'Excess anxiety' and 'less anxiety': both depend on vestibular function

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Purpose of review
To present evidence of a functional interrelation between the vestibular and the anxiety systems based on a complex reciprocally organized network. The review focuses on the differential effects of various vestibular disorders, on psychiatric comorbidity, and on anxiety related to vertigo.

Recent findings
Episodic vertigo syndromes such as vestibular migraine, vestibular paroxysmia, and Menière's disease are associated with a significant increase of psychiatric comorbidity, in particular anxiety/phobic disorders and depression. Chronic unilateral and bilateral vestibulopathy (BVP) do not exhibit a higher than normal psychiatric comorbidity. Anxiety related to the vertigo symptoms is also increased in episodic structural vestibular disorders but not in patients with chronic unilateral or bilateral loss of vestibular function. The lack of vertigo-related anxiety in BVP is a novel finding. Several studies have revealed special features related to anxiety in patients suffering from BVP: despite objectively impaired postural balance with frequent falls, they usually do not complain about fear of falling; they do not report an increased susceptibility to fear of heights; they do not have an increased psychiatric comorbidity; and they do not report increased anxiety related to the perceived vertigo. Subtle or moderate vestibular stimulation (by galvanic currents or use of a swing) may have beneficial effects on stress or mood state in healthy adults, and promote sleep in humans and rodents. The intimate structural and functional linkage of the vestibular and anxiety systems includes numerous nuclei, provincial and connector hubs, the thalamocortical network, and the cerebellum with many neural transmitter systems.

Summary
The different involvement of emotional processes and anxiety – to the extent of 'excess anxiety' or 'less anxiety' – in structural vestibular disorders may be due to the specific dysfunction and whether the system activity is excited or diminished. Both psychiatric comorbidity and vertigo-related anxiety are maximal with excitation and minimal with loss of peripheral vestibular function.

Keywords
anxiety, bilateral vestibulopathy, Menière's disease, psychiatric comorbidity, unilateral vestibulopathy, vestibular disorders, vestibular migraine, vestibular paroxysmia

INTRODUCTION

The vertigo–balance–anxiety interface has been an integral component of medical literature since antiquity [1]. This is true for Roman, Greek, and Chinese texts in which a few detailed accounts were suggestive of specific vestibular disorders such as Menière's disease and vestibular migraine [2]. The comorbidity of vertigo and anxiety was already described in ancient classical medicine. Vertigo had the ambiguous meaning of both a disease *per se* and a symptom of other diseases like hypochrondriacal melancholy [1]. Today the psychiatric comorbidity, especially of anxiety disorders and depression, among patients with vertigo and dizziness is well recognized [3–5]. Anxiety plays a central role in the behaviour of patients with vestibular morbidity. Anxiety, traumatic stress, obsessive, and depressive disorders may be primary causes of

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KEY POINTS

- There is convincing evidence in the literature of an intimate functional interaction between the vestibular and anxiety systems, which is based on a complex reciprocally organized neuronal network.
- Most structural vestibular disorders which cause episodic excitation or a tone imbalance of bilateral vestibular function are associated with a significant increase of psychiatric comorbidity, in particular anxiety disorders or depression. Typical examples are vestibular migraine, vestibular paroxysmia, and Menière's disease. Aside from this comorbidity, these patients report increased anxiety related to vertigo.
- Chronic unilateral and BVP with loss of peripheral vestibular input do not exhibit a higher to normal psychiatric comorbidity of anxiety disorders and depression. The lack of vertigo-related anxiety in peripheral vestibulopathy is a novel finding.
- Several studies revealed four special features of the vertigo/balance – anxiety relationship in BVP. Afflicted patients usually do not complain about fear of falling, although they are frequent fallers; they do not have an increased susceptibility to fear of heights; they do not have an increased psychiatric comorbidity; and they do not report increased anxiety related to perceived dizziness, oscillopsia, or postural imbalance.
- This prompts the question of whether intact vestibular function is relevant for distressing anxiety or – in other words – whether loss of vestibular function reduces the liability to anxious behaviour.
- Noninvasive moderate vestibular stimulation (galvanic current or using a swing) may have beneficial effects on stress and mood in healthy adults and promote sleep in humans and rodents.

episodic and chronic vestibular symptoms or secondary complications of other vestibular disorders [6,7]. Fear of falling is a frequent complaint of dizzy patients and the extent to which threat-related changes in postural control are sensitive to threat-related changes in emotions has been thoroughly studied [8▪]. In dizzy patients, body posture is often characterized by a stiffening of the musculoskeletal system with increased open-loop diffusion activity of body sway, a lowered sensory feedback threshold for closed-loop balance control, and increased cocontraction of antigravity leg and neck muscles [9]. Walking is slow, cautious, and broad-based. Anxiety appears to be the critical symptom that causes the typical but not specific eye and body motor behaviour, which can be described as tonic immobility [9].

