Aus dem Institut für Klinische Neurowissenschaften

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Impaired Vestibulo–Spinal Interaction in Cerebellar Patients

Dissertation

zum Erwerb des Doktorgrades der Medizin

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität München

Vorgelegt von

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aus

Rosenheim

im Jahr

2010

Mit Genehmigung der Medizinischen Fakultät

der Universität München

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Tag der mündlichen Prüfung:	1. Juli 2010

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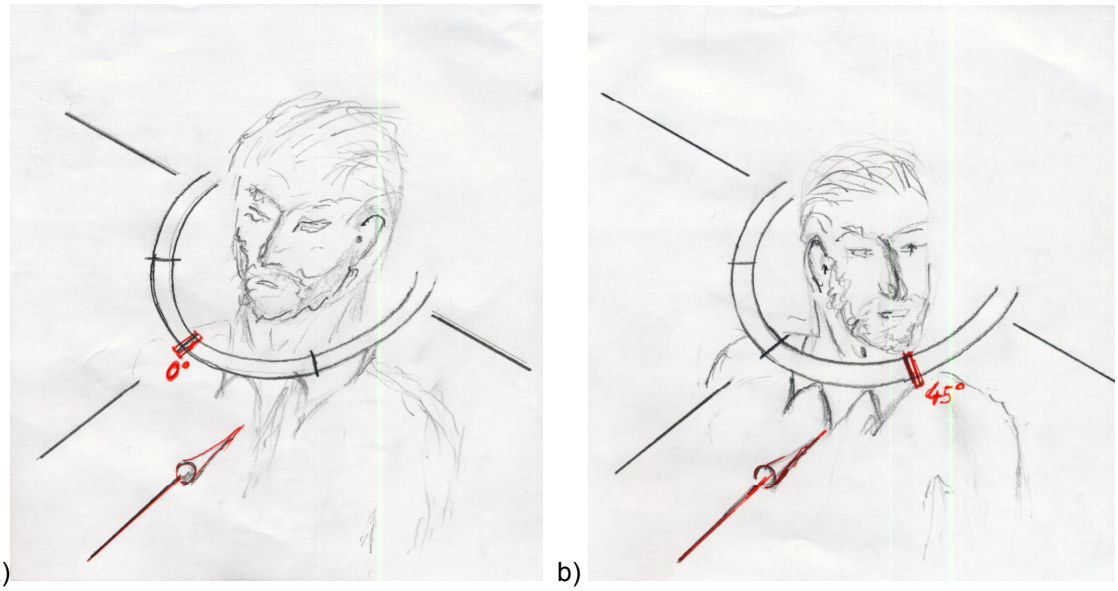
1 Introduction

Imagine a man walking down a gravelly pavement. He may trip over a stone in his path and tumble. In such an instance, an intact balance control system allows preventing a fall.

The vestibular organs, deep inside the temporal bones on each side of the skull, are essential for this ability. They can detect movements of the head in space, like the sudden propulsion when tripping over a stone. Information from these sensory organs is sent to the brain by the vestibular nerve. There, a complex program of compensatory muscle activity is calculated in order to counter-act – and eventually to compensate for – the disturbance: muscle activity in torso and limbs keeps the individual in balance.

The same mechanism applies for an upright standing man being pushed against the chest (Figure 1a). With the head pointing straight ahead, the perceived acceleration backwards – relative to head and trunk – must be counter-acted by postural control, such as by leaning forward or taking a step back. Here, head and trunk are aligned in a neutral position to each other.

Figure 1



a) b)

Figure 1:

Figure 1a depicts a man receiving a backward push, while his head is pointing straight ahead. In figure 1b the head is turned off-centre in the head-horizontal plane during an identically directed frontal push. In both situations the body is perturbed in the same way, whereas the vestibular system situated in the head receives different information.
Figures drawn by the author.

However, if the head is turned horizontally away from the neutral position during an identical frontal push against the chest, the head-based vestibular sensors measure a completely different set of input signals. This situation is depicted in Figure 1b. To ensure body stability with lateral head excursion and a different vestibular perception, the compensatory postural reaction has to be directed forward relative to the body in both situations.

This sensory re-alignment has to be performed by converting the head-centred vestibular signals into body-centreed coordinates, taking into account the relative head-on-trunk excursion. The key to this mechanism must be the interaction of vestibular and neck-proprioceptive input signals [Kleine et al 2004].

Generally, a variety of unplanned perturbations, like unstable surfaces or a sudden external force, can affect the body in daily life. An adequate postural response must rely on correct and accurate information on how the head and body are situated against each other, how they are moving in space and in which direction a perturbing force affects the body. A re-alignment of vestibular coordinates is of the essence. The relative position of the vestibular sensor array against the rest of the body with its posture control muscles has to be taken into account [Gdowski et al 1999, Kleine et al 2004]. Failure in adequate central computation of compensation movements results in imbalance and possible falling, irrespective of otherwise fully sufficient compensating force.

The head of higher vertebrates is mobile against to the trunk in three planes by the neck with extensive range: rotation in the horizontal plane, pitch in the sagittal plane, roll in the frontal plane and certain translational shift. The head can assume almost any position relative to the trunk [Day et al. 1997, Gdowski et al 1999, Fitzpatrick et al 2004, Cathers et al 2005]. The possible positions of the vestibular system relative to the trunk, accordingly, are just as variable.

The sensor array detecting mobility of the head against the trunk is the neck proprioceptive system with its specific tissue sensors. This sensory system measures how the joints and muscles of the neck are situated relative to each other and, thus, the relative head-on-trunk position. Its cues allow referring head-related vestibular coordinates to body-related movement coordinates in the central nervous system.

Generally, one sensory quality alone is subject to the physical and computational constraints of the respective sensor array. For the example, the vestibular system may measure movement in space

correctly, but information on head movement alone lacks information on the alignment of the head relative to the body. The raw unprocessed data from this input cannot directly give rise to a fully-compensatory postural body reaction. Combining information from more than one sensor system, i.e. adding neck proprioception for head-on-trunk position, averts this dilemma by factoring in details, which are missed by one single sensory system with its limited features [Angelaki et al. 2004]. The central nervous system can form a valid and thorough internal representation of the outside world, i.e. what the brain assumes to be position of the individual in space, based on such combined sensory information. A valid internal model is compulsory for correct compensatory reactions to external perturbation.

It has to be postulated, that both vestibular- and neck-proprioception-related signals interact at a special population of neurons, at least at one site in the brain. There, both information on movement in space (recorded by the vestibular system) and the relative position of the vestibular sensors to the trunk (detected by the neck proprioceptors) has to be merged into a new signal, which can induce or modulate motor commands in other parts of the central nervous system:

To transfer information from one coordinate system into another, such a central instance has to account for the relative shift of both coordinate systems against each other, in order to compensate for a relative head-on-trunk shift [Gdowski et al 1999, Kleine et al 2004]. After correct translation into new trunk coordinates, the central nervous system may then compute adequately directed compensatory muscle action to a specific perturbation, acting in the adjusted, trunk-related coordinate system of postural control.
These “coordinate systems” do not necessarily reflect Carthesian coordinates, but may be seen as a surrogate for specific neural activity in a certain neuron population, representing a spatial reference frame for motor coordination. In the following, the merging of vestibular and proprioceptive data for correct re-alignment of head and trunk coordinates will generally be referred to as “vestibular-proprioceptive interaction”.

Contemporary findings in cerebellar and vestibular research have defined probable sites of vestibular and proprioceptive convergence:
Manzoni, Pompeiano and co-workers [Pompeiano et al 1997, Manzoni et al 1998, Manzoni et al 1999, Manzoni et al 2004] investigated the characteristics of Purkinje cells in the cerebellar anterior lobe vermis of decerebrated and

anesthesised cats during physical vestibular stimulation, unveiling convergence of neck displacement signals and vestibular information. Their studies found evidence for vestibular-proprioceptive interaction in the cerebellar vermal cortex.

