Research

Psycho-Neuro-Endocrine-Immunology and Vestibular Disorders: A prospective study

Viviana Mucci[*], Carolina Beppi[**], Enrico Armato[***]

Received 26 February, revised 10 March, accepted 14 March
Online first: 26 March 2025

[*] School of Science, Western Sydney University, Australia.
viviana.mucci@gmail.com/v.mucci@westernsynday.edu.au
[**] Zurich Neuroscience Center, University of Zurich and ETH Zurich, Switzerland. Interdisciplinary Center for Vestibular and Neurological Visual Disorders, Department of Neurology, University Hospital Zurich, Switzerland.
carolinabeppi@gmail.com
[***] Department of Neurosciences, University of Padova, Italy.
enrico.armato@unipd.it
Research Unit DevAH – Development, Adaptation and Handicap, Faculty of Medicine, University of Lorraine, France.
enrico.armato@univlorraine.fr

*** Correspondence: viviana.mucci@gmail.com**

Please cite: Mucci V., Beppi C., Amato E. (2025). Psycho-Neuro-Endocrine-Immunology and Vestibular Disorders: A prospective study. *PNEI Review.* DOI: 10.3280/pnei2025oa19824

Abstract: *Psycho-Neuro-Endocrine-Immunology (PNEI) is a scientific field of study that investigates the link between the bidirectional communication between the nervous, endocrine and immune systems and the correlation of this interaction with physical health. The innovative medical approach of PNEI represents a "paradigm shift" from a "compartmentalized" – strictly biomedical and largely pharmacology-focused – view of health and disease, to a more multi-systemic view, which relies on the integration of interdisciplinary approaches. The key element of the PNEI approach is the concept of a bidirectional dialogue between the psycho-neuro-endocrine and immune systems. In this manuscript, the PNEI hypothesis is considered in application to various*

peripheral and central vestibular disorders. Overall, this study offers an overview of holistic approaches in the treatment of patients with vestibular disorders.

***Keywords**: Balance disorders, vestibular problems, PNEI, hormones, vestibular pathologies – peripheral or central, stress.*

Abbreviations
ACH – Acetylcholine
BVD – Bilateral Vestibular Deafferentation
CGRP – Calcitonin Gene-Related Peptide
fMRI – Functional Magnetic Resonance Imaging
GR – Glucocorticoid Receptors
HPA – Hypothalamic-Pituitary-Adrenal Axis
GCs – Glucocorticoids
MdDS – Debarkation Syndrome or Mal de Débarquement
MD – Ménière's syndrome
MI – Migraine
MR – Mineralocorticoid Receptors
MVN – Medial Vestibular Nucleus
NK – "Natural Killer" cells
PNEI – Psycho-Neuro-Endocrine-Immunology
PPPD – Persistent Postural-Perceptual Syndrome
TVS – Trigeminal Vascular System
UL – Unilateral labyrinthectomy
UVD – Unilateral Vestibular Deafferentation
UVN – Unilateral Vestibular Neurectomy
VC – Vestibular Compensation
VID – Visually Induced Dizziness/Vertigo
VM – Vestibular Migraine

Introduction

The Psycho-Neuro-Endocrine-Immunology (PNEI) is a new theory that studies the bidirectional communication between the nervous system, the endocrine system, the immune system and the psyche (Demori *et al.*, 1975). The dynamic dialogue between these systems results in an overall influence on a patient's health. Scientific evidence suggests that hormones may be involved in vestibular pathophysiology, particularly in peripheral vestibular disorders (Demori *et al.*, 1975). Specifically, steroid, amine and peptide hormones are all implicated in influencing the peripheral vestibular system. For

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

example, vasopressin hypersensitivity of the endolymphatic sac is linked to Ménière's syndrome (MD). In addition, modulation of central vestibular pathways by neuroactive steroids may involve effects on the g-aminobutric acid and glutaminergic pathways. The vestibular nuclei also express enzymes that are important in the synthesis of steroids and the modulation of their activities (Seemungal *et al.*, 2001). Steroids mediate stress with both deleterious and beneficial vestibular compensations. This article provides an overview of peripheral and central vestibular conditions, describing their association with and influence on the endocrine system, the immune system and psychological states, within the PNEI model (Ortega *et al.*, 2024; Saman *et al.*, 2020).

The influence of gonadal hormone fluctuations on vestibular function is well documented, although their interactions remain partially unexplored and unorganized to enable direct conclusions and integration into routine clinical practice (C. Ishii *et al.*, 2009; Jeong, 2020; Mucci, Jacquemyn *et al.*, 2018; Price *et al.*, 1994; P. F. Smith *et al.*, 2019). Hormonal fluctuations, especially in women during puberty, the menstrual cycle, pregnancy and menopause, have been shown to modulate vestibular symptoms in several disorders, including Benign Positional Paroxysmal Vertigo (BPPV) (8), Vestibular Migraine (VM) (Tang *et al.*, 2021), MD (Andrews *et al.*, 1992; Jian *et al.*, 2019) and Mal de Débarquement Syndrome (MdDS) (Mucci *et al.*, 2020; Mucci, Jacquemyn *et al.*, 2018).

In addition to hormonal changes, most vestibular patients with a peripheral or central disorder are also known to suffer from secondary mood disorders such as anxiety and stress (Bittar & von Söhsten Lins, 2015; Staab, 2019). In light of this, this manuscript aims to shed light on the main peripheral and central vestibular disorders for which the integration of endocrine, psychological and immunological components supports or fits into the PNEI model.