In the current review, we will focus on seemingly controversial effects of various vestibular disorders on, first, the psychiatric comorbidity and, second, the vertigo-related anxiety level. Some of these disorders, such as vestibular migraine, are characterized by inadequate vestibular stimulation associated with 'excess anxiety', others, such as bilateral vestibulopathy (BVP), by loss of function with 'less anxiety' [10▪▪].

INTERRELATION OF VESTIBULAR FUNCTION AND ANXIETY

Comorbidity of vestibular vertigo syndromes and psychiatric disorders

Several studies revealed a comorbidity, most frequently of anxiety/phobic, somatoform, and affective disorders in patients suffering from structural vertigo and balance disorders [3–5]. The same psychiatric comorbidity pattern was found in humans with fear of heights [11].

In cross-sectional diagnostic studies with patients recruited from specialized interdisciplinary treatment centres for vertigo/dizziness, nearly 50% of all dizzy patients had an active psychiatric disorder detected by standardized, clinician-administered, psychiatric diagnostic interviews (Structured Clinical Interview for DSM-IV Axis I, SCID-I) [4,12]. However, the prevalence of psychiatric comorbidity was not uniform across all structural vestibular disorders (for review see [13,14]). The highest rates were found in patients with vestibular migraine (49%) and vestibular paroxysmia (51%). Lower rates were seen in vestibular neuritis (37%) and bilateral vestibular failure (24%) [4]. These results were in line with an earlier study that used both structured interviews and psychometric tests and found a high point prevalence of psychiatric comorbidity in patients with vestibular migraine (65%) and Menière's disease (57%), but lower rates in patients with vestibular neuritis (22%) and benign peripheral paroxysmal positional vertigo (15%) [3]. By comparison, the prevalence of psychiatric morbidity in the general population is about 20% [15]. Patients with active psychiatric disorders had more vertigo-related handicaps, more physical and psychological symptoms, and a lower psychological quality of life than their counterparts without psychiatric comorbidity [4,16]. With respect to anxiety/phobic disorders only, in a cross-sectional study on a sample of 547 patients the frequency was lowest for unilateral and BVP (17.2, 17.8%) and highest for vestibular migraine (32.6%), vestibular paroxysmia (32.6%), and Menière's disease (25.9%) [4].

Distinct from the vestibular disorders with unusual and therefore unadapted vestibular excitation discussed above, moderate stimulation of the healthy vestibular system may have beneficial effects.

Beneficial emotional and mood effects of gentle vestibular stimulation

Noninvasive galvanic vestibular stimulation caused a significant diminution of the anxiety level in healthy young adults [17]. This confirmed a modulating effect of vestibular stimulation on mood state, emotional control, and anxiety level [18]. Preliminary data showed that moderate vestibular stimulation using swings may alleviate stress among college students [19], or symptoms of premenstrual syndromes [20]. The role of the vestibular system in promoting and balancing sleep is a common experience and is scientifically based on reliable neurophysiological studies [21▪,22]. This is in line with animal experiments demonstrating that rocking promotes sleep in the mouse equipped with electroencephalography and electromyography electrodes and that this effect requires functioning otolith input [23▪].

Loss of vestibular function is not associated with increased psychiatric comorbidity and vertigo-related anxiety level

As mentioned above, unilateral and bilateral vestibular loss were the only common vestibular disorders without a significantly increased comorbidity of anxiety/phobic disorders [3,4]. These two chronic vestibular disorders have further exceptional features with regard to the anxiety and mood system: first, the susceptibility to visual height intolerance (fear of heights) in BVP was not higher than that of the general population (28%), whereas susceptibility was higher in patients with other structural vestibular vertigo syndromes (vestibular migraine 61%, vestibular paroxysmia 56%, Menière's disease 48%) [24▪]. This was unexpected, since fear of heights is dependent on body posture, and visual control of balance at heights can no longer substitute vestibular input. Second, patients with acquired BVP rarely complain of being anxious about falling. This is also surprising, since this condition impairs postural stability and thus causes frequent falls [25], in particular during locomotion on uneven ground and in darkness when vision cannot substitute. In a controlled cross-sectional study, the rate of recurrent fallers was increased in BVP patients despite a low-to-normal fear of falling as determined by the Falls-Efficiency-Score-International [26]. Third, BVP patients – separate from their low psychiatric comorbidity – also have less vertigo-related anxiety.

