

Review

Anxiety and otovestibular disorders: Linking behavioral phenotypes in men and mice

Allan V. Kalueff^{a,*}, Kotaro Ishikawa^b, Andrew J. Griffith^b

^a *Laboratory of Clinical Science, Building 10, Room 3D41, National Institute of Mental Health (NIMH),
10 Center Dr. MSC 1264, NIH, Bethesda, MD 20892-1264, USA*

^b *Otolaryngology Branch, National Institute on Deafness and Other Communication Disorders (NIDCD), NIH, Rockville, MD, USA*

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Abstract

Human anxiety and vestibular disorders have long been known to co-occur. Paralleling human clinical and non-clinical data, mounting genetic, pharmacological and behavioral evidence confirms that animal anxiety interplays and co-exists with vestibular/balance deficits. However, relatively few animal models have addressed the nature of this relationship. This paper examines side-by-side human psychiatric and otovestibular phenotypes with animal experimentation data, and outlines future directions of translational research in this field. Discussed here are recently developed specific animal models targeting this interplay, other traditional animal tests sensitive to altered anxiety and vestibular domains, and the existing problems with translation of animal data into human phenotypes. The role of hearing deficits and their contribution to anxiety and vestibular phenotypes are also outlined. Overall, the overlap between anxiety and balance disorders emerges as an important phenomenon in both animal and clinical studies, and may contribute markedly to the complexity of behavioral and physiological phenotypes. Animal experimental models that focus on the interplay between anxiety and vestibular disorders are needed to improve our understanding of this important biomedical problem.

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Keywords: Anxiety spectrum disorders; Vestibular and balance disorders; Animal (experimental) models; Behavioral phenotyping; Genetic and pharmacological models; Interplay; Co-morbidity; Otovestibular phenotypes

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1. Introduction

Anxiety is a complex psychopathology that includes generalized anxiety, panic, phobic, post-traumatic stress

and obsessive-compulsive disorders [73,104]. Like some other psychiatric disorders [40,79,99,123,140], human anxiety has long been associated with vestibular/balance dysfunctions (VBD), suggesting their pathogenetic interplay [2,5,60–62,86,116,117,119,139]. Several reviews have comprehensively evaluated clinical data linking stress-related disorders with VBD, and discussed several theories of their interplay, including anxiety-evoked VBD (psychosomatic theory), VBD-

* Corresponding author. Tel.: +1 301 594 0126; fax: +1 301 402 0188.

E-mail addresses: kalueva@mail.nih.gov, avkalueff@inbox.ru (A.V. Kalueff).

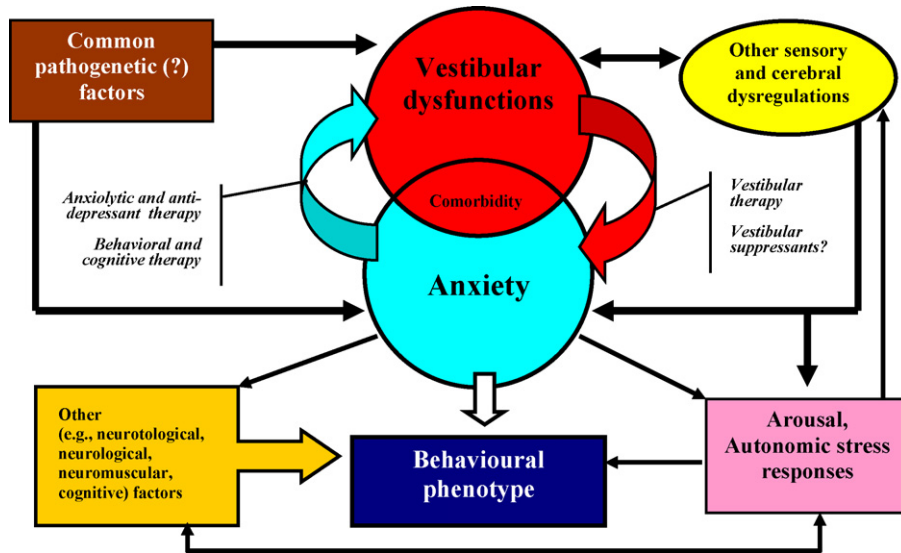


Fig. 1. Pathogenetic links between vestibular dysfunctions and anxiety, their interplay in determining behavioral phenotype, and possible ways of therapeutic interventions (see text for details).

evoked anxiety (somatopsychic model) and the possibility of common pathogenetic mechanisms for both states (Fig. 1) [7,8,39,42,61,62,121,139].