Methodology

This article reviews the available literature on peripheral and central vestibular disorders, chronic symptoms, the influence of stress, hormonal states and psychological disorders (such as depression and anxiety), to determine their relationship with the PNEI theory and to assess whether this theory is applicable in patients with different vestibular conditions.

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

Main vestibular disorders and the applied pnei theory

Central vestibular disorders

The central vestibular disorders that we will hereby consider are persistent postural-perceptual vertigo (PPPD) (Indovina *et al.*, 2021; Staab & Ruckenstein, 2007), VM (Formeister *et al.*, 2018; Lempert, 2009; Sacco *et al.*, 2012) and MdDS (Cha *et al.*, 2008; Mucci *et al.*, 2018). These disorders are known to have a clear female pre-dominance and their symptomatic manifestation appears to be related to hormonal fluctuations (P. F. Smith *et al.*, 2019; Stolte *et al.*, 2014). Furthermore, these disorders are associated with secondary mood disorders such as anxiety and major depressive disorder (Furman *et al.*, 2013; Indovina *et al.*, 2021; Mucci *et al.*, 2018; Riccelli *et al.*, 2017; P. F. Smith & Darlington, 2013).

VM is a subtype of migraine (MI) and is one of the most common central vestibular disorders. VM is characterized by episodes of vertigo or dizziness, often associated with typical MI symptoms. The pathophysiology of VM appears to be modulated by gonadal hormones (Tang *et al.*, 2021). In clinical practice, VM is often misdiagnosed and poorly managed, with only 8-20% of patients being correctly identified (Yan *et al.*, 2020). Patients with VM report symptomatic fluctuations due to the impact of gonadal hormones, according to the so-called "oestrogen withdrawal theory" (Sacco *et al.*, 2012). In addition, patients with VM present higher levels of anxiety than MI patients (Kutay *et al.*, 2017) and usually have a clinical history of MI. The main characteristics of patients with VM are similar to those of MI patients, with or without aura (Huang *et al.*, 2019). Studies implementing functional magnetic resonance imaging (fMRI) have demonstrated the presence of brain dysfunction in patients with VM, particularly in relation to pain, vestibular processing and multisensory integration (Zhe *et al.*, 2023). Increased functional connectivity during nociception between vestibular and visual cortex regions has been observed in patients with VM (Mucci *et al.*, 2022; Wang *et al.*, 2014). Furthermore, an abnormal immune response and cytokine dysregulation appear to play a significant role in VM, as well as in other vestibular conditions, including MD. A recent clinical study observed that patients with MI and VM show a type 1 lymphoid cell response, mediated by natural killer (NK) cells, involving an interleukin signaling cascade (IL-1, IL-2, IL-15 and IL-18). Consequently, VM fits perfectly with the theoretical hypothesis of PNEI, which considers how a neuroendocrine imbalance can reflect on the immune system and have a psychological impact. A dysfunction of the neuroendocrine system, evidenced by an immunological and inflammatory response, can therefore manifest itself with a psychological component, e.g. by affecting mood.

The pathophysiology of MI is complex and controversial. In addition to the

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

widely accepted theory involving the trigeminal-vascular system (TVS), the relevance of propagated cortical depression (CSD) has re-emerged in recent years (Espinosa-Sanchez & Lopez-Escamez, 2015). CSD is an electrophysiological phenomenon involving a massive transient neural depolarisation, which slowly propagates through the cortex. It has been hypothesised that CSD may be a trigger for MI with silent aura, as aura is not present in most MI patients. According to this theory, MI could be a pathological condition in which alterations of diverse neural networks play a role (Charles, 2013). Headache in migraineurs could result from a dysfunction within diencephalic structures and the brainstem/thalamic nuclei that modulate trigeminal nociceptive and vestibular inputs, thus affecting multisensory integration. In summary, VM involves an interaction between the nociceptive and vestibular pathways.

Considering the PNEI theory, we pose two specific hypotheses:

- A patient with specific comorbidities (such as major depression) might be more prone to develop an altered neuroendocrine system, which in turn triggers an immunological and inflammatory response, manifesting in an altered brain state.
- Alternatively, is there a genetic predisposition that makes such patients more prone to develop a dysfunctional immune system (e.g. neuroinflammation and systemic inflammation)?

This second hypothesis could be a key aetiopathogenic mechanism involved in the onset and development of affective disorders, which could lead or predispose to VM attacks. Although only a hypothesis, this possibility opens up a new view on vestibular disorders (in this case, the pathophysiology of VM): these cannot be understood in isolation, but rather as part of a multisystemic context, involving the dynamic interaction between different factors and systems, in with with the PNEI theory (Ortega *et al.*, 2024). Overall, the discussed evidence suggests that patients with VM require a holistic, and not "compartmental", management approach to address all pathophysiological aspects.

A similar hypothesis can be extended to two other significant central vestibular disorders: PPPD and MdDS. Similarly to VM, PPPD and MdDS also present a female prevalence, with a female-to-male ratio of 2:1 (Bittar & von Söhsten Lins, 2015; Staab & Ruckenstein, 2007). Previous studies have shown how hormonal fluctuations in MdDS (33) influence patients' symptoms. MdDS not only affects significantly more women (approximately 80%), but in particular, women going through a specific hormonal phase: the onset of menopause (Matchock, Levine, Gianaros, 2008). Among patients of reproductive age, a causal relationship between hormonal fluctuations in the menstrual cycle and increased severity of MdDS symptoms and sensitivity to triggers has been reported (Mucci *et al.*, 2020; Mucci, Canceri *et al.*, 2018). Given the clear female predominance (Van Ombergen, Van Rompaey *et al.*, 2016; Van

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

Ombergen, Wuyts *et al.*, 2016), recent studies have investigated the role of gonadal hormones in this context (Mucci, Canceri *et al.*, 2018; Mucci, Jacquemyn *et al.*, 2018), showing that hormonal changes correlate with the onset of MdDS, with most patients developing the condition during the menopausal transition phase (Mucci, Canceri *et al.*, 2018).

