The dizzy patient: don't forget disorders of the central vestibular system

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Abstract | Vertigo and dizziness are among the most common complaints in neurology clinics, and they account for about 13% of the patients entering emergency units. In this Review, we focus on central vestibular disorders, which are mostly attributable to acute unilateral lesions of the bilateral vestibular circuitry in the brain. In a tertiary interdisciplinary outpatient dizziness unit, central vestibular disorders, including vestibular migraine, comprise about 25% of the established diagnoses. The signs and symptoms of these disorders can mimic those of peripheral vestibular disorders with sustained rotational vertigo. Bedside examinations, such as the head impulse test and ocular motor testing to determine spontaneous and gaze-evoked nystagmus or skew deviation, reliably differentiate central from peripheral syndromes. We also consider disorders of 'higher vestibular functions', which involve more than one sensory modality as well as cognitive domains (for example, orientation, spatial memory and navigation). These disorders include hemispatial neglect, the room tilt illusion, pusher syndrome, and impairment of spatial memory and navigation associated with hippocampal atrophy in cases of peripheral bilateral vestibular loss.

Vertigo and dizziness are common complaints in neurological patients. In a general academic emergency department, these symptoms were evident in 1–10% of the overall attendances[1,2], and they account for about 13% of neurological consultations[3,4]. Up to 25% of patients who present with vertigo and dizziness are discovered to have central disorders[2,5,6]. Dizziness is often attributable to benign conditions, in particular, peripheral vestibular syndromes (32%) or orthostatic hypotension (13%); however, a serious neurological diagnosis — most frequently, cerebrovascular disease — has been established in 5% of cases[7].

According to the International Bárány Society for Neuro-Otology, "vertigo is the sensation of self-motion when no self-motion is occurring; dizziness is the sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion; and imbalance or unsteadiness is the feeling of being unstable while seated, standing, or walking without a particular directional preference" (REF. 8). These sensations can all occur in peripheral, central and 'higher' vestibular disorders.

In this Review, we will focus on central vestibular disorders. We will present key signs and symptoms of these disorders, as indicated by the patient's medical history and appropriate bedside tests. Typical central vestibular disorders elicited by dysfunction within the temporoparietal cortex, thalamus, brainstem and cerebellum can be classified by characteristic perceptual and ocular motor manifestations, as well as sensorimotor control of posture and gait. Furthermore, we describe examples of 'higher' (cognitive) vestibular disorders[9], such as hemispatial neglect, room tilt illusion, and deficits in spatial memory and navigation in patients with bilateral peripheral vestibulopathy.

Vestibular disorders

The manifestation of vestibular disorders is determined by how the vestibular system is functioning: the patient's perception of body position and motion, ocular motor control, posture, gait, and spatial orientation are all considered. Among the various causes of vertigo and balance disorders, peripheral vestibular syndromes, such as benign paroxysmal positional vertigo, Ménière disease and acute unilateral vestibulopathy, are well known and are usually correctly diagnosed (FIGS 1,2). However, for disorders of the central vestibular system, which manifest with similar signs and symptoms, the diagnosis is more challenging. In addition to the structurally defined peripheral and central vestibular disorders, functional (somatoform)

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Key points

- About 13% of neurological patients in emergency units complain of vertigo or dizziness; a diagnosis of a central vestibular disorder is established in about 25% of all outpatients who visit dizziness units
- Vestibular migraine, the most frequent form of spontaneous episodic vertigo, must be differentiated from attacks of Ménière disease
- Central and peripheral acute vestibular syndromes can be quickly distinguished by the head impulse test and a search for spontaneous nystagmus, gaze-evoked nystagmus, ocular skew deviation, and deficits in smooth pursuit and saccadic eye movements
- Sustained rotational vertigo usually occurs in unilateral peripheral labyrinth, vestibular nerve or vestibular nuclei disorders, but rarely with lesions of vestibular structures in the upper brainstem, thalamus or cortex
- Disorders of higher vestibular function affect multisensory modalities and cognition; examples include hemispatial neglect, the room tilt illusion, pusher syndrome, and bilateral vestibular loss with spatial disorientation
- A European network for vertigo and balance research, known as DIZZYNET, was founded in 2014 to establish clinical and educational standards for the management of dizzy patients

and psychiatric dizziness syndromes comprise about 18% of vertigo and dizziness cases (FIG. 1). These conditions have recently been redefined[10,11], and will not be discussed in detail here.

Classification. Vestibular disorders are traditionally classified by the anatomical site of the lesion, namely, is it peripheral or central? Sites such as the labyrinth (semicircular canals and otoliths) and the vestibular nerve — that is, the first-order neurons — are classified as peripheral (FIG. 2). By contrast, conditions involving the vestibular nuclei in the pontomedullary brainstem, and the vestibular pathways that project from these nuclei to the vestibulocerebellum (via the cerebellar peduncles), brainstem, thalamus and cortex, are grouped as central disorders (FIG. 3). FIGURE 1 summarizes the frequency of different peripheral, central and functional or psychiatric syndromes seen in an interdisciplinary outpatient dizziness unit. In this setting, central vestibular disorders, including vestibular migraine, comprise about 25% of the established diagnoses.

Diagnosis. The diagnosis of a vestibular disorder is primarily based on a careful patient history that differentiates between five categories of key symptoms[12] (BOX 1). These symptoms cover ten distinct disorders that together account for about 80% of the diagnoses made in outpatient dizziness clinics. The diagnosis is established according to the type of vertigo or dizziness (rotatory, to-and-fro or unsteadiness), duration of attacks (seconds to days), frequency, triggers or modulating factors, and associated non-vestibular symptoms. For example, benign paroxysmal positional vertigo manifests with rotatory vertigo and nystagmus lasting less than 1 min, and is typically precipitated by rapid head and body movements relative to gravity.