Büttner, Kleine and co-workers [Büttner et al 1991, 2003 and 2004] investigated so-called “vestibular-only cells” in the fastigial nucleus, a deep cerebellar nucleus, in macaque monkeys. Single cell recordings found action potentials modulated in tune with both vestibular stimulation and head-on-trunk excursions. They argued that the fastigial nuclei provide another decisive interaction site of vestibular and proprioceptive information.

These landmark studies indicated that both the cerebellar cortex and the deep cerebellar nuclei are probably key sites in the inter-sensory vestibular and proprioceptive coordination and the re-alignment of head and trunk reference frames. However, is this data from single neurons, as investigated in animals, also alienable to humans?

Consecutively, cerebellar lesion in human patients might possibly impair the re-adjustment of a vestibular reference frame into a trunk-centred reference frame for motor commands with respect to head-on-body proprioceptive cues. This would manifest in inadequate postural control under vestibular stimulation during different head-on-trunk positions.

At a given frequency, binaural sinusoidal galvanic vestibular stimulation [Cathers et al 2005] is known to evoke sinusoidal body sway in the head frontal plane at the same frequency as the stimulus [Fitzpatrick et al 1994, Kleine et al 1999(2), Cathers et al 2005, Iles et al 2007]. In different static horizontal head excursions, the body sway evoked by this vestibular stimulus changes – and keeps aligned with – the head-frontal plane, as has been shown previously in healthy subjects [Lund et al 1983, Tokita et al 1989, Hlavacka et al 1993, Day et al 1997, Manzoni et al 1998, Fransson et al 2000, Latt et al 2003, Fitzpatrick et al 2004, Cathers et al. 2005]. This suggests modulation of the vestibular stimulus by neck proprioception, as a re-alignment of head and trunk coordinate frames.

Can such a paradigm provoke inadequate postural reaction in humans with cerebellar lesions, where the merging of vestibular and proprioceptive input is supposed to be situated?

If combined vestibular and proprioceptive stimulation in human subjects with cerebellar deficiency could impair the postural response patterns, findings would supply striking evidence for the cerebellum as one key site for merging of vestibular- and neck-sensory characteristics.

So far, cerebellar patients previously have not been exposed to galvanic vestibular stimulation, nor has their postural response to this stimulus been recorded before. Combining galvanic stimulation with horizontal head turn has not been attempted in cerebellar patients or any other specific patient population to the present day.

In this study we investigated cerebellar patients during galvanic vestibular stimulation and different static horizontal head-on-trunk-excursions in order to unveil effects of cerebellar lesions on postural control. In addition, patients' vestibular-proprioceptive interaction was tested clinically, by having these patients stand and walk with lateral head excursions.

2 Background

This study concerns the interaction of the vestibular and the proprioceptive system. To interpret findings, profound analysis of the anatomy and physiology of the underlying neural structures and the mechanisms of the employed methods is required. We analyze the anatomy and function of the peripheral vestibular system, the neck proprioceptive structures and the brainstem with the cerebellum, its associated nuclei, giving a review of contemporary knowledge on vestibular-proprioceptive interaction.The method of galvanic vestibular stimulation will be illustrated with its mechanism of effect, site of action and the evoked movement illusion.

2.1 Anatomical and functional review of the underlying circuitry

Figure 2

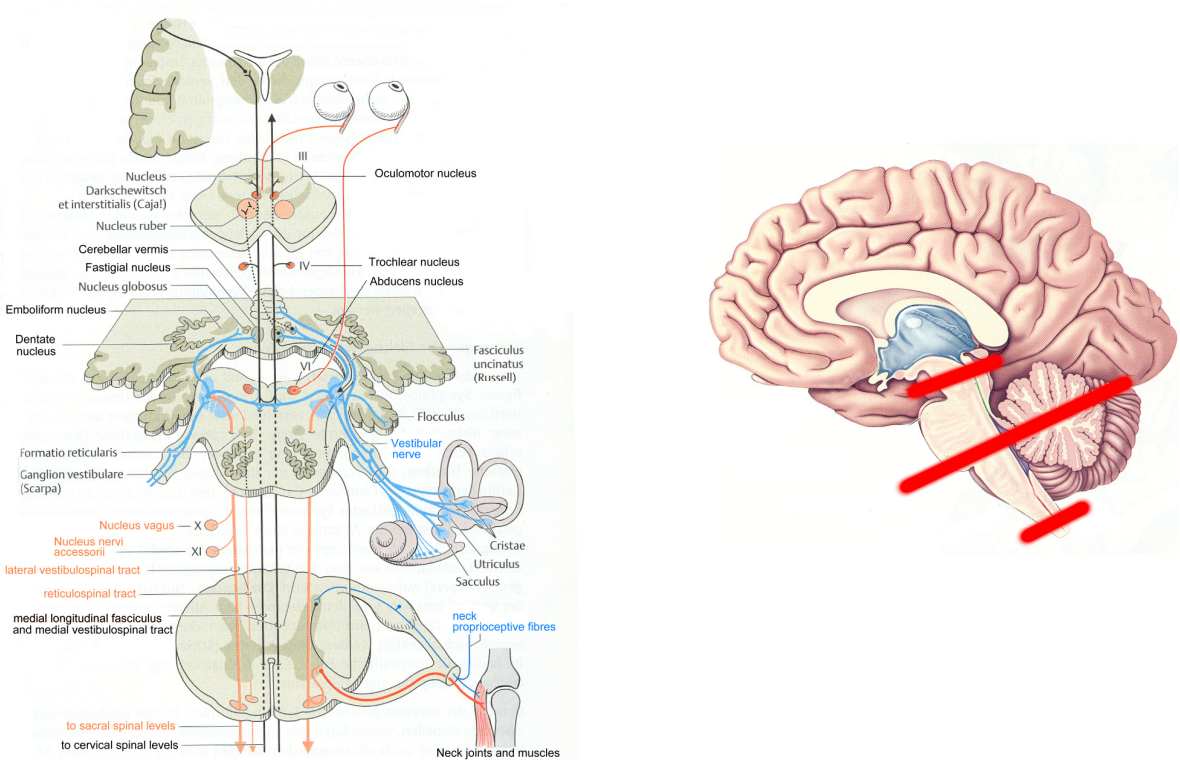


Figure 2:

On the left, three transverse slices through the central nervous system: on top, mesencephalic structures are shown, in the middle a cut through the pontomedullary transition with the cerebellum in the background. The lowest slice represents a cervical spinal layer. The cerebral cortex, thalamus, eyes, the peripheral vestibular system and the neck joints are shown. The peripheral vestibular afferents (blue) project to the vestibular nuclei; projections to the cerebellum are illustrated. Efference to eyes, brainstem and spinal levels are shown in orange and black. On the right, a medial view of the brain and upper spine is shown as a localizer.

Images: left part of Figure 2 from Duus' neurologisch-topische Diagnostik p.189, right figure from Bear's Neuroscience p.212

Figure 2 depicts an overview of the anatomical structures involved in vestibular-neck interaction in three brainstem levels. The following sections will detail the peripheral vestibular system, its brainstem nuclei, the cerebellum with its deep nuclei, the inferior olive and descending spinal tracts.

2.1.1 The peripheral vestibular system and its afferents

The peripheral vestibular system comprises the three semicircular canals, the two macular organs (utriculus and sacculus) and the peripheral vestibular nerve. One set of vestibular organs lies on each side of the skull base, bilaterally in the respective temporal bone. The vestibular nerve together with the auditory nerve is referred to as the "vestibulo-cochlear nerve" (or "eighth cranial nerve"). It enters the brainstem in the cerebello-medullar angle. In the brainstem, primary vestibular fibres mainly terminate in the vestibular nuclei, whereas some fibres continue on, e.g. to the cerebellum.

Like in any sensory organ, a specialized sensory epithelium is subject to a specific physical stimulus. Epithelial cells modulate their electrical membrane potential dependent on the stimulus, consecutively emitting neural transmitters. Transmitter emission excites the respective downstream afferent nerve cell, thus delivering information on changing physical stimuli into the brain.
The specialized vestibular sensory cells are mechanoreceptor "hair cells". Together with supporting cells for hair cell nutrition, they lie atop a basement membrane. Movement encoding in the vestibular system uses an inertial delay in movement of the individual together with its sensory epithelium relative to an inert gelatinous mass lagging behind. Movements of the overlying inert mass are translated into neurotransmitter ejection and afferent nerve signals in the vestibular nerve [Wersäll 1972, Fitzpatrick et al 2004] (Figure 3).