Moreover, symptoms appear to be more frequent and more severe during menstruation (Mucci, Canceri *et al.*, 2018) and reduce (or resolve completely) during the first two trimesters of pregnancy, as observed in MI patients (Mucci, Canceri *et al.*, 2018). These studies have generated the hypothesis that the pathophysiology of MdDS may be driven by specific hormonal fluctuations and phases (Mucci *et al.*, 2020; Mucci, Jacquemyn *et al.*, 2018). A recent study (Mucci *et al.*, 2020) hypothesised that patients with MdDS may have experienced a specific hormonal phase (low E2) at the time of disease onset that altered their GABAergic system, as well as their calcitonin gene-related peptide (CGRP) levels (Mucci, Jacquemyn *et al.*, 2018). CGRP is known to be implicated in the pathophysiology of MI and is a common comorbidity factor for MdDS (Balaban *et al.*, 2011; Cha, 2015; Mucci, Jacquemyn *et al.*, 2018). Animal studies have also shown that CGRP receptors support vestibular functions (Luebke *et al.*, 2014; Ohno *et al.*, 2016). In particular, CGRP-positive neurons have been found in the vestibular nuclei and in the vestibulo-cerebellum (Ohno *et al.*, 2016), and could therefore be relevant for neuroplasticity mechanisms within the vestibular system, influencing neurotransmitters such as the brain-derived neurotrophic factor (BDNF) (Buldyrev *et al.*, 2006; Wu *et al.*, 2015).

The model proposed by Mucci *et al.* (2020) describes how a specific neurochemical imbalance, involving the GABAergic network, can lead to imbalances in the inhibitory transmission or to disproportions in the levels of CGRP and BDNF (e.g. low levels of oestrogen and high levels of CGRP and BDNF), predisposing susceptible and vulnerable individuals (Mucci *et al.*, 2020). While this hypothesis has been proposed mainly in relation to MdDS, similar mechanisms could also be involved in VM and PPPD, likewise predisposing susceptible and vulnerable individuals (Mucci *et al.*, 2020; Mucci, Jacquemyn *et al.*, 2018). The PNEI model aligns closely with the theory previously proposed by Mucci (Mucci, Jacquemyn *et al.*, 2018), according to which patients with MdDS report a potential inflammatory response and neuroendocrine dysregulation that could influence multisensory integration in the vestibular nuclei. The immunological component, in specific relation to MdDS and PPPD, remains unexplored. Further research is needed to consider the application of the PNEI theory to the discussed pathologies.

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

Peripheral vestibular disorders

Ménière's syndrome: MD describes a condition of the labyrinth of the inner ear whereby there is an accumulation of endolymphatic fluid. MD is responsible for tinnitus, vertigo, hearing loss and a feeling of air pressure, aka "fullness within the ear". The syndrome is related to conditions of excessive stress that can generate neural hyperactivity of the autonomic sympathetic system. Stress can consequently impact hormonal regulation and the immune response, leading to a progression and exacerbation of the syndrome (Horner & Cazals, 2003; M. Ishii *et al.*, 2022; S.-H. Lee & Kim, 2010; Söderman *et al.*, 2004). If chronicised, stress can alter the production and release of hormones – including cortisol – that can affect the immune response, in turns accentuating ear inflammation (Saman *et al.*, 2012). Steroids, known for their anti-inflammatory properties, have been used to manage MD symptoms. In this context, one study (Barrs *et al.*, 2001) showed that intratympanic steroid injections (specifically, 4 mg/mL dexamethasone for 4 weeks) may offer temporary relief of persistent vertigo in patients with MD. Moreover, relief was maintained in 52% of cases at 3 month follow-up, and in 43% of cases at 6 month follow-up. This suggests that modulation of the immune response may relieve symptoms.

Similarly, a more recent study (Barrs *et al.*, 2001) showed that intratympanic therapy with gentamicin or dexamethasone is an effective approach to treat MD symptoms (incl. the "fullness within the ear" sensation), with negligible side effects. Specifically, the former shows greater efficacy than the latter, if one selectively considers the complete control of vertigo. In contrast, dexamethasone causes higher improvements in tinnitus, albeit without statistical significance. Gentamicin, on the other hand, seems to cause more hearing loss than dexamethasone at high frequencies. Using methylprednisolone and/or dexamethasone, another study (Dodson *et al.*, 2004) supports that intratympanic steroid injections are, in approximately 50% of MD patients, an effective treatment for temporary symptom relief, but that they do not result in relief of vertigo and hearing loss in the long-term. Overall, the evidence supports the PNEI theory, emphasising the interrelation between psychological stress, the immune function and the clinical manifestations of MD. The low long-term efficacy of monofactorial treatments in some studies may suggest that holistic, i.e. multisystemic, approaches are needed to achieve more significant and sustained effects over time. A patient with MD might therefore benefit from complementing mere pharmacological interventions with multisystemic interventions aimed at reducing the patient's stress level, e.g. by introducing mindfulness, physical exercise and a targeted diet (Koukoulithras *et al.*, 2022; Oğuz *et al.*, 2021).