Peripheral versus central syndromes. In the emergency room, it is imperative to quickly differentiate central from peripheral vestibular syndromes through reliable bedside tests such as the head impulse test (HIT) for high-frequency vestibulo-ocular reflex function[6,13–15], preferably performed with video-oculography[16–18], and ocular motor testing to determine spontaneous and gaze-evoked nystagmus or skew deviation. If the patient

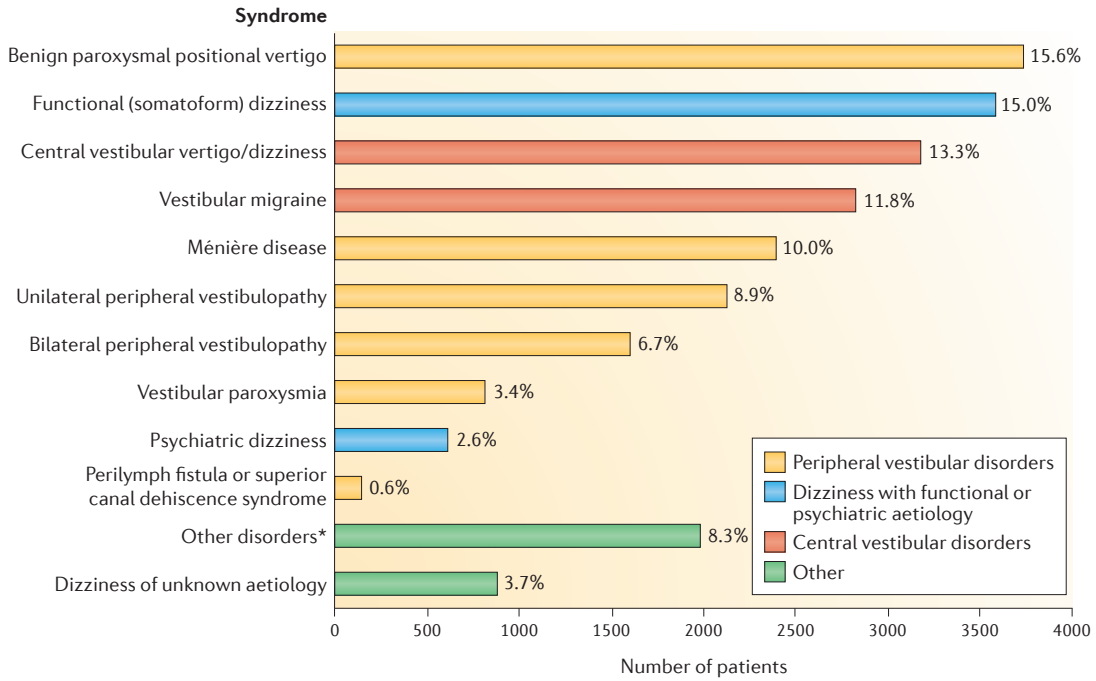


Figure 1 | **Frequency of vertigo and dizziness syndromes.** The graph shows the frequencies of different vertigo and dizziness syndromes in 23,915 patients seen in an outpatient dizziness unit at the German Center for Vertigo and Balance Disorders, Munich, Germany. *Other conditions include polyneuropathy, ocular myasthenia and orthostatic tremor.

Head impulse test
(HIT). A test that determines the function of the vestibulo-ocular reflex by eliciting passive, rapid head movements in the planes of the semicircular canals.

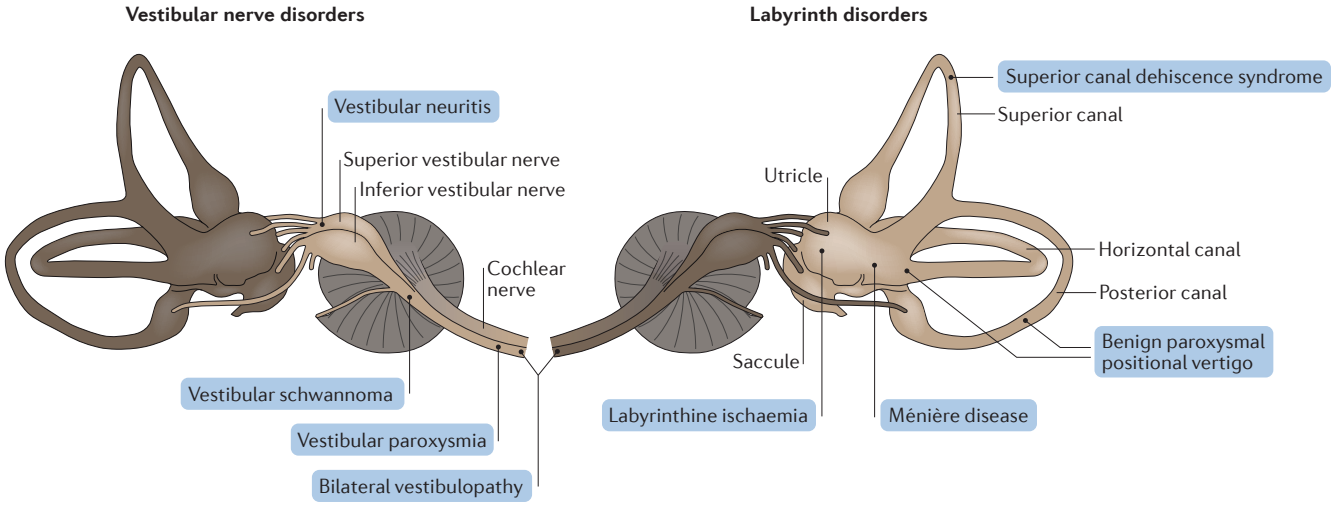


Figure 2 | **Common peripheral vestibular disorders.** The figure shows the locations of common peripheral vestibular disorders that affect the vestibular nerve (left) or labyrinth (right). In multidisciplinary dizziness units, these disorders account for ~45% of outpatient cases (FIG. 1). Typical vestibular nerve disorders include unilateral peripheral vestibulopathy (for example, vestibular neuritis or vestibular schwannoma), bilateral vestibulopathy, and vestibular paroxysmia caused by neurovascular cross-compression. Labyrinthine disorders include benign paroxysmal positional vertigo due to canalolithiasis of the posterior or horizontal semicircular canals, Ménière disease with endolymphatic hydrops, superior canal dehiscence syndrome due to a bony defect, and the rare labyrinthine ischaemia.

presents with the key symptom of acute vertigo (acute vestibular syndrome, or AVS), we recommend performing the following five-step examination procedure already in the emergency room[19]. First, administer the HIT to test the vestibulo-ocular reflex. Second, search for vertical divergence of the eyes (skew deviation) by means of the cover test. Third, use Frenzel's glasses to look for vestibular spontaneous nystagmus. Fourth, test for gaze-evoked nystagmus in horizontal and vertical directions. Last, check for smooth pursuit and saccadic eye movements in horizontal and vertical directions. This five-step procedure is more sensitive than the three-step HINTS test (see below) for detecting central disorders, because additional ocular motor deficits of smooth pursuit and saccades are examined.