Figure 3

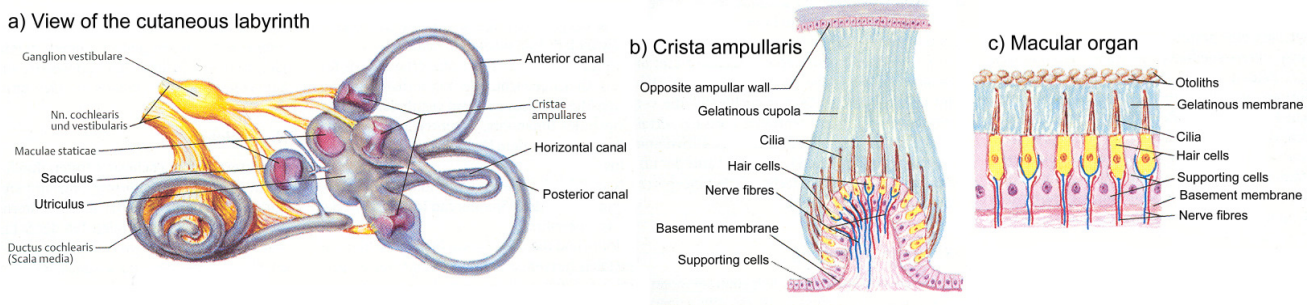


Figure 3:

a) The cutaneous labyrinth of the inner ear is shown, a membrane filled with potassium-rich endolymph and the sensory epithelia
b) In the semicircular canals, a water-tight gelatinous cupola reaches from the sensory epithelium to the opposite wall. Head movements let the water-like endolymph lag behind the movement of head and canals, deflecting the cupola in two possible directions.
c) In the maculae, hair cells are embedded in a gelatinous "pudding" with otoliths on top, increasing the mass and inertia of the device. Movement of the head deflects the gelatinous mass and the cilia accordingly.

Images: Figures 3a, b and c modified from Netter's Neurology p. 87

On top of the hair cells lies a group of stereocilia with increasing length towards a single kinocilium.

Each is connected to its neighbours by protein chains (Figure 4).

Figure 4

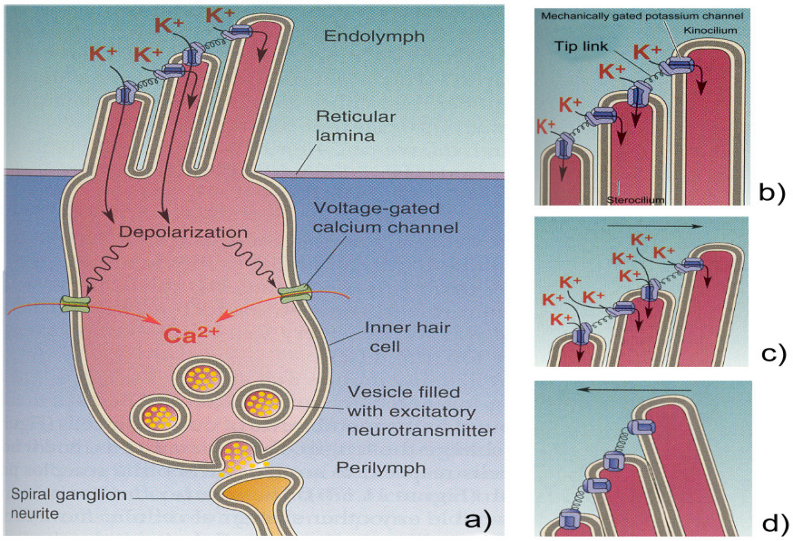


Figure 4:

a) Figure 4a shows a vestibular canal hair cell with its processes reaching into the potassium-rich endolymph. Upon activation of the apical mechanism, the cell is depolarized and allows calcium ions to enter through voltage-gated channels. Transmitter molecules are ejected into the synaptic gap towards the vestibular nerve neuron.
b) Each process bears potassium channels which are opened by mechanical pull. The channels are coupled by protein chains ("tip links"), linking the opening lids of all potassium channels to the movement of the cilia.
c) Deflection of the cilia towards the kinocilium pulls the potassium channels open and allows large amounts of potassium ions to stream in: a maximal amount of transmitter substance is released.
d) Deflection away from the kinocilium presses all potassium channels shut tightly. Very little or no potassium can stream in and – accordingly – little or no transmitter is set free. In positions between c) and d), potassium channels are only lightly shut, allowing small amounts of potassium flow and small amounts of transmitter to be released.

Images: Figure 4 modified from Bear's Neuroscience p.365

The direction in which the stereocilia are deflected, decides upon depolarization (excitation) or hyperpolarisation (inhibition) of the hair cell. Adequate stimulation, as illustrated in Figure 4 [Wersäll 1972] allows for gradual release of the neurotransmitter glutamate [Raymond et al 1988, Usami et al 2001], which modulates the activity of the downstream vestibular nerve [Goldberg et al 1982]. The vestibular nerve just after the synaptic gap is thought to be the working point of galvanic stimulation, which can imitate the gradual natural stimulation and inhibition, as will be illustrated in Chapter 2.2.1.

2.1.1.1 The semicircular canals

The three semicircular canals – anterior, posterior and horizontal canal – form an array of angular acceleration sensors. They are oriented orthogonally to each other, covering the whole range of possible head accelerations in three-dimensional space [Markham et al 1972].

In the canals, the gelatinous substance on top of the hair cells forms the cupola (see Figure 3b). It is a water-tight membrane, filling out the entire diameter of the canal [Dohlman 1935]. The endolymph, with similar specific weight compared to the cupola, flows strictly laminar in the canal. The relative momentum of the inert endolymph inside the canal circle deflects the cupolar membrane in either direction, with according deflection of of the embedded hair cell cilia. In summary, the angular acceleration of the head in space is measured by an inertia difference between endolymph and the respective semicircular canal with its cupola and hair cells [Dohlman 1935, Jones et al 1972, Wersäll et al 1972].

The vertical anterior canal of one side and the contralateral vertical posterior canal are oriented in parallel planes with respect to each other. The parallel distance between their planes of orientation may be functionally disregarded. Rotation in the right anterior and left posterior plane (“RALP”) and rotation the left anterior and right posterior plane (“LARP”) each stimulate a corresponding set of anterior and posterior vertical canals (Figure 5).

The canals of one vertical plane code for a rotation in their common plane with depolarization in one vertical canal and hyperpolarization in the other corresponding vertical canal: pitching the head in the left anterior - right posterior (LARP) plane in a nose-down direction excites the ampullar hair cells of the left anterior canal, whereas the hair cells of the in-plane contralateral right posterior canal are

simultaneously inhibited – and vice versa for the right anterior - left posterior plane RALP.

In the horizontal canals, rotation of the head in the horizontal plane ("yaw") leads to depolarization of hair cells in the horizontal canal ipsilateral to the horizontal head turn: a horizontal turn of the head to the right side excites hair cells in the right horizontal canal. In the corresponding contralateral horizontal semicircular canal, hair cells are hyperpolarized by the stimulus [Büttner et al 1988, 2003 and 2005, Kleine et al 2004, Siebold et al 1997 and 1999]. Exciting and inhibiting directions for the semicircular canals are shown in Figure 5.