Benign Paroxysmal Positional Vertigo: BPPV is a disorder of the inner ear caused by small calcium carbonate crystals (otoliths) that, when displaced, cause disturbances

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

such as episodes of vertigo of short duration (<60-sec) depending on the head's position and angle. Additional disturbances include nausea and nystagmus. When patients with BPPV develop visual-induced dizziness (VID), we refer to postural instability associated with peripheral vestibular conditions. Although BPPV is considered a purely mechanical disorder, patients with anxiety disorders have a higher risk of developing BPPV, highlighting the link between psyche and vestibular function (Chen *et al.*, 2016). Furthermore, chronic stress can influence the immune response and hormonal regulation, potentially aggravating BPPV symptoms (Saman *et al.*, 2020; L. J. Smith *et al.*, 2024).

The interaction between the endocrine system and vestibular syndromes is twofold. Vestibular deficits can cause hormonal changes at different times, such as during acute crises or compensation phases. Specific hormonal profiles may also increase susceptibility to vertigo. For instance, the prevalence of BPPV increases with age, particularly in postmenopausal women due to decreased levels of oestrogen and progesterone, which affect the microcirculation of the inner ear. Diabetic patients are more likely to develop BPPV, with 46% of patients with type 2 diabetes affected, compared to 37% without diabetes. Hyperglycaemia is a risk factor for recurrence of BPPV. BPPV is also linked to thyroid disorders such as goiter (i.e. thyroid volumetric increase), thyroiditis, hypothyroidism and hyperthyroidism. MD, common in anxious individuals, can be induced by stress-related increases in vasopressin. Hypothyroidism has also been associated with MD. Hormonal changes have been observed at different stages of vestibular pathology. The syndrome begins with an acute crisis characterised by dizziness and anxiety, followed by a phase of functional recovery mediated by vestibular compensation. The vestibular system's connections with the hypothalamic-pituitary-adrenal (HPA) axis lead to changes in the stress hormone profile, demonstrated by altered levels of cortisol and acetylcholine (ACH). Central vestibular compensation varies between patients and is slower in those experiencing stress.

Vestibular neuritis is an inflammation of the vestibular nerve, which is part of the peripheral vestibular system. It causes intense vertigo and a sudden loss of balance, although without affecting hearing. The symptoms of unilateral vestibular neurectomy (UVN) can cause stress and activate the HPA, leading to postural, oculomotor, perceptual and neurovegetative syndromes. In a 2003 study on guinea pigs, unilateral vestibular deafferentation (UVD) (n=6) and sham intervention (n=6) were compared. The UVD intervention resulted in a significant increase ($P<0.05$) in nocturnal cortisol concentrations compared to pre-operative salivary cortisol concentrations, also showing a significant interaction ($P<0.05$) between nocturnal cortisol concentration and time. No significant difference was shown in terms of morning salivary cortisol concentrations between pre- and post- UVD surgery, nor between pre- and post- sham surgery. This suggested that the oculomotor and postural imbalances might cause activation of the HPA (Gliddon *et al.*, 2003).

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

Another study in adult cats showed that prolonged activation of the HPA is a likeable index of the chronic stress experienced by the animals. This stress corresponds to the duration required for complete vestibular compensation and is no longer evident when the animals are completely free of postural-locomotor symptoms at 90 days (Tighilet *et al.*, 2009). The development of vestibular compensation after unilateral labyrinthectomy (UL) is significantly influenced by stress and stress-related steroids, as well as by conditions such as anxiety and major depression, which alter the normal HPA function. Glucocorticoids (GCs) released from the adrenal cortex, in response to stress-induced HPA activation, exert extensive actions throughout the body. In addition, they have significant modulatory effects on neurons and synapses within the brain. GCs can have a direct impact on membrane ion channels and neurotransmitter receptors to regulate their function or alter gene expression in neurons via specific intracellular receptors, including glucocorticoid receptors (GR) and mineral corticoid receptors (MR). Moreover, GCs can be rapidly converted by various enzymes into active neurosteroids. Neurosteroids derived from sex steroid progesterone also influence neuronal and synaptic function in the vestibular system and the cerebellum.

Several studies indicate that glucocorticoids and neurosteroids can modulate the vestibular system's function and compensation. Anxiety and stress in patients with vertigo substantially delay recovery from vestibular symptoms. In contrast, treatment with the GR steroid methylprednisolone has been reported to improve vestibular compensation. The acute stress that accompanies behavioural symptoms immediately after UL could facilitate cell plasticity in medial vestibular nucleus (MVN) neurons. An essential site of glucocorticoid action during vestibular compensation (VC) appears to be the cerebellar flocculus. However, an optimal level of GR activation seems to be necessary in that additional stress, such as restraint applied to a compensatory animal after UL, may hinder behavioural recovery.

The interactions between HPA, glucocorticoids and vestibular plasticity have potentially important implications for the treatment and management of patients with balance disorders. The effectiveness of vestibular rehabilitation exercises in promoting VC may be partly due to the acute stress resulting from initially aversive movements, which facilitate the brain plasticity mechanisms required for VC. It is also possible that patients who fail to compensate adequately after UL may either (A) have pre-existing alterations in their HPA function due to depression or anxiety or (B) develop changes in their HPA due to vestibular dysfunction and associated symptoms. This could cause inappropriate stress responses to vestibular, visual and postural challenges, impeding the necessary cellular plasticity in vestibular pathways for VC. Further investigations are needed to shed light on the cellular mechanisms of stress steroids on VC in animal models and to study the function of the

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

HPA in patients with balance disorders (Dutia & Straka, 2009). In addition to this, there is to consider that the contrast to the effects of UVD, following bilateral vestibular deafferentation (BVD) in rats, where their serum corticosterone was not elevated when compared to sham surgery at 3 weeks (59) or 6 months (Russell *et al.*, 2006) or 9 months (Zheng *et al.*, 2008). However a reduction in anxiety was observed in animals after BVD (Zheng *et al.*, 2008) suggesting that the interactions between the vestibular and limbic systems are chronically altered (Saman *et al.*, 2012).