In addition to rich clinical evidence [11,34,38,100,159,162], many non-clinical human studies also show that balance/postural control negatively correlates with state and trait anxiety levels [1,15,21,22,109,132,157], implying that both normal and pathological brain mechanisms participate in anxiety–VBD interplay. For example, separation anxiety in children triggers their balance dysfunctions [34]. However, VBD in anxious group in this study were not associated with overt neurological or neurotological phenotypes, suggesting that anxiety led to balance defects, and not the otherwise. Although poor

balancing and postural control is particularly pronounced in the elderly (accompanied by increased anxiety and specific fears of falling [34]), postural control negatively correlates with anxiety in both older and younger adults [21,22], implying that anxiety–vestibular interplay represent a fundamental physiological aspect, rather than an age-specific problem. The fact that vestibular training may reduce some forms of anxiety, while cognitive and behavioral therapy of anxiety improves balancing performance [21,53,62,162] further supports the overlap between human anxiety and VBD (Figs. 2 and 3).

In line with frequent comorbidity of VBD with anxiety, they also show overlapping psychopharmacology, including sensitivity to different classes of anxiolytics and antidepressants

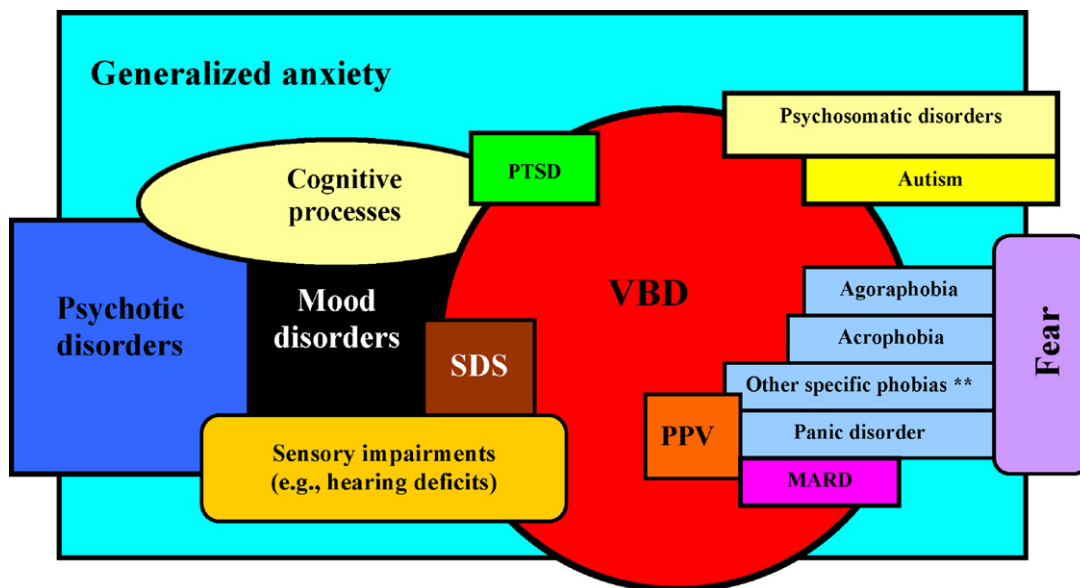


Fig. 2. Pathogenic clusters related to stress/anxiety and vestibular/balance disorders (VBD): PTSD, posttraumatic stress disorder; PPV, phobic postural vertigo; SDS, serotonin reuptake inhibitors discontinuation syndrome; MARD, migraine-anxiety associated dizziness; **specific phobias can include fears of falling (especially in a social embarrassment context), or that vestibular problems may be a sign of more serious or even fatal disorders.