Figure 5

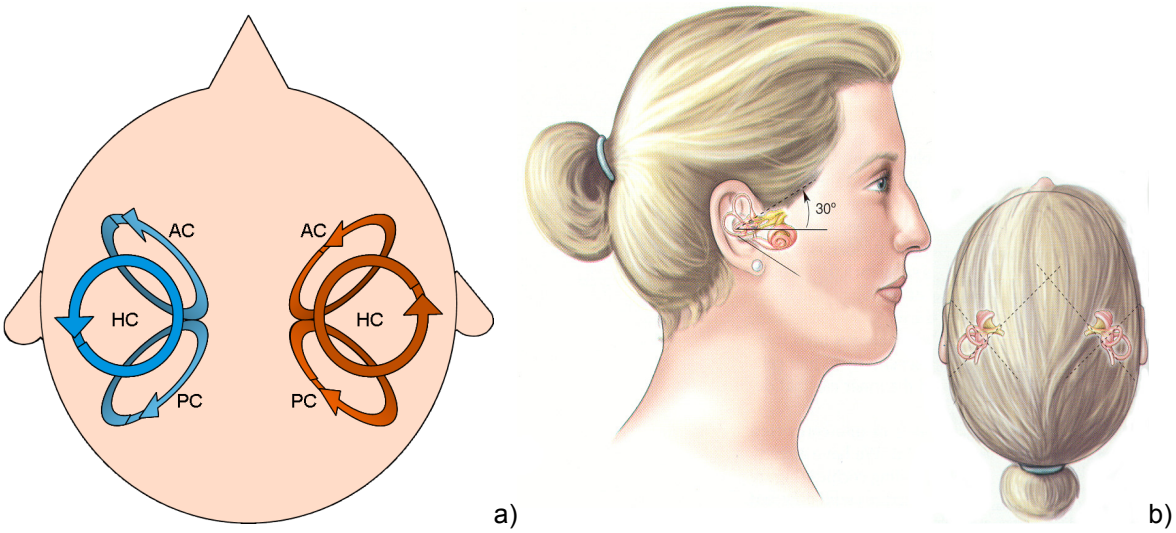


Figure 5:

a) On the left, a schematic on-top view of a human head with the semicircular canals is shown (AC = anterior canal; HC = horizontal canal; PC = posterior canal).
In the **left** vestibular organ shown here, blue arrows illustrate the direction of head movements **exciting** the corresponding canal hair cells, while in the **right** vestibular organ **inhibiting** directions of head turning are shown for the individual canals: turning the head down left between left ear and nose excites the left anterior canal, while inhibiting the right posterior canal. Turning the head down left between left ear and occiput excites the left posterior and inhibits the right anterior canal. As for the horizontal canals, turning the head horizontally to the left excites the left horizontal canal, while inhibiting the contralateral right horizontal canal.
This implies that movement in any canal plane towards one side excites the ipsilateral canal hair cells and inhibits hair cells of the corresponding contralateral canal.
Either side can bei excited or inhibited, depending on the direction of head movement; this figure is merely schematic.

b) The right image displays the three-dimensional position of the semicircular canals relative to the head. The horizontal canal plane is tilted about 30° backward in the head-transversal plane [Pompeiano et al 1997, Fitzpatrick et al 2004, Manzoni et al 1998 and 2004].

Images: Figure 5a drawn with MS Office, Figure 5b derived from Bear's Neuroscience p. 386

Across angular accelerations ranging from 0.1 to 5 Hz and beyond, gain and phase characteristics of the hair cells remain constant, i.e. across the band of physiological head movements and well beyond, concise integration of the head angular acceleration into a head velocity related signal is possible with the mechanical properties of the cupola-endolymph system. Head acceleration is measured, but a velocity-related signal is conveyed to the brainstem [Jones et al 1972].

2.1.1.2 The macular organs

Utriculus and sacculus lie next to the vestibular canal system (Figures 3a and 3c). They are related orthogonally to each other [Fernandez et al 1979]. The utriculus is turned laterally about 5° to 10° [Fernandez et al 1979, Fitzpatrick et al 2004] and tilted backwards around 30°, similar to the plane of the horizontal semicircular canal [Tribukait et al 2001, Fitzpatrick et al 2004]. The upright sacculus lies close to the head sagittal plane, tilted laterally by about 20° [Fernandez et al 1979].

In summary, the sacculi lie close to the head sagittal plane, whereas the utriculi are tilted 30° backwards from the head transverse plane, like the horizontal canal.

Both otolith organs respond to linear acceleration ("vection") and tilt [Angelaki et al 2004, Fitzpatrick et al 2004]. The utriculus responds to movements in the head horizontal plane; the sacculus responds to vertical stimuli.

Macular organs are constructed differently in comparison to the canal organs: their hair cells are covered by a widespread cupula of elastic material with calcite "statoconia" (or "otoconia") imbedded on top. These crystals increase the inertia and mass of the whole sensory device [Wersäll et al 1972].

Both vection and static tilt to one side deflect the inert substance on top of the hair cells from its resting position. This deflection of the statoconia together with the elastic cupola either depolarises or hyperpolarises the hair cells underneath, depending on hair cell orientation relative to the cupula deflection. More or less transmitter is ejected, depending on cell polarity, like in vestibular canal hair cells.

Both maculae are divided in half by the "Striola" line, running diametrally through the organ. It divides the utriculus into a lateral and medial, the sacculus into a superior and an inferior compartment. Tribukait and colleagues investigated the morphological orientation of hair cells in utriculus [Tribukait et al 2001] and sacculus [Tribukait et al 2005]. Their results are summarized in Figure 6.

Figure 6

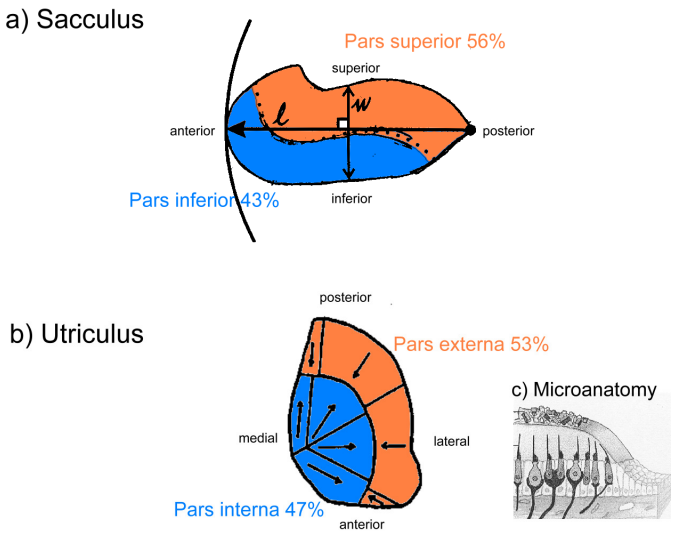


Figure 6:

In both macular organs, hair cells are uniformly distributed, i.e. area size is proportional to peripheral sensory weighting.

a) In the saccular organ, the excitatory direction of cupola displacement is away from the striola, separating the sacculus in pars superior and inferior: pars superior hair cells are excited by cupola deflection upwards; pars inferior hair cells are excited by cupola deflection downwards. The pars superior is significantly larger (mean 56.5%, n =14).

b) In the utriculus, pars interna hair cells are excited by cupola displacement laterally, towards the striola (by either ipsilateral head tilts or contralateral translation). Pars externa hair cells increase their transmitter release upon medially directed cupola displacement, such as by contralateral head tilts or ipsilateral vection. The pars externa was in mean significantly larger (53%, n = 43).

Images: Figure 6a adapted from Tribukait et al 2005; 6b from Tribukait et al 2001. 6c taken from Netter's Neurology p. 87

The vertical position of the sacculus allows sensing the gravitational forces, for example while starting or stopping in an elevator or or during a headstand. Hair cells in the slightly larger superior part are depolarized through upward displacement of the statoconia. They can be excited by a stopped rising elevator or a headstand. Accordingly, the pars inferior can be excited by a stopped descending elevator or standing upright [Tribukait et al 2005]. In saccule-related vestibular nerve fibres, regularly discharging fibres coding for "lift" (pars superior-related) have a higher resting discharge than those coding for "drop" (pars inferior-related). This is believed to compensate for the gravity pull on the saccular gelationous cupola in upright stance [Fernandez et al 1979].

The utriculus allows sensing both static tilt to either left or right and vection in the head-horizontal plane [Tribukait et al 2001].