This is supported by a survey on a total of 7083 outpatients with the key symptoms of vertigo, dizziness, and balance disorders all diagnosed in the German Center for Vertigo and Balance Disorders, Munich, Germany. In the years from 2010 to 2012 (group 1, $N = 687$) and 2015 to 2017 (group 2, $N = 6396$), the Vertigo Handicap Questionnaire (VHQ; [27]) was performed to measure physical and psychosocial handicap using 25 items [10▪▪]. The VHQ allows two subscale scores, handicapped activity and anxiety, to be generated. Moreover, all patients completed the Beck Anxiety Inventory (BAI; [28]) and the Trait Anxiety subscale of the State-Trait Anxiety Inventory (STAI; [29]) as further measures to assess anxiety in general. A total of 547 patients in group 1 were additionally examined with the Structured Clinical Interview for DSM-IV (SCID-I; [30]) to assess patients' mental disorders and psychiatric comorbidity independently of their diagnoses (for details see [31]). The VHQ anxiety scores were lowest for patients with chronic BVP and unilateral vestibulopathy and highest for patients with functional vertigo (Fig. 1). Significantly higher VHQ anxiety scores, as compared with BVP, were found for benign paroxysmal positional vertigo, vestibular paroxysmia, Menière's disease, vestibular migraine, and functional vertigo. Regarding the scores on the BAI and the STAI-trait, patterns for the diagnostic groups showed no significant group differences, which means that the VHQ anxiety scores cannot simply be explained by psychiatric comorbidity of anxiety disorders. Vestibular hypofunction is associated with both a lower Vertigo Symptom Scale-anxiety and lower frequencies of psychiatric comorbidity compared with vestibular hyperfunction or an acute vestibular tone imbalance (Fig. 2). These data strongly suggest the view that a functioning peripheral vestibular system is the prerequisite for the development of anxiety related to vertigo, and explains why anxiety scores were low in BVP patients [10▪▪].

Various animal studies on the effects of experimental vestibular loss have yielded conflicting results from reduced anxiety to increased anxiety [33]. Overall they do not support the hypothesis that rodents exhibit increased anxiety-like behaviour, and suggest that cognitive deficits in spatial memory may be independent of the emotional effects of vestibular loss [34].

Structural and functional linkage between the vestibular and anxiety systems

There is accumulating evidence that the vestibular system – by means of reciprocal interconnections with various nodes of the multilocal anxiety system – influences both cognition and emotional regulation in animal models and humans [35▪]. This complex vestibular-anxiety circuitry further involves thalamocortical and cerebellar networks, all of which subserve sensorimotor functions, emotional,