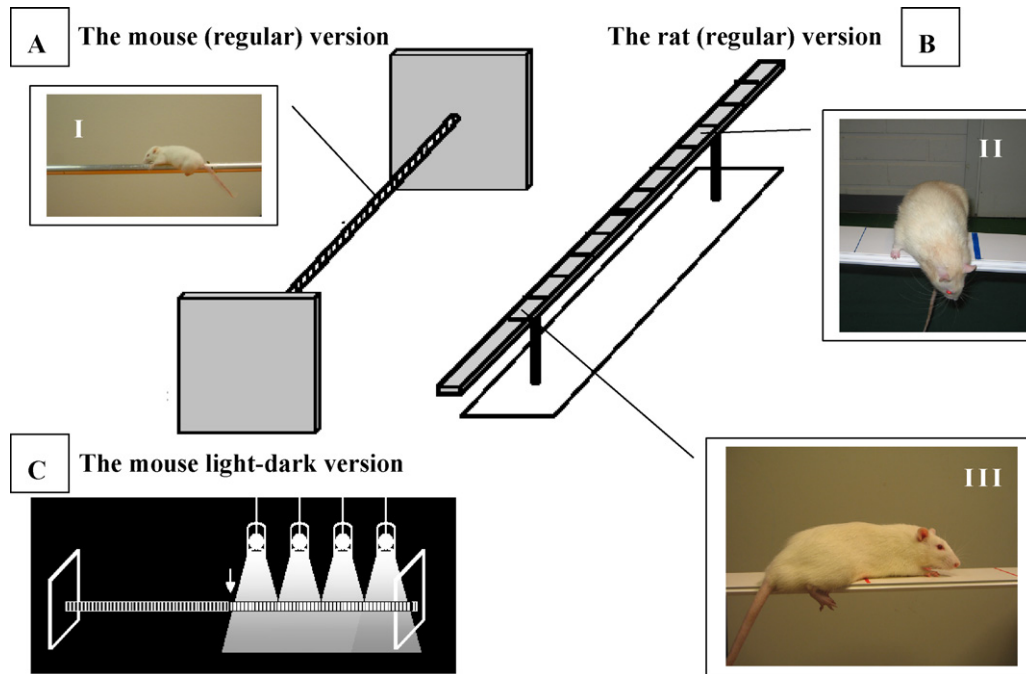


Fig. 3. Rodent Suok test (ST) behaviors relevant to vestibular and anxiety phenotypes. The regular ST is based on rodent balancing on a horizontal elevated rod (mice; A) or alley (rats; B), and measures balance control (falls and missteps) and anxiety (assessed by reduced horizontal, vertical and directed exploration). The light-dark ST (C) consists of the same apparatus, half of which is brightly lit (aversive area) in the dark experimental room. (I) A mouse of anxious BALB/c strain; note an anxiogenic freezing-like behavior and misstep (hindleg slip); (II) rat down-directed exploration (head dip); (III) rat horizontal locomotion and misstep (hind leg slip) [67–69].

(Table 2). Moreover, while serotonergic antidepressants (such as SSRIs; selective serotonin reuptake inhibitors) improve vestibular function in humans, their discontinuation provokes acute vestibular deficits, conceptualized as SSRI discontinuation syndrome (SDS) [12,138]. Other recently suggested subtypes of VBD include phobic postural vertigo (PPV) [52,118], migraine-anxiety related dizziness (MARD) [40] and chronic psychogenic dizziness (CPD) [140], contributing to the growing recognition of heterogeneity and complexity of VBD associated with anxiety spectrum disorders (Fig. 2).

Animal models are indispensable tools for examining the effects of physiological, pharmacological, behavioral and genetic manipulations, as well as for testing neurobiological hypotheses and finding candidate genes for human psychiatric and neurological disorders [9,16,23–25,28,71,72,107]. The growing recognition of pathogenetic link between anxiety and VBD [5,8] prompts the need for animal models that target their interplay and further corroborate clinical data.

Despite vast clinical literature, and well-established animal screens for stress or vestibular functions (Table 1), relatively few animal studies have addressed the problem of anxiety–VBD interplay. The aim of the present paper is to parallel animal and human behavioral and neurological data in order to improve our understanding of anxiety–VBD pathogenesis, and to outline further directions of translational research in this field.