2.1.1.3 The vestibular nerve

Neurons code for stimuli directed in a preferred direction and in a direction opposite to it with a modulation of firing rate around a resting discharge [Fitzpatrick et al 2004] in a “push-pull”-system. The vestibular nerve transmits hair cell de- or hyperpolarization to the vestibular nuclei.

Vestibular nerve cells can generally be divided into regularly and irregularly discharging neurons. Each group receives preferential input from specific types of vestibular hair cells. Irregular type units, accounting for a quarter of primary vestibular afferents, are highly sensitive to acceleration and exhibit shorter refractory periods than regular fibres. Irregular-type fibres preferentially innervate type I hair cells; type II cells are preferred targets of regularly firing type fibres. The amphora-shaped large type I cells are typically enfolded by a single afferent fibre, whereas cylindrically shaped type II cells are innervated by several afferent fibres [Goldberg et al 1982 and 1984, Fitzpatrick et al 2004]. Irregular-type fibers are preferred targets of galvanic vestibular stimulation (see Chapter 2.2.1).

The discharge rates of human vestibular nerve neurons are unknown, but are commonly believed to be similar to those found in macaque monkey neurons. In rhesus monkey the resting rate of a regularly-discharging neuron is around 90 to 115 Hz with a dynamic range from 0 Hz up to around 300 Hz [Goldberg et al 1979, Fitzpatrick et al 2004]. This implies that depolarization (i.e. excitation) of the vestibular nerve may have higher central influence in comparison to inhibition, which can only reduce nerve activity to zero. The resting discharge rate of macular-related fibres is around 60 Hz in utriculus-related fibres and slightly higher for fibres innervating the sacculus in higher primates, and supposedly also in humans [Fernandez et al 1979].

In the sensory epithelium, the vestibular nerve fibres course without a glial sheath for about 10 to 50 µm before penetrating the basement membrane [Goldberg et al 1982 and 1984, Wersäll 1972]. Here, the transduction from supra-threshold excitatory postsynaptic potentials (EPSPs) into action potentials (APs) and the effect of galvanic vestibular stimulation are believed to take place [Goldberg et al 1982 and 1984] (compare Chapter 2.2.1).

Below the basement membrane of the sensory epithelium, the vestibular nerve fibres are first enveloped by peripheral Schwann glia, later by oligodendroglia. The perikaryon of the bipolar nerve

cell is located in Scarpa's ganglion [Carpenter 1967, Wersäll 1972, Goldberg et al 1982].

Fibres of some hair cell organs already join before merging into the definite vestibular nerve: sacculus and posterior canal fibres course in the inferior vestibular nerve to the posterior ganglion of Scarpa; fibres originating from the utricle, the ventral sacculus tip, anterior canal and horizontal canal fibres project through the superior vestibular nerve to the anterior ganglion of Scarpa [Carpenter 1967, Wersäll 1972, Fernandez et al 1979]. The vestibular nerve then courses into the brainstem at the level of the lateral vestibular nucleus [Büttner-Ennever 1992] together with cochlear fibres as the VIIIth cranial nerve.

Immunohistochemistry studies suggest glutamate to be the primary neurotransmitter for primary vestibular nerve neurons, with glycine and acetylcholine as possible co-transmitters [Ito 1972, Carpenter 1988, Raymond et al 1988, Bäurle et al 2001].

There appears to be a high amount of convergence at the vestibular nerve level. Every primary vestibular afferent fibre receives input from a series of hair cells.

Within the vestibular nuclei, nearly every fibre divides into an ascending and a descending branch [Büttner-Ennever 1992]. The descending branch terminates at the medial, lateral and inferior nucleus, whereas the ascending branch is sent to the superior vestibular nucleus and terminates in the cerebellum via the superior cerebellar peduncle [Carleton et al 1984].

2.1.1.4 The efferent vestibular fibres

Myelinated efferent vestibular fibres arise ipsilaterally from the anterior-inferior lateral vestibular nucleus, regions in and around the medial vestibular nucleus and from the reticular formation. Bilateral fastigial nucleus fibres also contribute to the efferent vestibular system [Iurato et al 1972, Wersäll 1972, Carleton et al 1983, Schwarz et al 1989].

Efferent vestibular fibres terminate presynaptically on type II and postsynaptically on the calyceal endings of type I hair cells [Iurato et al 1972, Goldberg et al 1979], either directly attached to the target cell or established by "en passent" synapses [Iurato et al 1972]. The transmitter substance is probably acetylcholine, with a variety

of co-transmitters [Iurato et al 1972, Raymond et al 1988, Schwarz et al 1989, Bäurle et al 1999].

They may inhibit hair cell systems [Llinas et al 1972, Goldberg et al 1979], possibly attenuating certain afferent signals. The exact function of the efferent vestibular system and its possible influence on galvanic vestibular stimulation remains mostly unknown to the present date.

2.1.2 The vestibular nuclear complexes

The superior (SVN), medial (MVN), lateral (LVN) and inferior (IVN, sometimes also called "descending") vestibular nuclei [Brodal 1972(2), Büttner-Ennever 1992] and smaller cell groups [Pompeiano 1972, Batton et al 1977, Korte 1979, Brodal 1984, Carleton et al 1983 and 1984, Carpenter 1988, Büttner et al 1988 and 2005] form a centre of vestibular and proprioceptive interaction in the brainstem. The SVN only plays a minor role in postural control [Review in Büttner et al 1988 and 2005]. They are altogether referred to as a "vestibular nuclear complex" [Brodal 1972(2)], one situated on each side of the brainstem midline. We describe vestibular inputs from the vestibular nerve, the cerebellum, the spinal cord, vestibular commissural fibres and vestibular nuclear efferences.

Predominantly ipsilateral primary vestibular afferents form the largest source of input [Brodal 1972(2), Fukushima et al 1979, Carpenter 1988, Büttner-Ennever 1992], although not all vestibular nucleus neurones receive primary vestibular afferents [Korte 1979, Precht 1979]. Only a "central zone" (rostro-medial MVN, ventro-medial LVN, dorso-medial IVN) receives all vestibular canal and macular modalities [Ito 1972, Korte 1979, Precht 1979, Brodal 1972(2) and 1984, Carleton et al 1983 and 1984, Carpenter 1967 and 1988, Büttner-Ennever 1992] (Figure 7).

Most neurons (about 60%) receive spatially and temporally converging input from more than one canal or macula (macular-canal and canal-canal), while other neurones receive individual vestibular organ signals [Markham et al 1972, Pompeiano et al 1997].

Figure 7

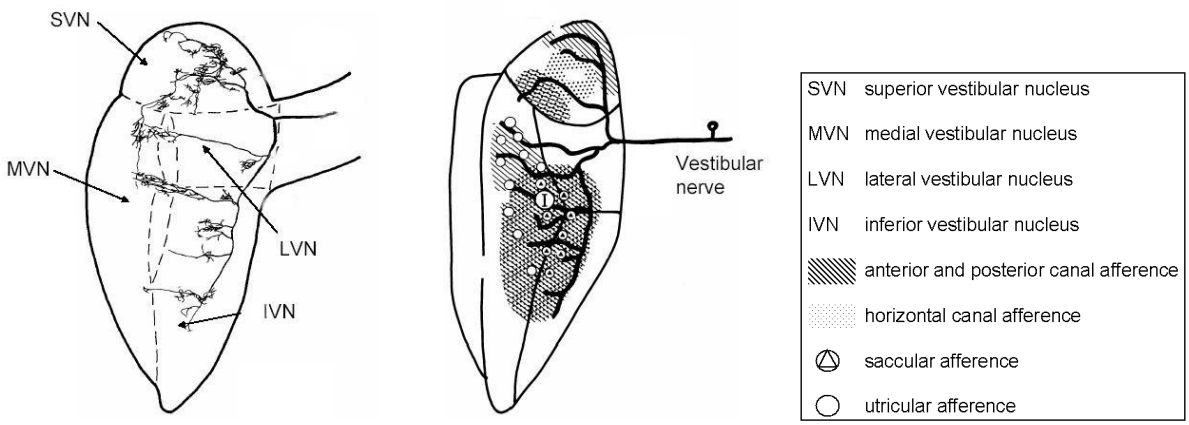


Figure 7:

Vestibular nuclear complex with the targets of primary vestibular afferents. Zone "I" in the right illustration marks the central zone, which receives all primary vestibular modalities.