The HIT, combined with tests for gaze-evoked nystagmus and skew deviation, can quickly distinguish a central from a peripheral AVS. In an AVS, the presence of skew deviation, a normal HIT[6], and a gaze-evoked nystagmus, either in the opposite direction to that of spontaneous nystagmus or in a vertical direction, indicates a central lesion within the brainstem or cerebellum[13] (FIG. 4). If the root entry zone of the vestibular nerve is affected — for example, by lacunar infarcts or multiple sclerosis (MS) plaques — the HIT might be pathological, suggesting a labyrinthine or peripheral nerve disorder. Even a three-step bedside test, known as HINTS (HIT, nystagmus, test of skew deviation), can detect central ischaemia with a sensitivity of more than 90% and, thus, is superior to early MRI with diffusion-weighted sequences (88% sensitivity)[13]. This procedure allows the general neurologist to detect a central cause[13,15,16,20] that requires an instant work-up for further diagnosis, for example, in cases of monosymptomatic brainstem strokes.

If available, a quantitative video-HIT should be performed in the emergency room to help differentiate the unilateral and highly asymmetrical semicircular canal dysfunction in peripheral AVS from abnormalities seen in central AVS[16,21]. HIT gains and compensatory saccades may differ between pontine–cerebellar strokes and acute peripheral lesions. Peripheral lesions cause an ipsilateral gain reduction. Central lesions caused by posterior inferior cerebellar artery strokes are characterized by contralateral gain bias, whereas anterior inferior cerebellar artery strokes are characterized by more-symmetrical bilateral gain reduction[16,21]. Some anterior inferior cerebellar artery strokes with unilateral labyrinthine ischaemia are at risk of being misclassified if judged only by vestibulo-ocular reflex gain[16].

Peripheral vestibular disorders

In peripheral vestibular disorders, specific dysfunctions such as spontaneous or positional nystagmus can be precisely ascribed to the affected labyrinthine structure. For example, in benign paroxysmal positional vertigo, canalolithiasis of the vertical or horizontal canals can be unambiguously identified by the direction of the positional nystagmus elicited by head movements in the plane of the affected canal. By contrast, identical central vestibular disorders can originate from separate and distinct lesions within the vestibular circuitry, especially in the brainstem and cerebellum[22–25]. This phenomenon is best illustrated by a vestibular tone imbalance due to unilateral lesions of the central graviceptive pathways. The graviceptive pathways originate from the labyrinthine otoliths and vertical semicircular canals, and they mediate our perception of verticality and stabilize the gaze, head and body in the upright position. Lesions of the peripheral ascending pathways,

Spontaneous nystagmus
Involuntary oscillatory eye movements with quick and slow phases that are elicited by an acute vestibular dysfunction.

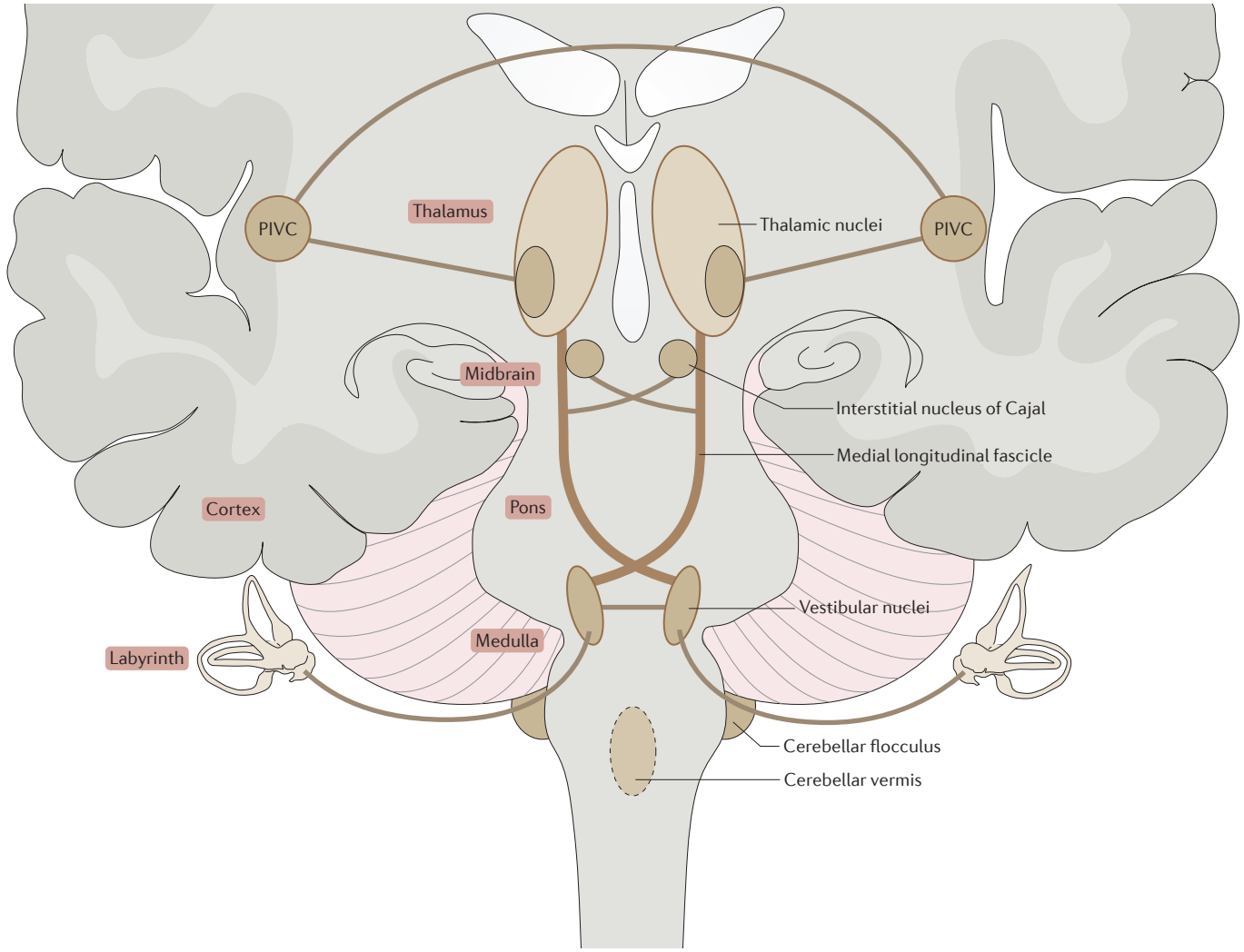


Figure 3 | **The central vestibular system.** This schematic drawing shows the bilateral structural organization of the central vestibular system from the vestibular nuclei to multisensory vestibular cortex areas such as the parieto-insular vestibular cortex (PIVC) and the medial superior temporal area (MST) of the visual cortex. Vestibular input from the labyrinth and vestibular nerve ascends ipsilaterally and contralaterally, mainly via the medial longitudinal fascicle, to the midbrain tegmentum with the interstitial nucleus of Cajal. From there, pathways travel via dorsolateral thalamic nuclei to vestibular cortex areas. The system includes at least three brainstem crossings: one between the vestibular nuclei, one in the pons superior to the vestibular nuclei, and one in the rostral midbrain tegmentum. Two transcallosal crossings connect the PIVC or the MST (not shown) of the right and left hemispheres. No crossing is observed between the thalamic nuclei of the two hemispheres. The two main cerebellar structures involved in central vestibular function are the cerebellar flocculus and the cerebellar vermis. Here, the cerebellar vermis, demarcated by a dashed line, is projected onto the level of the medullary brainstem.

which travel from the peripheral end organ to the vestibular nuclei, and of their centrally located projections to the ocular motor nuclei and the midbrain integration centre for eye–head coordination in the pitch and roll planes, can cause similar syndromes of vestibular tone imbalance in the roll plane[23] (FIG. 5).