Stress modulation and symptoms

It is crucial to understand the interaction between the vestibular and endocrine systems. There is an urgent need to determine how hormonal profiles influence patients with vertigo and their vestibular conditions. Preclinical and clinical studies are essential to develop diagnostic tools to identify different types and stages of vestibular disorders and to create targeted therapies. These therapies aim to prevent vestibular disorders, reduce vertigo attacks and promote rapid recovery. There is currently a lack of information on the proportion of vestibular disorders linked to hormonal factors or profiles. Filling these gaps in the scientific knowledge could significantly improve the management and clinical outcomes of patients with vertigo and instability (El Khiati *et al.*, 2023).

Stress has been shown to influence vestibular symptoms (3). Whether one considers peripheral or central disorders, the vestibular system is influenced by stress responses (i.e. activation of the HPA, and the autonomic nervous system, through the release of "stress mediators" such as neuropeptides, steroids and monoamine hormones). The activation of the stress response may be necessary for vestibular compensation (Ortega *et al.*, 2024). However, excessive stress may adversely affect compensation (Saman *et al.*, 2012), highlighting the fine line separating healthy and pathological states. It is known that, in patients with MdDS, stress causes an aggravation of symptoms (Mucci *et al.*, 2018). Similarly, in PPPD, (Popkirov *et al.*, 2017) psychological distress modulates symptoms (Bittar & von Söhsten Lins, 2015; J. O. Lee *et al.*, 2018). When considering peripheral disorders, stress not only influences symptomatology, but also prevents vestibular compensation mechanisms and thus a complete recovery of functionality.

Future studies for hypothesis-validation

Based on the discussed evidence, we propose to determine whether the PNEI theory may apply to central and peripheral vestibular disorders. To this end, it would be necessary that future studies examine patients with a multidisciplinary approach. Immunological studies and genetic assessments of vestibular patients would be of particular relevance, as the literature in this context is still very scarce. For example, it is assumed

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

that, in the presence of the glucocorticoid polymorphism, patients report higher levels of anxiety and cortisol. It would hence be important to determine whether patients suffering from chronic vertigo and vestibular symptoms have a higher prevalence of polymorphisms that prevent them from fully compensating, thus predisposing them to developing secondary mood disorders (i.e. anxiety and depression).

As discussed, women are more prone to various vestibular disorders (including VM, PPPD and MdDS) and kinetosis. Therefore, another key research question would be to investigate how gonadal hormones, stress and dysfunctions of neuroendocrine modulation might influence the symptomatology or pathophysiology of vestibular disorders. In conclusion, these abovementioned aspects highlight the association between immunoendocrine and psychological factors in vestibular disorders, as well as the importance of a combined "mind-and-body" management in patient care.

Author Contributions: Conceptualization, writing – original draft preparation: V.M., C.B., E.A., writing – review and editing, V.M., C.B, E.A. Funding: No funding. Conflicts of Interest: The authors declare no conflict of interest.

References

Andrews, J. C., Ator, G. A., & Honrubia, V. (1992). The exacerbation of symptoms in Meniere's disease during the premenstrual period. *Archives of Otolaryngology--Head & Neck Surgery*, *118*(1), 74–78. https://doi.org/10.1001/archotol.1992.01880010078020.

Balaban, C. D., Jacob, R. G., & Furman, J. M. (2011). Neurologic bases for comorbidity of balance disorders, anxiety disorders and migraine : neurotherapeutic implications. *Expert Rev. Neurother*, *11*(3), 379–394. https://doi.org/10.1586/ern.11.19.

Barrs, D. M., Keyser, J. S., Stallworth, C., & McElveen, J. T. J. (2001). Intratympanic steroid injections for intractable Ménière's disease. *The Laryngoscope*, *111*(12), 2100–2104. https://doi.org/10.1097/00005537-200112000-00003

Bittar, R. S. M., & von Söhsten Lins, E. M. D. (2015). Clinical characteristics of patients with persistent postural-perceptual dizziness. *Brazilian Journal of Otorhinolaryngology*, *81*(3), 276–282. https://doi.org/10.1016/j.bjorl.2014.08.012

Buldyrev, I., Tanner, N., Hsieh, H., Dodd, E., Nguyen, L., & Balkowiec, A. (2006). Calcitonin gene-related peptide enhances release of native brain-derived neurotrophic factor from trigeminal ganglion neurons. *J Neurochem*, *99*(5), 1338-1350. https://doi.org/10.1111/j.1471-4159.2006.04161.x

Cha, Y.-H. (2015). Mal de debarquement syndrome: new insights Yoon-Hee. *Ann N Y Acad Sci.*, *1343*(1), 63–68. https://doi.org/10.1111/nyas.12701.Mal

Cha, Y.-H., Brodsky, J., Ishiyama, G., Sabatti, C., & Baloh, R. W. (2008). Clinical features and associated syndromes of mal de debarquement. *Journal of Neurology*, *255*(7), 1038–1044. https://doi.org/10.1007/s00415-008-0837-3

Charles, A. (2013). Migraine: a brain state. *Current Opinion in Neurology*, *26*(3), 235–239. https://doi.org/10.1097/WCO.0b013e32836085f4