Images: modified from Büttner-Ennever 1992

The terminations of vestibular fibres are distributed by their origin. Fibres from the semicircular canals predominantly terminate in the rostral parts of MVN and IVN [Ito 1972, Precht 1979, Brodal 1972(2) and 1984], utriculus-related fibres in the rostral IVN, MVN and ventral LVN [Precht 1979, Carpenter 1988, Büttner-Ennever 1992] and sacculus projections mainly target the LVN and IVN nuclei and group "y" [Precht 1979, Carpenter 1988, Büttner-Ennever 1992].

The LVN with its ventral and dorsal subdivisions [Ito 1972, Boyle et al 1992, Büttner-Ennever 1992] is special: its ventral zone – as a part of the "central zone" [Büttner-Ennever 1992] – receives primary vestibular afferents and very little cerebellar input. The dorsal part, by contrast, receives combined cerebellar, reticular and spinal input, but is mostly spared by primary vestibular fibres [Ito 1972, Pompeiano 1972, Korte 1979, Carpenter 1967 and 1988, Fanardjian et al 1988, Boyle et al 1992, Büttner-Ennever 1992].

The vestibular nuclei receive prominent input from cerebellar structures: fibres from the cerebellar anterior lobe vermis longitudinal zone "b" target the MVN, dorsal LVN and IVN [Ito 1972, Carleton et al 1983, Brodal 1972(2) and 1984, Ekerot et al 1979, Fukushima et al 1979, Carpenter 1988, Fanardjian et al 1988, Büttner-Ennever 1992, Voogd et al 1989 and 1998, Büttner et al 1988 and 2005]. The MVN receives ipsilateral fastigial nucleus input [Carleton et al 1983, Brodal 1984, Fukushima et al 1979, Carpenter 1988, Büttner et al 1988 and 2005]. Bilateral fastigial input reaches the IVN and dorsal LVN: input to the IVN is predominantly contralateral [Ito 1972, Brodal 1984, Carleton et al 1983, Mori et al 2004], dorsal LVN input is mostly ipsilateral [Carleton et al 1983].

Spinal structures convey proprioceptive input to the vestibular nuclei [Fukushima et al 1979, Pompeiano 1972 and 1979, Carleton et al 1983, Brodal 1972(2) and 1984] as cerebellar input fibre collaterals (Chapter 2.1.3).

A wide network of commissural fibres spreads throughout both vestibular nuclear complexes. They predominantly connect the MVN nuclei of both sides [Precht 1979, Carpenter 1988, Raymond et al 1988]. The LVN does not emit, but instead only receives commissural fibres [Fukushima et al 1979, Carleton et al 1983, Carpenter 1988].

Vestibular nuclear efferences fall into vestibulo-ocular, vestibulo-cerebellar, vestibulo-spinal, vestibulo-olivary, vestibulo-reticular and vestibulo-thalamic fibres [Brodal 1972(1), Pompeiano 1972, Korte 1979, Carleton et al 1983, Brodal 1984, Carpenter 1988, Fanardjian et al 1988]. The vestibular nuclei also give rise to the large vestibulo-spinal tracts, which are decisive for postural control (Chapter 2.1.4).

MVN and IVN bilaterally project to the anterior lobe vermis [Brodal 1984, Carleton et al 1983, Carpenter 1988]; LVN however only targets the ipsilateral anterior lobe vermis [Carpenter 1988]. The deep cerebellar fastigial nucleus projects to most of the vestibular nuclei, sparing only the IVN [Carleton et al 1983, Carpenter 1988].

Vestibulo-thalamic fibres from all main vestibular nuclei bilaterally project to the thalamus, in particular the oral lateral division of nucleus ventro-posterior (VPL_o) [Mergner et al 1981, Büttner et al 1979, Bense et al 2001]. From there, a cortical network around the "vestibular cortex" [Guldin et al 1992] is addressed, consisting of the posterior insular vestibular cortex (PIVC), VIP (ventral intra-parietal), Areae 2 and 3a and others [Büttner et al 1979, Guldin et al 1998, Fitzpatrick et al 2004, Fasold et al 2008]. They are multi-sensory areas, uniting vestibular, proprioceptive and visual characteristics [Fasold et al 2008]. In this network, the mental concept of "head in space" is probably formed.

Figure 8 illustrates the connectivity of the three main vestibular nuclei described here. The superior vestibular nucleus (SVN) is not included, due to its predominant involvement into oculomotor tasks [Büttner et al 1988 and 2005].

Figure 8

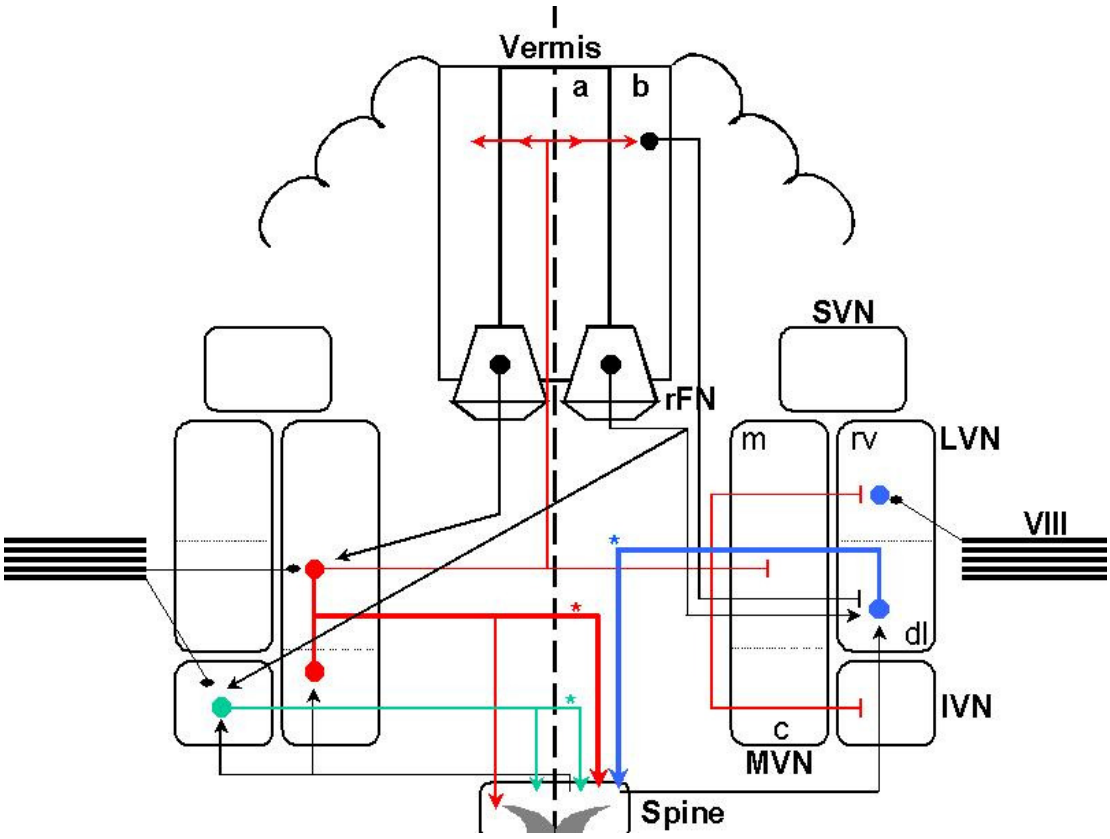


Figure 8:

The main vestibular nuclei on both sides of the midline, frontal view: medial vestibular nucleus (MVN) with medial (m) and caudal (c) part, lateral vestibular nucleus (LVN) with rostro-ventral (rv) and dorso-lateral (dl) part, inferior vestibular nucleus (IVN) and superior vestibular nucleus (SVN).
Other involved structures are the cerebellar vermis with longitudinal zones “a” and “b”, the rostral fastigial nuclei (rFN) the vestibular nerve (VIII) and the spinal cord. Vestibulo-spinal tracts are marked with stars (*).
Connectivity is illustrated for the MVN with the medial vestibule-spinal tract (MVST, red), LVN with the lateral vestibule-spinal tract (LVST, blue) and IVN with the inferior vestibule-spinal tract (IVST, cyan) with “ —o ” for excitatory, “ —| ” for inhibitory and “ —> ” for unspecified synapses.
The common primary target of the network shown here is the left spinal half of the depicted individual, to avoid redundance.