Roll planes
The three major planes of action of the vestibular system, namely, the horizontal yaw plane and the two vertical planes — the sagittal pitch plane and the frontal roll plane.

Central vestibular disorders

The central vestibular system. The bilateral structure of the vestibular system helps us to understand its sensorimotor, perceptual and cognitive functions, as well as its disorders. These functions can be separated into four anatomically distinct groups: control of balance by vestibulospinal reflexes mediated at pontomedullary and spinal cord levels; reflexive control of gaze during head and body movements by the vestibulo-ocular reflex mediated at pontomesencephalic and cerebellar levels; perception of orientation and self-motion and integration of voluntary motion with reflexive motion and balance control, mediated at cortical and subcortical levels; and higher vestibular functions involving multisensory integration and cognitive domains such as spatial memory and navigation, mediated mainly by the hippocampal formation and the temporoparietal lobes[26].

Box 1 | **Diagnosis of vestibular disorders**

The diagnosis of a vestibular disorder is primarily based on a careful patient history that differentiates between the following five categories of key symptoms. For each category, the two relevant diseases are mentioned, with the more frequent one appearing first.

Paroxysmal positional vertigo
Benign paroxysmal positional vertigo or central positional vertigo

Spontaneous recurrent vertigo attacks
Vestibular migraine or Ménière disease

Longer-lasting attack of rotational vertigo (>24 h)
Acute unilateral peripheral vestibulopathy or central 'pseudo' peripheral vestibulopathy

Frequent spells of dizziness or imbalance
Vestibular paroxysmia or superior canal dehiscence syndrome

Postural imbalance (without other neurological symptoms)
Functional (somatoform) dizziness or bilateral peripheral vestibulopathy

The bilateral organization of the vestibular system requires a continuous interaction between the right and left circuits at all levels — and especially between the two hemispheres — in order to produce a global percept and adequate motor reactions to the actual sensory input, so as to maintain balance within the gravitational field. Bilateral representation of vestibular functions allows substitution of unilaterally damaged pathways and provides a basis for central compensation of a tone imbalance in the case of acute unilateral dysfunction[27,28]. The latter process is mediated by several crossings between the right and left circuits at brainstem and cortical levels. These crossings were recently visualized in humans by combined structural and functional MRI-based connectivity mapping[29]. The vestibular network has a 'rope ladder' structure extending from the brainstem to the temporoparietal cortex (FIG. 3). Substitution and compensation of vestibular dysfunction can also be accomplished by multisensory — in particular, visual–vestibular — interactions, as the visual system also senses orientation and motion within the 3D environment.

The functional characteristics of the vestibular system are distinct from those of other sensory systems. The system lacks a primary vestibular cortex, because all natural vestibular stimuli simultaneously affect multiple senses (visual, vestibular, somatosensory and auditory) to mediate awareness of body position and orientation, and the perception of self-motion. Also, the bilateral central vestibular system exhibits lateralization of functional weight (dominance), which is influenced by three factors. First, the input of the ear ipsilateral to a stimulus is stronger than that of the contralateral ear. Second, with bilateral stimulation, the input of the right ear is stronger than that of the left ear[30,31]. Third, hemispheric dominance occurs in the right hemisphere in right-handed individuals and in the left hemisphere in left-handed individuals. These findings were obtained through brain imaging in healthy volunteers subjected to caloric irrigation[31], galvanic stimulation of the vestibular nerve[32], or auditory evoked vestibular otolith stimulation[33,34]. The existence of a human homologue of the parieto-insular vestibular cortex (PIVC), which was originally identified in monkeys[35], was confirmed by a meta-analytical functional connectivity study, and includes the so-called opercular area[36]. In right-handed individuals, the PIVC showed right-hemisphere dominance. In a meta-analysis, Lopez and co-workers[37] delineated the human vestibular cortex areas using various types of vestibular stimulation — caloric, galvanic and sound-induced. The main regions were found in the insular and retroinsular cortex, the Sylvian fissure, the frontoparietal operculum, and the superior temporal gyrus.

The findings described above indicate that vestibular dominance and handedness are reciprocally located in the two hemispheres. The question of whether handedness is determined by the lateralization of the vestibular system or vice versa may be related to the ontogenetic evolution of these functions early in life[31,38–40]. Both vestibular control of balance and handedness mature simultaneously in the first few years of life, and definite handedness is attained at the age of 3–7 years[41]. Therefore, handedness and vestibular dominance — each of which requires its own egocentric (self-anchored handedness) versus allocentric (world-anchored vestibular) coordinate reference system — can slowly mature in infancy[38].

Mimics of peripheral vestibulopathy. If acute lesions affect the root entry zone of the eighth nerve, the vestibular nucleus, or the pathways (in the cerebellar peduncles) from the vestibular nucleus to the cerebellar flocculus and vermis, then an AVS is elicited. This type of AVS, which was originally termed 'vestibular pseudoneuritis', mimics the symptoms of a unilateral peripheral vestibulopathy[6,13,14,16,42,43]. The central sites in which lesions most frequently mimic an acute peripheral vestibulopathy are the inferior cerebellar peduncle, the medial and superior vestibular nucleus, the nucleus prepositus hypoglossi, the superior cerebellar peduncle, the cerebellar vermis (uvula and nodulus), the cerebellar tonsil and flocculus, and the root entry zone in the pons[42,44–52].

FIGURE 4 depicts the overlap of causative ischaemic lesions in 23 patients who presented with an AVS[46–49,51]. Following a single acute episode of vertigo, the risk of stroke in the next 4 years was found to be 6% — threefold higher than in a control group[53]. Additional vascular risk factors increase the risk of an impending stroke 5.5-fold.