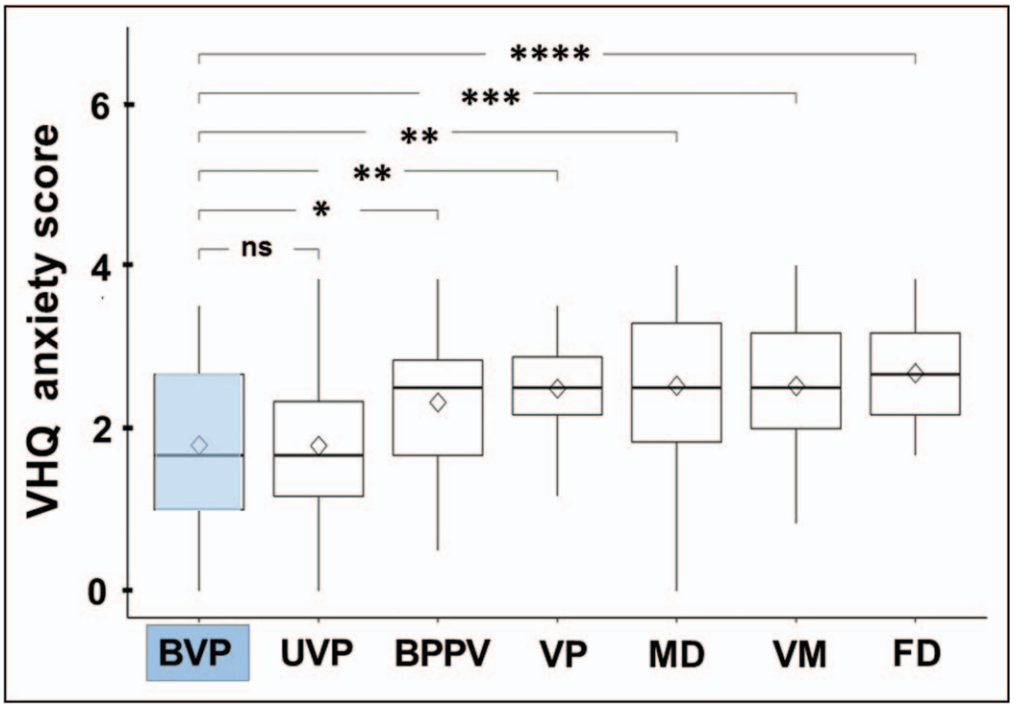

FIGURE 1. Vertigo Handicap Questionnaire anxiety score boxplots from different vestibular syndromes of consolidated datasets for each disease and a *t* test significance level compared with the reference group of bilateral vestibulopathy (in blue) ($^{*}P \leq 0.05$; $^{**}P \leq 0.01$, $^{***}P \leq 0.001$; $^{****}P \leq 0.0001$, $^{ns}P > 0.05$). The vestibular syndromes were bilateral vestibulopathy, unilateral vestibulopathy/vestibular neuritis, benign paroxysmal positional vertigo, vestibular paroxysmia, Menière's disease, vestibular migraine, and functional vertigo/dizziness. Note that the scores were lowest for bilateral vestibulopathy and unilateral vestibulopathy and highest for Menière's disease, vestibular migraine, and especially for functional vertigo/dizziness. Median (horizontal solid line), mean (diamond square), boxplot rectangle (lower 25% quantile and higher 75% quantile). Reprinted under CC BY license from and modified from [10▪▪].

cognitive, and visceral responses, and contribute to the composition and update of internal models of body orientation in space. The structural and functional separation of the two thalamic nuclei complexes allows a lateralization of right and left hemispheric functions to develop during cerebral maturation [36]. Furthermore, it makes possible the simultaneous performance of sensorimotor and cognitive tasks which require different spatial reference systems in opposite hemispheres, for example, egocentric manipulation of objects (handedness) and allocentric orientation of the self in the environment [36]. Based on a study using transcranial direct current stimulation, a possible link between anxiety and the vestibular system with respect to vestibular hemispheric dominance was suggested [37]. Notably, MRI imaging techniques on the functional connectivity of the vestibular system revealed a dominance of the right hemisphere in right-handers not only in the pari-eto-insular vestibular cortex [38] but also of vestibular functional connectivity in the upper brainstem and thalamus [39].

The interaction in the networks described above is based on intrinsic neurotransmitters of the inner ear, neurotransmitters of thalamocortical and limbic pathways, and serotonergic and nonserotonergic projections from locus coeruleus and nucleus raphe [40]. Understanding of vestibular function, including endocrine and autonomic stress responses, depends on the knowledge of the various transmitter systems. Corticotropin-releasing factor, for example, is a neuropeptide synthesized in the hypothalamic paraventricular nucleus. It has been implicated in stress and anxiety processes and acts on the lateral vestibular nucleus, which contributes to adjustment of postural balance [41▪]. This exemplifies the close interconnection of stress, anxiety, and balance control at the level of the pontomedullary vestibular nuclei.

Balaban *et al.* [42] described pathways that mediate autonomic control, vestibulo-autonomic interactions, and anxiety within a circuitry including a parabrachial nucleus network and its reciprocal connections with the central amygdaloid nucleus, the infralimbic and insular cortex, and the hypothalamus [43–45].