Image drawn with Microsoft Office © and Microsoft Paint ©

2.1.3 The cerebellum and the inferior olivary complex

The cerebellum is generally referred to as the “coordinator of movement” Ito 1984, Diener et al 1992, Thach et al 1992 and 2004. Cerebellar lesions lead to body and limb ataxia, dysarthria, dysdiadochokinesis and oculomotor coordination disorders (oculomotor disorders reviewed by Büttner and Büttner-Ennever Büttner et al 1988 and 2005). In cerebellar disease the executing of movements is affected.

We illustrate cerebellar anatomy, connectivity and function of the vermal cerebellar cortex, the underlying fastigial nuclei and the inferior olivary complex, which is closely related to cerebellar

function [Batton et al 1977, De et al 2000, Kistler et al 2000, Boyden et al 2004, Karakossian et al 2004]. Current theories on cerebellar function and decisive studies on the involvement of the cerebellar circuitry in postural control are reviewed.

Figure 9 shows an anatomical overview the cerebellum. Cerebellar connectivity regarding postural control is depicted at the end of this chapter in Figure 10 (page 29).

Figure 9

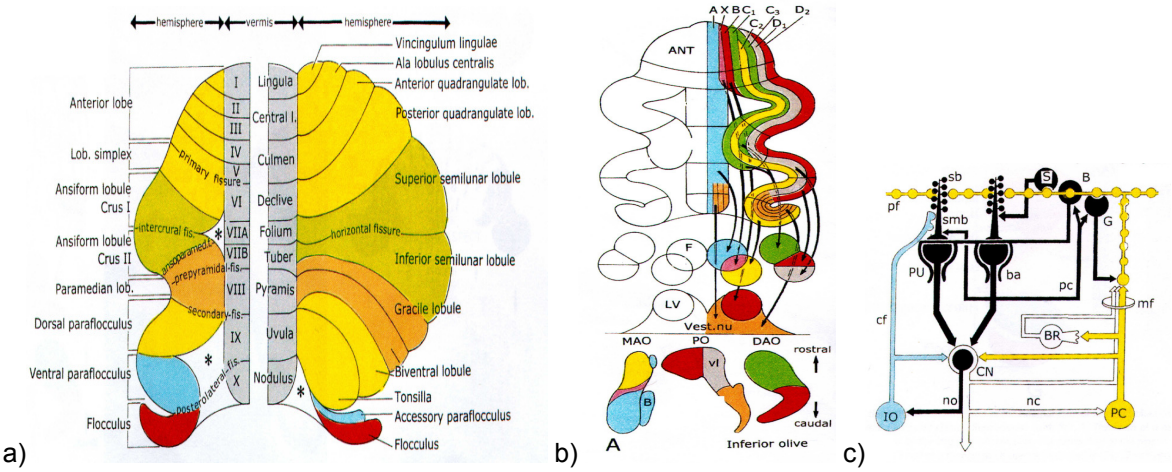


Figure 9:

a) posterior view on the verebellar cortex, horizontal macroscopic organisation (fis. fissure, lob. lobule).
b) longitudinal organisation of the cerebellar cortex with zones “a” to “d2” and their targets. (ANT anterior lobe, F fastigial nucleus, Vest.nu. vestibular nuclei, LV lateral vestibular nucleus, MAO/DAO medial / dorsal anterior olive, PO posterior olive)
c) Schematic microscopic connectivity of the cerebellar cortex. (Cell types in capitals; “B” basket cell with “ba” basket cell fibre, “BR” brush cell, “CN” deep cerebellar nucleus cell / fastigial nucleus cell with “no” nucleo-olivary- and “nc” extracerebellar projection, “E” extracerebellar cell with “mf” mossy fibres, “G” granule cell with “pf” parallel fibres, “PU” Purkinje cell with “pc” collateral.

Images: Voogd et al 1998; Figure 9a taken from Fig.2. G and H, 9b modified from Fig.3.A. and 9c adapted from Fig.1.E

2.1.3.1 The cerebellar cortex

2.1.3.1.1 General features

The medial part of the cerebellum (“vermis”) – and its anterior part in particular – is under scrutiny here, whereas the cerebellar hemispheres are not discussed further. The border between vermis and hemispheres is not sharply delineated.

Macroscopically, the cerebellar vermis divides into a series of horizontal lobules from rostral to caudal:

these are serially lingula (lobule I), central lobule (II and III), culmen (IV and V), declive (VI), folium (VIIa), tuber (VIIb), pyramis (VIII), uvula (IX) and nodulus (X). Lobules I to V are referred to as the anterior lobe vermis. The anterior lobe is clearly delimited from the posterior lobus simplex by the "primary fissure" between lobules V and VI [Bäurle et al 1998, Matsushita et al 1985, Voogd et al 1989 and 1998] (Figure 9a).

Apart from the horizontal subdivisions, there is a pattern of parasagittally oriented longitudinal zones [Voogd et al 1989 and 1998] (Figure 9b). Purkinje cells of a longitudinal zone have a common target among the deep cerebellar nuclei or brainstem structures. The longitudinal zones are arranged alphabetically, starting with "a" for the mesial part. Zone "a" targets the fastigial nucleus, an interposed zone "x" between "a" and "b" projects to cells between fastigial and posterior interposed nucleus and zone "b" targets the lateral vestibular nucleus; the other longitudinal zones are not further detailed here [Ito 1984, Carpenter 1988, Thach et al 1992, Pompeiano et al 1997, Voogd et al 1989 and 1998].

On a microscopic level, the cerebellar cortex is comprised of three main layers (from outside to inside): the molecular layer with its stellate and basket cells, the Purkinje cell layer and the granular layer, the innermost layer containing brush, granule and Golgi cells (Figure 9c). So-called "Bergman cells" form the glial superstructure of the cerebellum.

Cerebellar input can be divided by its origin. Most input fibres from extracerebellar structures arrive as "mossy fibres" at several cell types, whereas only the inferior olivary complex sends "climbing fibres" directly unto cerebellar Purkinje cells.

From various extracerebellar locations, afferent mossy fibres ascend into the cerebellar cortex, often with collaterals to the deep cerebellar nuclei before terminating on granule cells. Granule cells hail the unmyelinated parallel fibres, which reach along the longitudinal axes of the cerebellum. Purkinje, Golgi, basket and stellate cells all receive parallel fibre input.

Glutamatergic climbing fibres, originating from the inferior olive, entwine the dendritic tree of Purkinje cells. Purkinje cells receive input with their dendrite tree oriented orthogonally to the longitudinal orientation of the parallel fibres. They form the only output of the cerebellar cortex.

Inhibitory Purkinje cells project onto deep cerebellar nuclear cells by their GABAergic axons. About 30 Purkinje cells project to one cell of the deep cerebellar nuclei, whereas just as many deep nuclear

cells receive inhibitory input from one Purkinje cell in turn [Ito 1984, Raymond et al 1988, Thach et al 1992, Voogd et al 1989 and 1998, Eilers et al 1999, Aizenman et al 2000, Andjus et al 2005].

The anterior lobe vermis ("spino-cerebellum") is involved in spinal mechanisms such as posture and gait control [Siebold et al 1997, Thach et al 1992 and 2004]. There is certain functional somatotopy: e.g. the forelimb region relates to the caudal parts of the anterior lobe [Manzoni et al 1998, 1999 and 2004, Thach et al 1992 and 2004].