Central rotational vertigo. Clinical experience has shown that sustained rotational vertigo with spontaneous nystagmus and direction-specific falls is associated predominantly with peripheral lesions of the labyrinth and the vestibular nerve, and less frequently with lesions of the vestibular nuclei and vestibular cerebellum. Vestibular syndromes due to lesions above the level of the vestibular nuclei — that is, the midbrain, thalamic

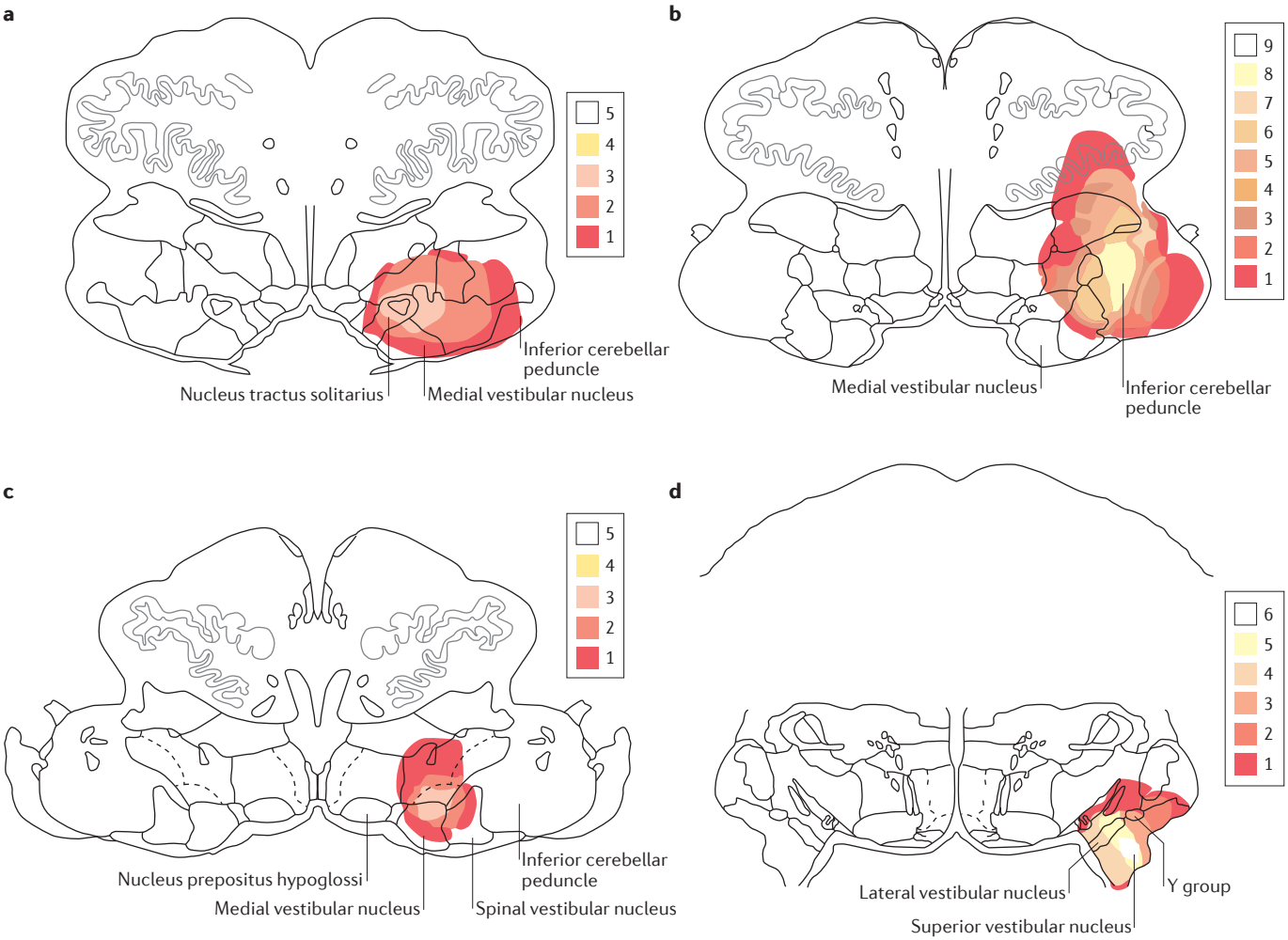


Figure 4 | **Brainstem lesions and acute central vestibular syndrome.** Overlap areas of brainstem infarct lesions in 23 patients who presented with an acute vestibular syndrome due to a central rather than a peripheral lesion. MRI data from the literature[45–48,50] are superimposed on four sections of the human brainstem (methods described elsewhere[61]). **a** | Overlap area focusing on the medial vestibular nucleus. **b** | Overlap area focusing on the inferior cerebellar peduncle. **c** | Overlap area within the medial vestibular nucleus. **d** | Overlap area within the superior vestibular nucleus and the lateral vestibular nucleus.

and cortical centres — only manifest with transient rotational vertigo in exceptional cases. These syndromes generally present with to-and-fro vertigo, disorientation, postural instability, or a static tone imbalance, as described for ocular tilt reaction (OTR) syndromes[54] (see below).

The absence of sustained rotational vertigo in cases of thalamic and cortical dysfunction can be explained by the change that takes place in the neuronal coding of vestibular signals en route from the vestibular nuclei to the cortex: velocity perception is transformed into perception of head position[55–57]. The perception of self-motion relies on different types of neurons, that is, neurons that code self-motion velocity (velocity cells) and direction (head direction cells), in cooperation with other cell types for orientation and navigation in space, such as place cells for mapping the environment and grid cells for measuring distances[55–59]. Integration from velocity to direction is necessary to update the awareness of body position in space. The velocity cells, which are mainly responsible for the sensation of rotation, are found primarily in the lower brainstem, whereas the head direction cell system is distributed in a network covering the anterior thalamus, hippocampal formation and cortical areas[60].

A concept has been proposed[61] to explain why acute unilateral vestibular cortex lesions — for example, due to infarction of the middle cerebral artery territory — rarely manifest with transient rotational vertigo[62,63]. The idea is that a continuous visual–vestibular interactive comparison is necessary for global perception of self-motion. Both the vestibular cortex and the visual cortex are able to sense self-motion, either via vestibular input of the semicircular canals and otoliths or via optic flow. If a vestibular mismatch exists between the two hemispheres, the hemisphere in which the vestibular and visual cortices are in agreement determines the global percept of body position and motion.