2. Basic research and behavioral animal models

Recent animal data show that the vestibular system is modulated by neuromediators (such as serotonin or gamma

aminobutyric acid; GABA) involved in the regulation of stress and anxiety responses [5,6,8,41,48,49]. Likewise, anatomic data show that vestibular nuclei (a site of sensorimotor integration, crucial for posture and motor activity) densely project to brain areas that are involved in the regulation of emotional behavior [6,48,49], collectively implying that commonality of neuromodiation and neural circuits may be one of the reasons why anxiety and VBD frequently co-occur.

Several animal studies have attempted to mimic specifically the pathogenetic link between anxiety and sensorimotor/balancing deficits. In their pioneering studies, Chapouthier's group [83,84] used the rotating beam test to assess balance control in two mouse strains that differ markedly in their anxiety levels. Analyses of sensitive behavioral parameters (such as the number of falls, missteps, position of tail and trunk) showed poorer balancing in highly anxious BALB/c (compared to non-anxious C57BL/6 [107]) mice, confirming that anxiety–VBD interplay does exist in animals. Studies have established a direct correlation between the level of spontaneous or induced anxiety and performance on the rotating beam, measured by balance and posture. Importantly, balance control and postural abilities of anxious mice were improved by acute anxiolytic drugs, whereas balancing performance in non-anxious mice was worsened by anxiogenic drugs, strongly supporting the link between rodent anxiety and balance control (Table 3).

Another study from the same group reported a model of spatial anxiety in mice, comprised of rotating tunnel and beam (controlled by computer), evoking visuo-idiopathic and kinesthetic sensory conflict during mouse active locomotion [125]. As can be predicted, anxious BALB/c mice (more than non-anxious

Table 1
Traditional animal models of stress and vestibular functions

Domains and models	
Anxiety	Many anxiety models are based on rodent exploratory behavior, and include the elevated plus maze, the open field test, holeboard, the light-dark test, mirrored chamber and free exploratory paradigm [33,71,72]. The elevated plus maze, based on fear of novelty and height, is relevant to modeling human generalized anxiety as well as more specific states of interest, such as agoraphobia and acrophobia [36] (other elevated mazes are also used in anxiety research [e.g., 33]). Widely used in behavioral neuroscience of stress, the open field test is based on fear of novel open arenas, and is relevant to modeling human generalized anxiety and more specific states of interest (such as agoraphobia) [25]. Conceptually similar to the open field, the holeboard test has an additional behavioral endpoint – head dipping (exploration of holes in the floor), sensitive to anxiety. Animal performance in these tests is sensitive to anxiolytic/anxiogenic drugs and manipulations, including anxiolytic action of chronic antidepressant [25,72,107].
Depression	Commonly used models include “despair” paradigms (such as Porsolt’s forced swim, tail suspension tests and learned helplessness), as well as maternal/social deprivation and “anhedonic” chronic stress [25,28,71]. In Porsolt’s test, rodents swim in an inescapable water tank and display despair-like immobility, which is generally reduced by antidepressant agents. Widely used as a test for antidepressant effects, this model also has some anxiety-related rationale (e.g., exploration, search for escape), and may be sensitive to some anxiolytic/anxiogenic drugs [73,107]. The tail suspension test is another traditional model of depression, based on despair-like immobility of animals suspended vertically by tail [25,28,71].
Vestibular functions	Testing of animal vestibular system usually includes assessment of righting reflexes, and their performance in the rotarod, horizontal beam, spin, tilt and unstable platform tests (also see [25,76,81,110,152] for details).

C57BL/6 mice) reduced locomotion in this test after sensory conflicts, suggesting that their higher spatial anxiety was associated with sensorimotor disintegration. Moreover, paralleling clinical data on efficacy of SSRIs in anxiety and vestibular disorders (Table 2), SSRI antidepressants have been shown to improve balance and postural control in anxious BALB/c mice, generally resembling positive effects on balancing and anxiety produced by benzodiazepine anxiolytics [153]. These findings have provided further experimental evidence for anxiety–VBD interplay, also implying the utility of SSRIs in treating anxiety-induced VBD.