Chen, Z.-J., Chang, C.-H., Hu, L.-Y., Tu, M.-S., Lu, T., Chen, P.-M., & Shen, C.-C. (2016). Increased risk of benign paroxysmal positional vertigo in patients with anxiety disorders: a nationwide population-based retrospective cohort study. *BMC Psychiatry*, *16*, 238. https://doi.org/10.1186/s12888-016-0950-2

Demori, I., Molinari, E., Rapallo, F., Mucci, V., Marinelli, L., Losacco, S., & Burlando, B. (1975). Online Questionnaire with Fibromyalgia Patients Reveals Correlations among Type of Pain, Psychological

Alterations, and Effectiveness of Non-Pharmacological Therapies. *MDPI Healthcare*, *10*. https://doi.org/10.3390/healthcare10101975

Dodson, K. M., Woodson, E., & Sismanis, A. (2004). Intratympanic steroid perfusion for the treatment of Ménière's disease: a retrospective study. *Ear, Nose, & Throat Journal*, *83*(6), 394–398. https://doi.org/10.1177/014556130408300611

Dutia, M. B., & Straka, H. (2009). Vestibular Compensation and Plasticity. In M. D. Binder, N. Hirokawa, & U. Windhorst (Eds.), *Encyclopedia of Neuroscience* (pp. 4186–4193). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-540-29678-2_6287

El Khiati, R., Tighilet, B., Besnard, S., & Chabbert, C. (2023). Vestibular Disorders and Hormonal Dysregulations: State of the Art and Clinical Perspectives. *Cells*, *12*(4). https://doi.org/10.3390/cells12040656

Espinosa-Sanchez, J. M., & Lopez-Escamez, J. A. (2015). New insights into pathophysiology of vestibular migraine. *Frontiers in Neurology*, *6*(FEB), 10–15. https://doi.org/10.3389/fneur.2015.00012

Formeister, E. J., Rizk, H. G., Kohn, M. A., & Sharon, J. D. (2018). The Epidemiology of Vestibular Migraine: A Population-based Survey Study. *Otology & Neurotology : Official Publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology*, *39*(8), 1037–1044. https://doi.org/10.1097/MAO.0000000000001900

Furman, J. M., Marcus, D. A., & Balaban, C. D. (2013). Vestibular migraine: Clinical aspects and pathophysiology. *The Lancet Neurology*, *12*(7), 706–715. https://doi.org/10.1016/S1474-4422(13)70107-8

Gliddon, C. M., Darlington, C. L., & Smith, P. F. (2003). Activation of the hypothalamic-pituitary-adrenal axis following vestibular deafferentation in pigmented guinea pig. *Brain Research*, *964*(2), 306–310. https://doi.org/10.1016/s0006-8993(02)04086-6

Horner, K. C., & Cazals, Y. (2003). Stress in hearing and balance in Meniere's disease. *Noise & Health*, *5*(20), 29–34.

Huang, T.-C., Wang, S.-J., & Kheradmand, A. (2019). Vestibular migraine: An update on current understanding and future directions. *Cephalalgia*, *40*(1), 107–121. https://doi.org/10.1177/0333102419869317

Indovina, I., Passamonti, L., Mucci, V., Chiarella, G., Lacquaniti, F., & Staab, J. P. (2021). Brain Correlates of Persistent Postural-Perceptual Dizziness : A Review of Neuroimaging Studies. *Journal of Clinical Medicine*, *10*(18), 4274. https://doi.org/10.3390/jcm10184274

Ishii, C., Nishino, L. K., Alberto, C., & Campos, H. De. (2009). Vestibular characterization in the menstrual cycle. *Brazilian Journal of Otorhinolaryngology*, *75*(3), 375–380. https://doi.org/10.1016/S1808-8694(15)30655-8

Ishii, M., Ishiyama, G., Ishiyama, A., Kato, Y., Mochizuki, F., & Ito, Y. (2022). Relationship Between the Onset of Ménière's Disease and Sympathetic Hyperactivity. *Frontiers in Neurology*, *13*, 804777. https://doi.org/10.3389/fneur.2022.804777

Jeong, S. H. (2020). Benign Paroxysmal Positional Vertigo Risk Factors Unique to Perimenopausal Women. *Frontiers in Neurology*, *11*(October), 1–6. https://doi.org/10.3389/fneur.2020.589605

Jian, H., Yu, G., Chen, G., Lin, N., & Wang, H. (2019). Correlation between auditory-vestibular functions and estrogen levels in postmenopausal patients with Meniere's disease. *Journal of Clinical Laboratory Analysis*, *33*(1), e22626. https://doi.org/10.1002/jcla.22626

Koukoulithras, I., Drousia, G., Kolokotsios, S., Plexousakis, M., Stamouli, A., Roussos, C., & Xanthi, E. (2022). A Holistic Approach to a Dizzy Patient: A Practical Update. *Cureus*, *14*(8), e27681. https://doi.org/10.7759/cureus.27681

Kutay, Ö., Akdal, G., Keskinoğlu, P., Balcı, B. D., & Alkın, T. (2017). Vestibular migraine patients are more anxious than migraine patients without vestibular symptoms. *Journal of Neurology*, *264*(Suppl 1), 37–41. https://doi.org/10.1007/s00415-017-8439-6

Lee, J. O., Lee, E. S., Kim, J. S., Lee, Y. B., Jeong, Y., Choi, B. S., Kim, J. H., & Staab, J. P. (2018). Altered brain function in persistent postural perceptual dizziness: A study on resting state functional connectivity. *Human Brain Mapping*, *39*(8), 3340–3353. https://doi.org/10.1002/hbm.24080