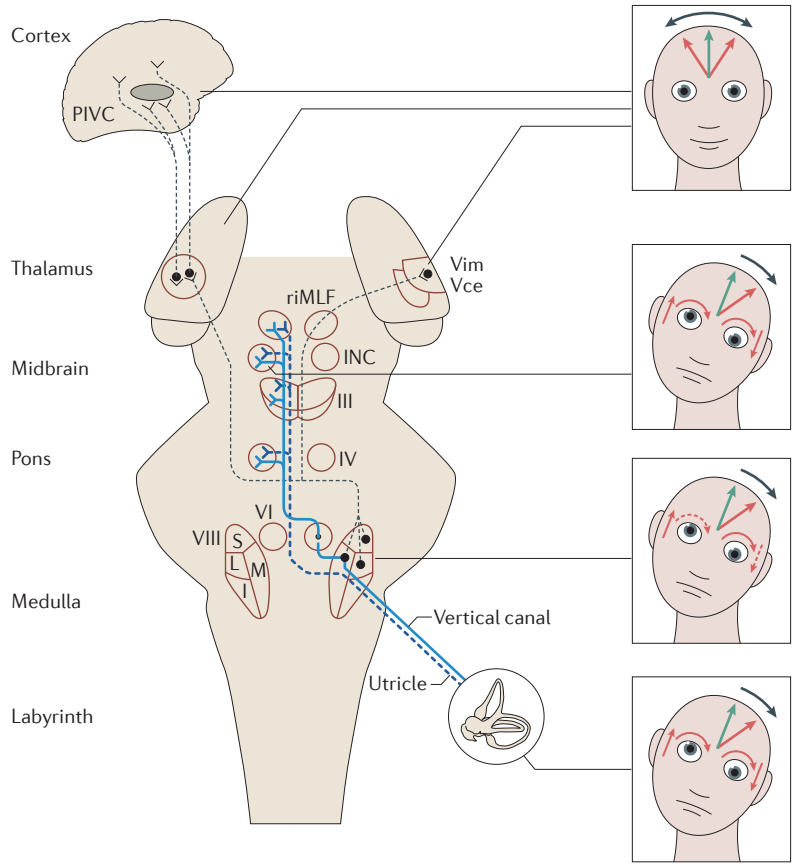


Figure 5 | **Vestibular lesions manifesting with ocular tilt reaction.** Pathways from the utricles and vertical semicircular canals mediate graviceptive function in the frontal roll plane. These pathways ascend from the vestibular nuclei (VIII) to the ocular motor nuclei, including the trochlear nucleus (IV), oculomotor nucleus (III) and abducens nucleus (VI). From here, they travel to the supranuclear centres of the interstitial nucleus of Cajal (INC), and the rostral interstitial nucleus of the MLF (riMLF) in the midbrain tegmentum. This circuitry is the basis for the vestibulo-ocular reflex, and is connected with vestibulospinal reflexes to control eye, head and body posture. Projections from the thalamus (Vim, Vce) to the parieto-insular vestibular cortex (PIVC) subserve perception of verticality. Unilateral lesions of the graviceptive vestibular pathways cause vestibular tone imbalance in the roll plane. Patients with such lesions can present with an ocular tilt reaction — an eye–head synkinesis with vertical divergence of the eyes (skew deviation), ocular torsion, head tilt, and tilt of the subjective visual vertical. Right-hand images depict the resulting vestibular syndromes according to the level of the unilateral graviceptive pathway lesion. These pathways cross at the pontine level, so the direction of tilt is ipsiversive with peripheral or pontomedullary lesions (bottom two heads) and contraversive with pontomesencephalic lesions above the crossing (head at midbrain level). In thalamic and vestibular cortex lesions, there are no eye and head tilts, and tilts of the subjective visual vertical are contraversive or ipsiversive (top head). Head images: green arrows in the forehead represent objective visual vertical; red arrows represent pathological subjective visual vertical; and red arrows around the eyes represent pathological vertical deviation and torsion of the eyes. I, inferior; L, lateral; M, medial; S, superior. Reproduced with permission from Wiley & Sons © Dieterich, M. & Brandt, T. *Ann. Neurol.* **36**, 337–347 (1994).

Ocular tilt reaction. A vestibular tone imbalance in the roll plane manifests in a pathological eye–head synkinesis called the OTR[64,65]. The OTR is characterized by a head tilt, vertical divergence of the eyes (skew deviation) with the undermost eye directed towards the head tilt, a cyclorotation of the eyes, and a tilt of the perceived visual vertical[22,23,66,67] (FIG. 5). All tilts — perceptual and motor — point towards the same side. As the graviceptive pathways from the labyrinth cross in the pons, the tilts are ipsilateral in peripheral vestibular and pontomedullary lesions and contralateral in pontomesencephalic lesions[22,25,68–70]. If the level of a circumscribed brainstem lesion is identified by associated symptoms, the OTR or its components allow us to determine the side of the lesion; if the side is known, the direction of the OTR determines the anatomical level of the lesion (FIG. 5). A complete OTR only occurs if the lesion lies between the vestibular end organ (in rare cases with complete vestibular loss)[70] or the vestibular nuclei and the midbrain[26]. Contralateral body lateropulsion has been described as a predominant symptom in some patients with unilateral infarction of the pontine tegmentum[71]. Tone imbalances in the roll plane above and below the pontomesencephalic brainstem circuit differ in that the perceptual components prevail in thalamic and vestibular cortex dysfunctions, whereas both perceptual and postural components (lateropulsion) prevail in medullary dysfunctions.

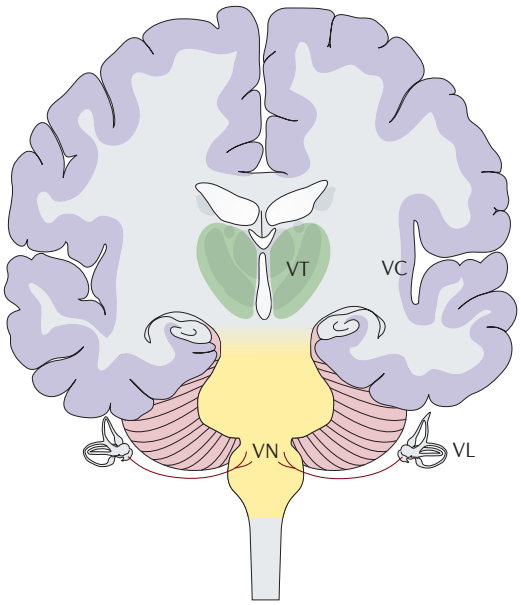
The course of an OTR is gradual recovery within days to months, as seen for tilts of the visual vertical, skew deviation and ocular torsion in medullary infarcts (Wallenberg syndrome)[66,72] and mesencephalic infarcts[54]. Recovery of the tone imbalance by central compensation, supported by physical therapy, is also reflected by normalization of the initially disturbed glucose metabolism reported in human ^{18}F-FDG–PET studies[54]. Central compensation in unilateral central vestibular lesions preferentially involves cerebellar and brainstem structures.