Taking a behavior-oriented approach, a different group introduced the Suok test (Fig. 3) for simultaneous profiling of rodent anxiety, activity and neurological/vestibular phenotypes [67–69]. Using this model, they assessed baseline anxiety (by reduced horizontal and side/down-directed exploration of the rod) in several mouse strains and, stressing these mice, demonstrated their higher anxiety and poorer balancing [67] (also see similar results in a later study in rats [68]). The Suok test reliably detected state and trait anxiety and balancing deficits in rodents, as assessed in anxious (129S1) vs. non-anxious (C57BL/6) strains, stressed vs. non-stressed groups, and anxiogenic-treated

(vs. control) animals [69]. In contrast, non-sedating doses of anxiolytic drugs reduced rodent anxiety and improved balancing performance in this test (Table 3).

Collectively, these studies strengthen integrative behavioral and neurological research of anxiety/vestibular interplay, and demonstrate its utility in modeling stress-evoked vestibular anomalies, screening potential anti-stress and vestibular-suppressant drugs, phenotyping genetically modified animals, and finding candidate genes responsible for vestibular/neurological disorders and modulating anxiety–VBD interplay.

3. Available genetic models

Genetic components regulating animal balance/sensorimotor performance in neurological tests [23,78,156], and animal emotionality in different behavioral paradigms [24,25], support the importance of genetic models based on VBD and anxiety-related phenotypes. As genetically-targeted (mutant or transgenic) animals are widely used to study anxiety and VBD, animals with disturbed vestibular system and altered anxiety [26,56,81,95,102,115,158] may be a useful tool to study

Table 2
Clinical pharmacology of anxiety and vestibular disorders

Drugs	Effects
Selective serotonin reuptake inhibitors ^a	Effective to treat vertigo associated with anxiety and panic/phobic disorders, and anxiety and depression associated with vestibular deficits (including patients resistant to benzodiazepine therapy). Discontinuation leads to dizziness, vertigo and motor incoordination [103,120,134,143,146]
Tricyclic antidepressants	Effective to treat vertiginous migraine [146]
[5pt] Benzodiazepines	Effective to treat anxiety, panic disorder and phobias, but can also be used as fast-acting vestibular suppressants (but only for a short time, due to sedative and cognitive effects) [103]
GABA ^b -mimetics	Phenibut (β -phenyl-GABA) is effective in anxiety, depression and vestibular disorders [82]. Piracetam exerts GABA-active anxiolytic effects, and is effective to treat vertigo of both central and peripheral origin [98,111]

^a Exert anxiolytic effects after chronic administration.

^b GABA: gamma-amino butyric acid.

Table 3
Experimental animal models relevant to mimicking pathogenetic link between anxiety and vestibular disorders

Experimental models and species	Effects on		References
	Anxiety	Vestibular functions	
Pharmacological manipulations			
Selective serotonin reuptake inhibitors (mice)	↓	↑	[153]
Benzodiazepines (diazepam; mice, rats)	↓	↑	[69,84,85,87]
Methyl β-carboline-3-carboxylate (mice)	↑	↓	[153]
Pentylentetrazole (mice, rats)	↑	↓	[68,69]
Genetic manipulations			
Anxious (vs. non-anxious) inbred strains (mice)	↑	↓	[67,83–85]
<i>Hdb</i> mutant heterozygous (+/–) mice	↑	↓	[97,122]
Behavioral manipulations			
Stressed (vs. non-stressed) animals (mice, rats)	↑	↓	[67–69]
Physiological manipulations			
Poorer recovery of balance functions (after labyrinthectomy) following immobilization stress (rats)	↑	↓	[161]

(↑) Increased and (↓) reduced.

anxiety-balancing interplay. A comprehensive Mouse Genome Informatics database [95] contains a growing number of mutant mice with simultaneously altered balance and anxiety, further illustrating the link between anxiety and vestibular dysfunctions, and offering genetic models potentially relevant to mimicking anxiety–VBD pathogenesis. For example, mice lacking β3 subunits of GABA-A receptors display pronounced neurological and balance deficits in different tests, accompanied by hyperarousal and higher behavioral responsivity [56]. Further useful information can be obtained through other publicly available on-line databases, analyzing spontaneous mutations (e.g., aberrant auditory physiology, severe motor/vestibular deficits, and panic-like freezing in the *shaker 1* (*Myo7a*) mice [63,122]) or anxiety and vestibular phenotypes of different inbred mouse strains [101].