Lee, S.-H., & Kim, J. S. (2010). Benign paroxysmal positional vertigo. *Journal of Clinical Neurology (Seoul, Korea)*, *6*(2), 51–63. https://doi.org/10.3988/jcn.2010.6.2.51

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

Lempert, T. (2009). Epidemiology of vertigo, migraine and vestibular migraine. *J.Neurol.*, *256*(3), 333–338. https://doi.org/10.1007/s00415-009-0149-2

Luebke, A. E., Holt, J. C., Jordan, X. P. M., Wong, Y. S., Caldwell, J. S., & Cullen, K. E. (2014). Loss of α-Calcitonin Gene-Related Peptide (αCGRP) Reduces the Efficacy of the Vestibulo-ocular Reflex (VOR). *The Journal of Neuroscience*, *34*(31), 10453–10458. https://doi.org/10.1523/JNEUROSCI.3336-13.2014

Matchock R.L, Levine M.E, Gianaros P.J, S. R. M. (2008). Susceptibility to Nausea and Motion Sickness as a Function of the Menstrual Cycle NIH Public Access. *Womens Health Issues*, *4*(November 2016), 328–335. https://doi.org/10.1016/j.whi.2008.01.006

Mucci, V., Canceri, J. M., Brown, R., Dai, M., Yakushin, S., Watson, S., Van Ombergen, A., Topsakal, V., Van de Heyning, P. H., Wuyts, F. L., & Browne, C. J. (2018). Mal de Debarquement Syndrome: a survey on subtypes, misdiagnoses, onset and associated psychological features. *Journal of Neurology*, *265*(3), 486–499. https://doi.org/10.1007/s00415-017-8725-3

Mucci, V., Canceri, J. M., Brown, R., Dai, M., Yakushin, S. B., Van Ombergen, A., Jacquemyn, Y., Fahey, P., Van de Heyning, P. H., Wuyts, F., & Browne, C. J. (2018). Mal de Debarquement syndrome : a retrospective Online Questionnaire on the influences of gonadal hormones in relation to Onset and symptom Fluctuation. *Frontiers in Neurology*, *9*(May), 1–16. https://doi.org/10.3389/fneur.2018.00362

Mucci, V., Hamid, M., Jacquemyn, Y., & Browne, C. J. (2022). Influence of sex hormones on vestibular disorders. *Current Opinion in Neurology*, *35*(1). https://journals.lww.com/co-neurology/Fulltext/2022/02000/-Influence_of_sex_hormones_on_vestibular_disorders.21.aspx. https://doi.org/10.1097/WCO.0000000000001019

Mucci, V., Indovina, I., Browne, C. J., Blanchini, F., Giordano, G., Marinelli, L., & Burlando, B. (2020). Mal de Debarquement Syndrome: A Matter of Loops? *Frontiers in Neurology*, *11*, 576860. https://doi.org/10.3389/fneur.2020.576860

Mucci, V., Jacquemyn, Y., Van Ombergen, A., Van de Heyning, P. H., & Browne, C. J. (2018). A new theory on GABA and Calcitonin Gene-Related Peptide involvement in Mal de Debarquement Syndrome predisposition factors and pathophysiology. *Medical Hypotheses*, *120*(August), 128–134. https://doi.org/10.1016/j.mehy.2018.08.024

Oğuz, E., Cebeci, A., & Geçici, C. R. (2021). The relationship between nutrition and Ménière's disease. *Auris Nasus Larynx*, *48*(5), 803–808. https://doi.org/https://doi.org/10.1016/j.anl.2021.03.006

Ohno, K., Takeda, N., Tanaka-tsuji, M., & Matsunaga, T. (2016). Calcitonin Gene-related Peptide in the Efferent System of the Inner Ear : A review. *Acta Oto-Laryngologica*, *6489*(March), 1651–2251. https://doi.org/10.3109/00016489309126206

Ortega, M. A., Fraile-Martinez, O., García-Montero, C., Diaz-Pedrero, R., Lopez-Gonzalez, L., Monserrat, J., Barrena-Blázquez, S., Alvarez-Mon, M. A., Lahera, G., & Alvarez-Mon, M. (2024). Understanding immune system dysfunction and its context in mood disorders: psychoneuroimmunoendocrinology and clinical interventions. *Military Medical Research*, *11*(1), 1–37. https://doi.org/10.1186/s40779-024-00577-w

Popkirov, S., Staab, J. P., & Stone, J. (2017). Persistent postural-perceptual dizziness (PPPD): A common, characteristic and treatable cause of chronic dizziness. *Practical Neurology*, *18*(1), 5–13. https://doi.org/10.1136/practneurol-2017-001809

Price, T. M., Allen, T. C., Bowyer, D. L., & Watson, T. A. (1994). Ablation of Luteal Phase Symptoms of Meniere's Disease With Leuprolide. *Archives of Otolaryngology–Head & Neck Surgery*, *120*(2), 209–211. https://doi.org/10.1001/archotol.1994.01880260079015

Riccelli, R., Indovina, I., Staab, J. P., Nigro, S., Augimeri, A., Lacquaniti, F., & Passamonti, L. (2017). Neuroticism modulates brain visuo-vestibular and anxiety systems during a virtual rollercoaster task. *Human Brain Mapping*, *38*(2), 715–726. https://doi.org/10.1002/hbm.23411

Russell, N. A., Horii, A., Smith, P. F., Darlington, C. L., & Bilkey, D. K. (2006). Lesions of the vestibular system disrupt hippocampal theta rhythm in the rat. *Journal of Neurophysiology*, *96*(1), 4–14. https://doi.org/10.1152/jn.00953.2005