Thalamic astasia and lateropulsion. Unilateral central vestibular lesions of the thalamus[73] or the vestibular cortex[74] were shown to manifest with tilts of the perceived visual vertical but without head tilt and skew torsion. These lesions can only be detected through perceptual deficits, which become apparent when the subjective visual vertical is measured. These tilts can be ipsilateral or contralateral, but are not direction-specific as is typical for lesions of the brainstem. In lesions of the posterolateral or centromedial thalamic subnuclei, postural imbalance with a transient tendency to fall can occur in the absence of motor weakness or sensory loss — this phenomenon is called thalamic astasia[75–77]. In the case of medullary lesions below the vestibular nuclei, tone imbalance in the roll plane can manifest as isolated body lateropulsion without associated ocular motor signs or limb ataxia[78–80]. This isolated lateropulsion occurs when the descending lateral vestibulospinal tract is affected[78]. If the medial or superior vestibular nucleus is affected in dorsolateral medullary infarcts (Wallenberg syndrome), the lateropulsion is combined with an ipsilateral OTR and transient torsional nystagmus[65–67]. Physical therapy is recommended to improve postural imbalance and gait in patients with these conditions.

Higher vestibular dysfunctions

The simple classification of vestibular disorders as peripheral or central disregards a third category (FIG. 6). In analogy to disorders of higher visual functions of the

Body lateropulsion
Direction-specific tilts or falls of the body due to a vestibular tone imbalance.



Cortex
- Cortical vertigo
- Pusher syndrome
- Room tilt illusion
- Spatial hemineglect
- Spatial memory deficit
- Vestibular epilepsy

Thalamus
- Thalamic astasia
- Pusher syndrome

Brainstem
- Lateropulsion
- Ocular tilt reaction
- Paroxysmal ataxia/ dysarthria
- Pseudoneuritis
- Room tilt illusion
- Skew–torsion
- Vestibular migraine

Cerebellum
- Downbeat nystagmus
- Episodic ataxia type 2
- Ocular tilt reaction
- Positional vertigo/ nystagmus
- Pseudoneuritis
- Upbeat nystagmus

Figure 6 | **Central vestibular syndromes and disorders of higher vestibular function.** This figure presents a list of syndromes that have been attributed to cortical, thalamic, brainstem or cerebellar lesions. Some disorders have been linked to central lesions at multiple levels; for example, the ocular tilt reaction can be caused by brainstem or cerebellar lesions, and the room tilt illusion can be caused by brainstem or cortical lesions. In some conditions, the topographic assignment is uncertain. VC, vestibular cortex; VL, vestibular labyrinth; VN, vestibular nucleus; VT, vestibular thalamus.

'what' and 'where' pathways[81], a new category, namely disorders of higher vestibular functions, which include cognition and other non-vestibular modalities, has been proposed[9]. The hemispheric dominance of cortical activation of the vestibular network, as described above, is reflected in several supratentorial neurological disorders involving higher vestibular function. These disorders include impairment of spatial orientation, spatial attention and balance control, and they are based on integration of multisensory — that is, visual, vestibular and somatosensory — input. To illustrate the characteristics of disorders of higher vestibular function, we describe four conditions: hemispatial neglect, room tilt illusion, pusher syndrome, and impairment of spatial memory and navigation associated with hippocampal atrophy in peripheral bilateral vestibular loss.

Hemispatial neglect. Hemispatial neglect is a disorder caused by interrupted attention to visual stimuli within one hemifield contralateral to the acute lesion (usually of the right temporoparietal cortex)[82]. In rare cases, transient neglect can occur after acute right or left lesions of the frontal premotor cortex[83]. A milder form of neglect, termed visual extinction, can occur if spatial attention is less severely disturbed, or during the course of recovery from neglect.

A critical cortical lesion site that causes hemispatial neglect includes the temporo-parieto-insular cortex, which contains the key region of the multisensory vestibular network[84–86]. The organization of multisensory spatial attention in each hemisphere, as well as the dominance of the right hemisphere, must be accounted for in computational modelling of the possible neuronal mechanisms of neglect[87,88]. Specific training programmes, including repetitive galvanic vestibular stimulation, have been developed to promote recovery from neglect[89].

Room tilt illusion. The room tilt illusion is a rare disorder of paroxysmal transient upside down vision, and it reflects cortical dysfunction of visual–vestibular interaction[90,91]. Apparent inversion of vision or 90° tilts of the environment are misperceptions of verticality. The spatial orientation of the visual scene is mediated by vestibular and visual cues; both sensory systems deliver input for the adjustment of verticality in a 3D environment. As we cannot perceive two different verticals — a visual vertical and a vestibular vertical — at the same time, the two senses must match their spatial coordinates. Thus, a room tilt illusion indicates a transient mismatch of the vestibular and visual coordinate systems, and is the erroneous result of an attempt to make a cortical match[90].

The causative lesions of the room tilt illusion are mostly subcortical, located within the brainstem or even the peripheral end organ. Examples are found in bilateral vestibular failure or Ménière disease[91]. As in hemispatial neglect, the cause of the disease is vestibular, but the misperception is mainly visual. The spontaneous course of episodic room tilt illusions is mostly benign[91]. Therapy depends on the underlying cause; for example, carbamazepine can be used to treat neurovascular cross-compression of the vestibular nerve.

Pusher syndrome. During acute stroke management, the pusher syndrome is often under-recognized by neurologists, but physical therapists are very familiar with its signs[92]. The syndrome is characterized by an apparent tilt of the perceived body position in space, which the patient attempts to counteract by actively pushing or tilting the body to the contralesional side. This pushing is performed by the nonparetic arm or leg[93,94]. Proposed causative lesion sites include the thalamus and — perhaps more likely — the posterior part of the insula[95,96]. These lesion sites contain components of the multisensory cortical vestibular network. The dominance of the right hemisphere of this network explains the significantly higher frequency of pushing behaviour in right hemispheric strokes as compared with strokes of the left hemisphere[97]. This observation is compatible with the experience of physical therapists, who find that recovery from pushing is slower after right hemispheric strokes[97].

Peripheral bilateral vestibular loss. Peripheral vestibular disorders can also cause deficits of higher vestibular function; examples include impairment of spatial memory, orientation and navigation in chronic peripheral bilateral vestibular failure[98,99]. Rodent studies have shown that intact vestibular function is important for spatial memory and navigation[100]. Navigation requires a continuous update of the model of the environment and the relationship of the individual relative to allocentric

Endolymphatic hydrops
Enlargement of the endolymphatic space of the inner ear.

surroundings. The 3D coordinates rely mainly on vestibular and visual input and provide the framework for the process of updating[98]. Even incomplete chronic bilateral vestibular loss can cause atrophy in the hippocampal formation, as well as subjective and objective navigational deficits[101]. Patients with bilateral vestibular loss benefit from physical therapy[102]; however, the efficacy of specific rehabilitation programmes for spatial memory deficits has not yet been tested.