However, as many of these genetic models display aberrant hearing (see further), this may limit the problem of anxiety–VBD interplay to “sensory” aspect, and be confounded by the impact on anxiety produced by reduced sensory inputs. From this point of view, of particular interest are animals with abnormally functioning vestibular organs, such as *Headbanger* (*Myo6*, *Hdb*) mutants, phenotypically different from the *shaker 1* mice [63,97,122] (Table 3). Born with normal vestibular and behavioral phenotypes, *Hdb*+/– mice develop progressive abnormal arrangement of the vestibular hair cells, and may allow a better focus on vestibular-related anxiety [97]. Indeed, neurological testing revealed progressive development of vestibular phenotype in these mice [122], while pilot behavioral tests confirmed their increased anxiety at the age of 1–2 months [97]. Taken together, this supports the notion that a detailed analysis of sensorimotor integration in animal genetic, pharmacological and behavioral models is crucial for comparison with clinical data, and to increase our understanding of the link between anxiety and vestibular functions in both animals and humans.

In addition to synergistically affected anxiety and vestibular profiles, transgenic and mutant animals with differentially affected vestibular and anxiety domains (e.g., impaired balance

but normal [81] or reduced [94] anxiety) may offer new insights to the problem of genetic and environmental factors underlying anxiety/VBD interplay, and neural mechanisms responsible for individual resistance to these overlapping disorders. However, caution is needed when interpreting these data, as genetically-evoked VBD may lead to specific animal behaviors (such as freezing/confusion, hyperactivity, increased thigmotaxis) which can be mistaken for increased or reduced anxiety.

In general, correct dissection between animal neurological, motor, cognitive (e.g., motor learning), behavioral (anxiety, stress) and vestibular deficits is becoming critical in neurobehavioral research using different genetic models [25,72,152]. For example, transgenic mice over-expressing amyloid precursor and presenilin-1, show a complex phenotype that includes increased locomotion, poor memory and learning, and marked balance deficits [3]. In a situation when several domains seem to interplay, this illustrates the importance of assessment of other domains and systems (beyond anxiety and vestibular functions) that may contribute to a complex phenotype of interest.

Another example may be vitamin D receptor (VDR) knockout mice that display hypoactive anxious phenotype, but normal horizontal rod balancing and unaffected righting reflexes [67,70]. Although this may be interpreted as unaffected balancing in VDR–/– mice and their resistance to anxiety-evoked balance deficits, further detailed phenotyping revealed aberrant swimming in these mice, suggesting specific vestibular deficits (also consistent with their aberrant inner ear development and hearing deficits; own unpublished data; [166]). Thus, the lack of balance deficits in some strains may be confounded by hypolocomotion and anxiety (e.g., more cautious rod retention), requiring more specialized tests to reveal their aberrant vestibular/hearing phenotypes (which may be clinically relevant [10]).

The importance of correct domain-by-domain dissection of complex behavioral phenotypes can also be seen in serotonin transporter (SERT) knockout mouse model. For example, SERT–/– mice on different genetic backgrounds display hypoactive anxious phenotype in many behavioral tests, also dis-

playing poorer rotarod retention [54,74] that may be interpreted as poor balancing associated with increased anxiety (stress-evoked VBD?), or a separate vestibular phenotype associated with central serotonin dysregulation. However, unaffected Suok test performance, righting reflexes, ability to swim [74] and unimpaired hearing functions (own unpublished data) in these mice suggest the lack of overt impairments in the neurotological domain. Thus, SERT^{-/-} mice appear to have unaltered otovestibular phenotype, although their overall behavioral performance may be confounded by reduced activity, high anxiety and likely neuromuscular problems. Collectively, these examples further support the importance of step-by-step behavioral dissection of complex phenotypes of genetically modified animals and their in-depth unbiased assessment in different tests [25,72], to minimize possible risks of misinterpretations.