Sacco, S., Ricci, S., Degan, D., & Carolei, A. (2012). Migraine in women : the role of hormones and their impact on vascular diseases. *J.Headache Pain*, *13*(3), 177–189. https://doi.org/10.1007/s10194-012-0424-y

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824

Saman, Y., Arshad, Q., Dutia, M., & Rea, P. (2020). Stress and the vestibular system. In *International Review of Neurobiology* (1st ed., Vol. 152). Elsevier Inc. https://doi.org/10.1016/bs.irn.2020.03.013

Saman, Y., Bamiou, D. E., Gleeson, M., Dutia, M. B., Peusner, K., & Washington, G. (2012). Interactions between stress and vestibular compensation – a review. *Frontiers in Neurology*, *3*(July), 1–8. https://doi.org/10.3389/fneur.2012.00116

Seemungal, B. M., Gresty, M. A., & Bronstein, A. M. (2001). The endocrine system, vertigo and balance. *Current Opinion in Neurology*, *14*(1), 27–34. https://doi.org/10.1097/00019052-200102000-00005

Smith, L. J., Pyke, W., Fowler, R., Matthes, B., de Goederen, E., & Surenthiran, S. (2024). Impact and experiences of vestibular disorders and psychological distress: Qualitative findings from patients, family members and healthcare professionals. *Health Expectations : An International Journal of Public Participation in Health Care and Health Policy*, *27*(1), e13906. https://doi.org/10.1111/hex.13906

Smith, P. F., Agrawal, Y., & Darlington, C. L. (2019). Sexual Dimorphism in Vestibular Function and Dysfunction. *Journal of Neurophysiology*, *1*(121 (6)), 2. https://doi.org/doi: 10.1152/jn.00074.2019.

Smith, P. F., & Darlington, C. L. (2013). Personality changes in patients with vestibular dysfunction. *Frontiers in Human Neuroscience*, *7*(October), 1–7. https://doi.org/10.3389/fnhum.2013.00678

Söderman, A.-C. H., Möller, J., Bagger-Sjöbäck, D., Bergenius, J., & Hallqvist, J. (2004). Stress as a trigger of attacks in Menière's disease. A case-crossover study. *The Laryngoscope*, *114*(10), 1843–1848. https://doi.org/10.1097/00005537-200410000-00031

Staab, J. P. (2019). Psychiatric considerations in the management of dizzy patients. *Advances in Oto-Rhino-Laryngology*, *82*, 170–179. https://doi.org/10.1159/000490286

Staab, J. P., & Ruckenstein, M. J. (2007). Expanding the differential diagnosis of chronic dizziness. *Archives of Otolaryngology--Head & Neck Surgery*, *133*(2), 170–176. https://doi.org/10.1001/archotol.133.2.170

Stolte, B., Holle, D., Naegel, S., Diener, H.-C., & Obermann, M. (2014). Vestibular migraine. *Cephalalgia*, *35*(3), 262–270. https://doi.org/10.1177/0333102414535113

Tang, B., Yu, X., Jiang, W., Zhang, C., Zhan, T., & He, Y. (2021). Clinical significance of serum sex hormones in postmenopausal women with vestibular migraine: potential role of estradiol. *Journal of International Medical Research*, *49*(5). https://doi.org/10.1177/03000605211016379

Tighilet, B., Manrique, C., & Lacour, M. (2009). Stress axis plasticity during vestibular compensation in the adult cat. *Neuroscience*, *160*(4), 716–730. https://doi.org/10.1016/j.neuroscience.2009.02.070

Van Ombergen, A., Van Rompaey, V., Meas, L. K., Van de Heyning, P. H., & Wuyts, F. L. (2016). Mal de debarquement syndrome : a systematic review. *Journal of Neurology*, *263*(5), 843–854.

Van Ombergen, A., Wuyts, F. L., & Cha, Y.-H. (2016). Letter to the Editor : comment and erratum to "Mal de debarquement syndrome : a systematic review". *Journal of Neurology*, *263*(5), 855–860. https://doi.org/10.1007/s00415-016-8102-7

Wang, D., Zhao, J., Wang, J., Li, J., Yu, S., & Guo, X. (2014). Deficiency of female sex hormones augments PGE 2 and CGRP levels within midbrain periaqueductal gray. *Journal of the Neurological Sciences*, *346*(1–2), 107–111. https://doi.org/10.1016/j.jns.2014.08.002

Wu, X., Zhang, J., Liu, J., Yang, S., Chen, T., Chen, J., & Wang, F. (2015). Calcitonin gene-related peptide erases the fear memory and facilitates long-term potentiation in the central nucleus of the amygdala in rats. *J Neurochem*, *135*(4), 787–798.

Yan, M., Guo, X., Liu, W., Lu, J., Wang, J., Hu, L., Xia, K., Ni, J., Lu, H., & Zhao, H. (2020). Temporal Patterns of Vertigo and Migraine in Vestibular Migraine. *Frontiers in Neuroscience*, *14*(April), 1–7. https://doi.org/10.3389/fnins.2020.00341

Zhe, X., Zhang, H., Tang, M., Lei, X., Zhang, X., & Jin, C. (2023). Brain functional connectivity patterns associated with symptoms of vestibular migraine. *Frontiers in Neuroscience*, *17*(December). https://doi.org/10.3389/fnins.2023.1231273

Zheng, Y., Goddard, M., Darlington, C. L., & Smith, P. F. (2008). Effects of bilateral vestibular deafferentation on anxiety-related behaviours in Wistar rats. *Behavioural Brain Research*, *193*(1), 55–62. https://doi.org/10.1016/j.bbr.2008.04.018

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa19824