Vestibular migraine

Vestibular migraine is the most frequent form of episodic vertigo, affecting both adults and children[103,104]. In the general population, lifetime prevalence is about 1%, with a 1-year prevalence of 0.9%[105]. The condition accounts for 7–11% of outpatients seen in specialized dizziness units[106,107] and 9% of outpatients seen in migraine units[106]. Women are affected 1.5–5.0 times more often than men[106,108,109].

Following the detailed clinical description of this entity[108], more than 15 years elapsed before the International Headache Society and the International Bárány Society for Neuro-Otology finally accepted the term 'vestibular migraine' and its clinical manifestations. The latter society developed a consensus document with diagnostic criteria for vestibular migraine[110]. The diagnosis of vestibular migraine was also included in the Appendix of the International Classification of Headache Disorders, third edition (beta version) as an emerging entity requiring further research[111]. The diagnostic criteria for vestibular migraine and probable vestibular migraine are outlined in BOX 2.

Diagnosis of vestibular migraine is difficult if typical migraine headache is absent, which is the case in about 30% of patients[106,108]. According to various studies, spontaneous vertigo is reported in 21–83% of attacks[108,109,112], positional vertigo or dizziness in 17–65% of attacks[108,113,114], and head motion intolerance and postural imbalance in 31–77% of attacks[109,111]. Vertigo can precede, accompany or even follow the headache[106,109]. The attack can last from seconds to days[106,108,113], but is most frequently in the range of minutes to hours. Central ocular motor dysfunctions, such as gaze-evoked nystagmus, pursuit deficits, central positional nystagmus, and dysmetric or slow saccades, manifest in 8.6–66.0% of the patients[108,109,112,113,115,116]. Over the course of the condition, interictal ocular motor abnormalities become more frequent and severe. In a study involving follow-up of 5.5–11.0 years, these abnormalities occurred in 16–41% of the patients[115], with central positional nystagmus being the most frequent dysfunction[116].

The differential diagnosis of vestibular migraine and Ménière attacks can be challenging, especially at an early stage of Ménière endolymphatic hydrops when aural symptoms are absent[117]. The diagnosis can be ambiguous, as auditory dysfunction, tinnitus and aural pressure were reported by 38% of patients with vestibular migraine[109,113,114]. Additional tests may be helpful; for example, cervical vestibular evoked potentials are often pathological on the affected ear in Ménière disease but not in vestibular migraine[118,119]. The picture is further complicated by the fact that Ménière disease and vestibular migraine often coincide[117,119]: the prevalence of migraine was found to be twofold higher in patients with Ménière disease than in otherwise healthy individuals[120]. In a retrospective study on familial clustering of migraine, episodic vertigo and Ménière disease, 13% of the patients fulfilled the diagnostic criteria for both Ménière disease and vestibular migraine[120].

Another important — though rare — differential diagnosis for vestibular migraine is episodic ataxia type 2 (EA2), an autosomal dominant disorder caused by a mutation in the calcium channel gene *CACNA1A*[121]. The clinical manifestations of vestibular migraine and EA2 are very similar, including central ocular motor abnormalities in the symptom-free interval[122], and genetic differentiation is sometimes necessary.

The pathophysiological mechanism of vestibular migraine, in particular, the simultaneous involvement of vestibular and cranial nociceptive pathways, remains unclear[123]. In humans, reciprocal interactions between the vestibular and trigeminal nuclei have been shown, along with enhanced excitability of the vestibular system during processing of sensory information. Spreading depression, the cortical cause of migrainous aura, has been shown to also occur in the brainstem of rats[124] and might contribute to vestibular migraine in humans[123].

Only two small randomized controlled trials of medical prophylaxis for vestibular migraine are available, one on the effects of flunarizine[125] and the other on the effects of propranolol and venlafaxine[126]. These drugs significantly reduced the frequency and severity of vertigo. Large, prospective, double-blind crossover trials are still lacking.

Box 2 | **Diagnostic criteria for vestibular migraine**

The International Bárány Society for Neuro-Otology and the International Headache Society have proposed the following criteria for the diagnosis of vestibular migraine[110,111].

A. At least five episodes fulfilling criteria C and D below

B. A current or past history of migraine without aura or migraine with aura

C. Vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 h

D. At least 50% of episodes are associated with at least one of the following three migrainous features:

- Headache with at least two of the following four characteristics: unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity
- Photophobia and phonophobia
- Visual aura

E. Not better accounted for by another diagnosis from the third edition of the International Classification of Headache Disorders, or by another vestibular disorder

Conclusions

Central vestibular disorders are caused by lesions — mostly infarcts and MS plaques — affecting the ipsilaterally and contralaterally ascending pathways and neuronal assemblies that originate from the vestibular nuclei and extend to the vestibular cortical network. Around one-quarter of patients who present with the key symptoms of vertigo, dizziness and imbalance are found to have central vestibular disorders. The lateralization of the vestibular cortex (right hemispheric dominance in right-handed individuals and left hemispheric dominance

Box 3 | **DIZZYNET**

Despite the high prevalence of vertigo and dizziness, afflicted patients often receive inadequate treatment, mainly because interdisciplinary cooperation among the physicians involved in their management is still weak or nonexistent[127]. A European network for translational research into the management of patients with vertigo and balance disorders, known as DIZZYNET, was founded in 2014 to improve patient care and support[128].

In the long term, an international network of interdisciplinary dizziness units will be established with various working groups responsible for organizing international clinical trials, setting standards for clinical management, professionalizing data banking, and modernizing teaching and training. The network will also promote public awareness of the socioeconomic need to improve quality and efficacy of the clinical management of dizzy patients.

in left-handed individuals) is reflected in the frequency and severity of disorders of higher vestibular functions, such as hemispatial neglect and pusher syndrome.

In the emergency room, distinguishing between acute central and peripheral vestibulopathies is vital. This task can be accomplished with great sensitivity by applying three-step or five-step bedside tests. Further elaboration of higher vestibular functions, which cover multisensory interaction, spatial memory, navigation and other cognitive functions, is necessary. Clinicians involved in the management of dizzy patients are aware of the deficiencies of multidisciplinary units for outpatients, and this issue is now being addressed by DIZZYNET, a European network for research into vertigo and balance disorders (BOX 3).

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