4. Future challenges and methodological considerations

Among many different subtypes, several forms of human anxiety, conceptualized as “space-and-motion discomfort” (agoraphobia, acrophobia and fear of falling), are particularly prone to interplay with balance disorders [60–62]. Thus, one possibility to foster translational research in this field may be developing new, disorder subtype-specific experimental models, such as animal models of PPV or MARD. For example, mounting data indicates that fear of falling modifies strategies of postural control in humans [1,121,159], suggesting the need to study this aspect further, including specific animal models that target this domain. On the other hand, recent human data showing utility of vestibular therapy to alleviate acrophobia [21,96,97,159] may lead to interesting animal behavioral models that may be clinically relevant to such therapy.

In addition to already mentioned animal models that specifically target anxiety–VBD interplay [67,83,84], many other popular tests (commonly used to study animal behavior) appear to be sensitive to VBD. For example, aberrant rodent swimming (e.g., in Porsolt’s test; Table 1), such as frequent sinking and circling, is suggestive of vestibular dysfunctions in these animals [56,76,112,114,128]. Aberrant animal behavior in the tail suspension test may be relevant to vestibular functions, and VBD can indeed be seen in this model (for example, manifest in specific “spinning” phenotype) [29]. Likewise, thigmotaxis (staying close to the walls vs. open zones) and hole poking in some traditional novelty-based anxiety tests (Table 1) are sensitive to both vestibular anomalies and anxiety [74,141]. Similarly, several anxiety-sensitive behaviors (such as elevated plus maze head dips [down directed exploration] and vertical rears in novel arenas [31,112,124]) strongly rely on vestibular stimuli and therefore are sensitive to vestibular deficits [14] in addition to mimicking animal “agoraphobia” and/or “acrophobia” [36]. For example, experimentally induced vestibular deficits may lead to reduced vertical activity and shift animal exploration to increased horizontal activity [112]. Since these behavioral alterations may be misinterpreted as “reduced anxiety”, it may be suggested that a balance between vertical and horizontal activity is monitored in behavioral phenotyping research, to rule out aberrant behavior due to VBD.

Recent studies confirming that rodents may be tested in virtual reality models [55], may lead to further interesting behavioral paradigms to study anxiety–VBD interplay (consistent with common use of virtual reality tests to study human VBD and anxiety-related disorders [145,155]). The sex difference in anxiety/vestibular phenotypes, as reported in some human and animal studies [86,127,155] represents another interesting aspect for further studies in this field. Given well-known sex differences in emotionality and anxiety in animals and humans, it will be interesting to study whether animal anxiety and balancing phenotypes may be predictably modulated by gender, and whether steroid modulation (known to influence anxiety [73]) may play a role in treating VBD and their comorbidity with anxiety (see [161] for discussion).

Another interesting aspect that requires further investigation in both animal and human studies, is the role of somatic and other physiological mechanisms associated with both anxiety and balance disorders, such as hyperventilation and sleep apnea [116] (see, for example, [9] for animal models of hyperventilation; and [53] for discussion on human hyperventilation-evoked dizziness).

Finally, vestibular deficits are known to cause cognitive dysfunctions in both humans [9,18,130] and animals [93,129,137]. From this point of view, the role of cognitive factors has to be considered in detail for both anxiety–vestibular pathogenesis and the search for new strategies of its therapy [43]. Given a key role of cognitions in anxiety and other stress-precipitated brain disorders [73], and the important role of vestibular stimuli for behavior and cognitive processes [18,96,129,130,137,141], altered cognitive domain may contribute to frequent co-occurrence of VBD and anxiety disorders, as has already been suggested [60,93,131,133] (Fig. 2). Likewise, as behavioral phenotyping nowadays usually involves test batteries [25], the effects of prior test history on vestibular/balance control (in addition to their known effects on anxiety [152]) and anxiety–VBD interplay, merit further scrutiny.

5. Neurotological/otovestibular perspective

Although anxiety–vestibular interplay is the main scope of this paper, the importance of neurotological phenotypes should not be ignored in behavioral stress research. As auditory and vestibular systems are anatomically and physiologically interrelated [37,38,57,65], and their functions and dysfunctions sometimes share common genetic determinants [45,59,105,122], this relationship may further contribute to the complexity of animal and human behavioral phenotypes.