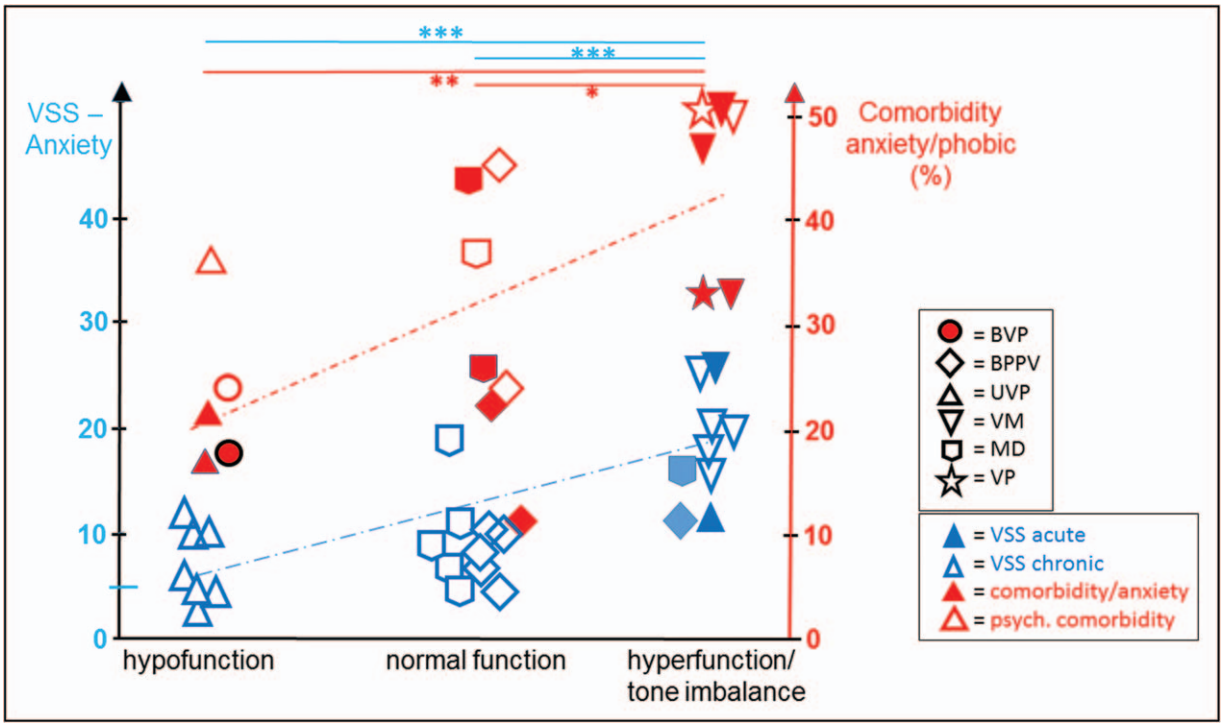

FIGURE 2. Vertigo-induced anxiety as measured by subjectively perceived symptom anxiety according to the Vertigo Symptom Scale-anxiety dependent on the organic diagnosis and the vestibular function (hypofunction, normal function, hyperfunction, or acute tone imbalance) (left side in blue). Values of 0 represent 'not at all', values of 100 'very high'. Frequency (in percentage) of psychiatric comorbidity (open red symbols) and comorbidity for anxiety/phobic disorders (filled red symbols) dependent on the organic diagnosis and the vestibular function (hypofunction, normal function, hyperfunction, or acute tone imbalance) (right side in red). Note that vestibular hypofunction is associated with both lower Vertigo Symptom Scale-anxiety values and lower frequencies of comorbidity compared with vestibular hyperfunction/acute tone imbalance. Two-sample *t* tests, significance level: $^{*}P \leq 0.05$; $^{**}P \leq 0.01$, $^{***}P \leq 0.001$; Vertigo Symptom Scale-anxiety $R^2 = 0.5614$, comorbidity $R^2 = 0.4394$. Filled blue symbols indicate Vertigo Symptom Scale-anxiety in the acute phase of the disease, open blue symbols Vertigo Symptom Scale-anxiety in the chronic phase of the disease after 6 weeks and 3, 6, and 12 months. BPPV, benign paroxysmal positional vertigo; BVP, bilateral vestibulopathy; MD, Menière's disease; UVP, unilateral vestibulopathy; VM, vestibular migraine; VP, vestibular paroxysmia. Data from [3,4,12,16,32].

CONCLUSION

The differential effects of vestibular disorders on the anxiety level, in terms of either 'excess anxiety' or 'less anxiety', can be attributed to whether vestibular function in the particular condition is increased (acute excitation or acute vestibular tone imbalance) or decreased (chronic vestibular loss). Examples of episodic excitatory vestibular disorders are vestibular migraine and vestibular paroxysmia; examples of diminution of vestibular function are unilateral and BVP.

The major point we want to make here is the separation between psychiatric comorbidity in dizzy patients on the one hand and anxiety triggered by particular vestibular disorders in patients who do not fulfill the diagnostic criteria of an associated psychiatric disorder on the other hand. Nevertheless, in patients with a bilateral loss of peripheral vestibular function, both anxiety related to vertigo and psychiatric comorbidity are low [10▪▪].

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Conflicts of interest

There are no conflicts of interest.

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