατη ώστε να θεωρηθεί η αιθουσαία αποκατάσταση ως η ασφαλέστερη και αποτελεσματικότερη θεραπεία εκλογής για τις μη-αντιρροπούμενες περιφερικές αιθουσαίες διαταραχές. Η γρήγορη έναρξή της φαίνεται να φέρει και καλύτερα κλινικά αποτελέσματα. Οι παράγοντες που θα μπορούσαν να επηρεάσουν το αποτέλεσμα της αιθουσαίας αποκατάστασης είναι οι διαταραχές της ψυχικής σφαίρας, η ημικρανίες, η περιφερική πολυνευροπάθεια καθώς και οπτικές διαταραχές. Η εφαρμογή οπτικοκινητικού ερεθισμού φαίνεται να μπορεί να υπερκεράσει αυτά τα εμπόδια ειδικά στις περιπτώσεις οπτικής εξάρτησης. Σε κάθε περίπτωση, η επίβλεψη είναι απαραίτητη για την επιτυχία του προγράμματος και η τεχνολογία προσφέρει τα κατάλληλα εργαλεία γι’αυτό. Η χρήση της εικονικής πραγματικότητας σε συνδυασμό με κινήσεις της κεφαλής φαίνεται να προσφέρει και ένα επιπλέον κλινικό κέρδος.

Η τεχνολογία παρέχει ένα πλεονέκτημα στην αποκατάσταση όσον αφορά την επίβλεψη, την συμμόρφωση και τα κίνητρα. Πρόσφατα αναπτύχθηκε μια σύγχρονη ψηφιακή πλατφόρμα για εξατομικευμένη εικονική καθοδήγηση ατόμων με διαταραχές ισορροπίας. Αυτή η πλατφόρμα (HOLOBalance) δημιουργεί ένα περιβάλλον επαυξημένης πραγματικότητας που παρέχει ασκήσεις ισορροπίας και γνωστικά παιχνίδια χρησιμοποιώντας αισθητήρες χαμηλού κόστους. Μια πιλοτική μελέτη διερεύνησε την επίδραση του εξοπλισμού χαμηλού κόστους (Head Mounted Display - HMD) σε θεραπευτικές ασκήσεις που χρησιμοποιούνται συχνότατα στην αιθουσαία αποκατάσταση. Τα αποτελέσματα αποκάλυψαν μια μείωση στην ταχύτητα εκτέλεσης της άσκησης αιθουσαίας-οφθαλμικής προσαρμογής στο οριζόντιο επίπεδο (0,97 Hz; $p < 0,001$) όταν οι υγιείς ενήλικες φορούσαν το HMD. Επίσης, όταν οι συμμετέχοντες χρησιμοποιούσαν το HMD στην άσκηση αιθουσαίο-οφθαλμοκινητικής προσαρμογής στο κάθετο επίπεδο και στην άσκηση ισορροπίας πάνω σε αφρώδες υλικό ανέφεραν 3.5 και 28 φορές μεγαλύτερη δυσκολία (OR = 3,64; p = 0,049 και OR = 28,28; p<0,001 αντίστοιχα). Για τους λόγους αυτούς, ο τεχνολογικός εξοπλισμός επαυξημένης πραγματικότητας θα πρέπει επίσης να ελέγχεται για κλινική χρησιμότητα πριν εφαρμοστεί στον κλινικό πληθυσμό ενδιαφέροντος.

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Glossary

Vestibular Compensation	A natural process of Central Nervous System that follows peripheral damage of the vestibular system, based on the intrinsic excitability of neurons, taking place not only at the level of synapses in the vestibular sensory organ but also in the vestibular nucleus and superior cortical networks.
Vestibular Ocular Reflex	A 3-neuron arc reflex stabilizing visual targets onto the retina during head movements.
Re-weighting of Sensory Inputs	A process in which more reliable sensory inputs gain weight during a conflict between contrasting sensory information.
Unilateral Vestibular Disorders	A series of vestibular pathological entities affecting the vestibular system unilaterally.
Vestibular Agnosia	A pathology where the main symptoms are the loss of self-motion and instability found in people with mild traumatic brain injury.
Bilateral Vestibular Dysfunction	A vestibular pathology where the partial or total loss of vestibular function bilaterally is recorded.
Adaptation	The change in gain in reflexive eye movements (Vestibular Ocular Reflex).
Habituation	Repeated exposure to provocative stimulus results to a reduction in the pathological response on that.
Sensory Substitution	The process of re-weighting the sensory inputs
Mixed Reality	An environment that merges a real-world environment and a computer-generated one.
Augmented Reality	An environment that alters, but does not replace, the physical world by integrating digital objects.