In general, the assessment of hearing is an important part of phenotyping research in animals and humans [37,45,65,89,101,105,113]. However, testing hearing is not what a behavioral laboratory (involved in anxiety research) will routinely do as their top priority. This situation is clearly unfortunate, since many background animal strains (including those commonly used for neurobehavioral research) do show various hearing deficits [50,65,101,108,151] that may affect all animal behaviors, including anxiety and balancing profiles in different tests. Although the exact pathophysiological mechanisms may

vary, analysis of hearing and vestibular phenotypes of different inbred [13,58,101] and mutant [64,66,95,122] mice shows a predictable overlap between these two domains. Given the growing number of animal genetic models that display both anxiety and hearing deficits [32,77,95,150,154], potential otovestibular factors in anxiety-balancing interplay should be considered in behavioral phenotyping research.

In general, animal genetic and behavioral data discussed here (also see [35]) strikingly parallel clinical findings, supporting overlap between human psychiatric and neurotological phenotypes (Figs. 1 and 2) [45,88,90,105,135,136,147,160,163,165]. These parallels are further corroborated by pharmacotherapy evidence showing the effects of psychotropic drugs in therapy of hearing deficits in humans. For example, in addition to their known positive effects on anxiety and VBD, serotonergic antidepressants (such as SSRIs) improve hearing abilities in patients [27,44], and the same phenomenon may exist in animals (including experimental models with pharmacogenic or genetic alterations in central serotonergic system [89]). Taken together, these data indicate the importance of audio-vestibulo-affective mechanisms (mediated through certain neuromediators, such as serotonin [89]) in the regulation of animal and human emotional behaviors.

Notably, several mouse strains show simultaneous anxiety, vestibular and hearing deficits [101,122], and may represent “neurotological” models relevant to targeting anxiety–audio–VBD interplay in humans [149]. For example, DBA/2 and BALB/c mouse strains have genetically-based audio-vestibular and anxious phenotypes, making them a useful genetic model relevant to anxiety–VBD interplay, as well as an interesting genetic background for various mutations that bidirectionally affect these domains [13,58,83,85,151]. Since this emphasizes the importance of in-depth parallel screening of hearing, vestibular and anxiety phenotypes, some research methods that allow simultaneous profiling of several relevant domains (e.g., acoustic startle: anxiety + hearing [30,148,152]; pre-pulse inhibition: hearing + cognitive processes [25,148]), may be particularly feasible for such high-throughput behavioral screening. However, mutated genes in the deaf/vestibular mouse models may also have other effects in the nervous system that can affect animal anxiety and other behaviors via mechanisms unrelated to VBD (see [76,92] for discussion) – the possibility that has to be considered when translating aberrant animal phenotypes into human behavioral disorders.

6. Conclusion

Human anxiety and VBD are an increasing clinical problem [7,57,73,104,106]. Like in humans, anxiety and balance profiles in animal behavioral models do not exist independently, but frequently overlap and interplay (so in some experimental models “initial” anxiety phenotype may subsequently provoke aberrant vestibular phenotypes, and vice versa). To address this problem in detail, more specific animal models (such as summarized in Table 3) may help establish common pathogenetic and genetic mechanisms linking anxiety and otovestibular dysfunctions, as well as further explore mechanisms of individual

resistance to anxiety/VBD, and find new effective treatments for these disorders [4,17,75,110,142,144,146]. Further research is also needed to understand more fully central vs. peripheral inputs in integral pathogenesis of vestibular [11,17,46,47,143], behavioral [72,76] and otological [38,51,160,164] disorders, as well as the role of other sensory modalities in the regulation and integration of anxiety [25,152] and VBD [19,20,126]. Finally, a careful domain-oriented dissection is needed to distinguish between psychogenic or somatopsychic types of anxiety–vestibular pathogenesis [42,147], as well as their comorbidity due to common pathogenetic factors, or co-occurrence due to unrelated mechanisms (that individually affect these domains at different levels [11,72,76,80,91]), also see Figs. 1–3. Collectively, these strategies of research will improve the validity of experimental models of brain and behavioral disorders, and foster their *integrative* modeling, importance of which is becoming recognized in the literature [72].

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