Experimental results indicate a merging of different vestibular and spinal characteristics and multi-sensory influence on vestibulo-spinal reflex arcs:

Input from different vestibular modalities is coordinated in the cerebellar cortex, including semicircular canal and macular – in particular utricular - characteristics [Kubin et al 1981, Pompeiano et al 1997, Kleine et al 1999(1)]. These vermal cortical cells respond to slow changes neck position [Boyle et al 1979(1), Denoth et al 1979] with convergence of neck proprioception and vestibular input [Kubin et al 1981, Pompeiano et al 1997, Manzoni et al 1998, Manzoni et al 1999, Manzoni et al 1998, 1999 and 2004].

Experimental temporary inactivation of longitudinal zone "b" Purkinje cells was found to decrease the gain of vestibulospinal reflexes, suggesting direct involvement of cerebellar longitudinal zone "b" on vestibulo-spinal circuitry [Kubin et al 1981, Manzoni et al 1996 and 1997, reviewed in Pompeiano et al 1997].

In summary findings like these detailed above support the idea of the cerebellar cortex acting as a key site for vestibulo-proprioceptive coordination in postural control.

2.1.3.1.2 Cerebellar cortex afferents

The primary afference to the cerebellar cortex hails from vestibular, spinal and olivary structures.

Mossy fibre afference from the brainstem is generally bilateral [Siebold et al 1997]. Its intra-lobular target is dependent on its origin: vestibular-related fibres target medial structures; pontine afferents occupy lateral targets with spinal input in between. Some mossy fibres arise from the reticular formation [Andre et al 2005, Ekerot et al 1979] and the external cuneate nucleus in the medulla (related to neck proprioception) [Andre et al 2005].

There is a mosaic of mossy fibre "fractured somatotopy", making a homunculus of representations impossible to draw [Thach et al 1992, Voogd et al 1989 and1998, De et al 2000]. Climbing fibre input to the vermis is also subject to somatotopic organization [Ekerot et al 1979, Voogd et al 1989 and 1998].

Primary vestibular mossy fibres arrive at the cerebellar cortex in the granule cell layer of longitudinal zone 'b' [Brodal 1972(1), Ito 1972, Llinas et al 1972, Denoth et al 1979, Carleton et al 1983 and 1984, Pompeiano et al 1997, Voogd et al 1989 and 1998]. They connect to the cerebellar vermis, including the anterior vermis, nodulus and uvula, while sparing the flocculus [Büttner et al 1988 and 2005].

Lateralization of primary vestibular fibres to the cerebellum has been subject to contradictory findings and discussions among the scientific community, possibly due to very scarce amount of cerebellar projection: terminations have been found bilaterally within the cerebellar vermis [Büttner-Ennever 1992] or strictly ipsilaterally [Brodal 1972(1), Carpenter 1988]. Possible terminations at the ipsilateral fastigial nucleus [Brodal 1972(1)] have also been discussed.

Secondary vestibular fibres from the vestibular nuclei reach the cerebellar cortex (and the fastigial nucleus) bilaterally, with ipsilateral preponderance [Kotchabhakdi et al 1978, Carpenter 1988, Siebold et al 1997, Büttner et al 2003].

Neck proprioceptive inputs reach the cerebellar cortex by a wide range of relay stations. About twenty different spinocerebellar pathways are known, ending as either mossy or climbing fibres in the cerebellar anterior vermis [Rexed 1952 and 1954, Ekerot et al 1979, Matsushita et al 1985, Thach et al 1992]. The only direct spinocerebellar pathways are the dorsal spino-cerebellar tract and the cuneo-cerebellar tract.

2.1.3.1.3 Cerebellar cortex efferences

Fibres emerging from the two halves of the cerebellar vermis strictly project ipsilaterally [Armstrong et al 1978, Büttner-Ennever 1992].

Longitudinal zone "a" of Voogd projects to the rostral fastigial nucleus, which in turn projects on to vestibulo-spinal and reticulo-spinal tract neurones [Moruzzi et al 1957, Armstrong et al 1978, Büttner et al 1991, Thach et al 1992, Pompeiano et al 1997, Siebold et al 1997, Andre et al 2005]. By contrast, zone "b" directly targets the IVN and dorsal LVN [Moruzzi et al 1957, Lund et al 1967, Matsushita et al 1971(1), Ito 1972, Armstrong et al 1978, Fanardjian et al 1988, Carleton et al 1983, Pompeiano et al 1997, Voogd et al 1989 and 1998, Manzoni et al 1999]. Both target vestibular nuclei emit direct vestibulo-spinal fibres.

2.1.3.2 The fastigial nucleus

2.1.3.2.1 General characteristics

In mammals, the deep cerebellar nuclei are divided into the medial, anterior interpositus, posterior interpositus and dentate nuclei [Matushita et al 1971, Ito 1972, Thach et al 1992]. The medial deep cerebellar nucleus, also called “fastigial nucleus”, is discussed here.

The fastigial nucleus is somatotopically organized [Moruzzi et al 1957, Armstrong et al 1978, Thach et al 1992, Siebold et al 1997, Voogd et al 1989 and 1998, Büttner et al 1991 and 2003]. Its rostral magnocellular part (“lower extremities”) is related to spinal and posture control mechanisms [Matsushita et al 1971(1), Thach et al 1992, Siebold et al 1997, Trouillas et al 1997, Büttner et al 1991 and 2003, Mori et al 2004, Thach et al 1992 and 2004, Ilg et al 2007] as a “cerebellar locomotor region” [Mori et al 2004]; the caudal part (“head”) is involved in oculomotor functions [Thach et al 1992, Siebold et al 1997, Kleine et al 1999(1), 1999(2) and 2004, Büttner et al 1988, 1991, 2003 and 2005] and may be referred to as the “fastigial oculomotor region” [Kleine et al 2004, Büttner et al 2005] (“FOR”). Distribution patterns of Purkinje cell inputs [Matsushita et al 1971(2)] indicate a complete re-arrangement of anterior vermal somatotopy: hindlimbs are situated anteriorly, proximal parts laterally [Thach et al 1992].

The vestibular part of the fastigial nucleus is a layer of cells in the anterior half of the nucleus, along the entire dorsoventral and mediolateral extent [Gardner et al 1975, Siebold et al 1997].
Some rostral fastigial neurons can be excited by contralateral rotation and inhibited by ipsilateral rotation [Gardner et al 1975, Siebold et al 1997] (“Type II”), which are mainly “vestibular only” neurones [Büttner et al 1991] (“VO”) without any eye-movement related characteristics [Jones et al 1972, Gardner et al 1975, Siebold et al 1997, Büttner et al 1991 and 2003, Kleine et al 2004].
VO neurones are able to unite different sensory inputs by linear summation [Kleine et al 1999(1) and 2004]. Their firing patterns resemble pure velocity-related cosine-tuning, indicating domination of vestibular canal-related signals [Kleine et al 1999(1)]. Galvanic vestibular stimulation is preferentially canal-related (Chapter 2.2).
These “VO” cells are of particular interest for the experimental study conducted here: its neurons respond only to vestibular input – and semicircular input in particular – by converging vestibular signals and spinal proprioceptive afference. The rostral fastigial nucleus with its “VO” neurones is probably one of the key sites for vestibulo-spinal interaction, as one of the cerebellar outputs to the vestibular nuclei [Kleine et al 1999(1), Büttner et al 2003].

Clinically, unilateral fastigial nucleus lesion in patients is known to cause a tendency of falling towards the ipsilateral side (like ipsilateral vermis lesions). This is in support of anatomical and functional studies, relating this nucleus to postural control [Siebold et al 1997, Büttner et al 2003, Matsuyama et al 2004, Thach et al 1992 and 2004].

In summary, the fastigial nucleus is a central structure in the processing of different vestibular modalities and proprioceptive signals. It is decisive for postural control.

2.1.3.2.1.1 Fastigial input

All deep cerebellar nuclei including the fastigial nucleus, receive input from three different origins [Ito 1972]: excitatory mossy fibres from extracerebellar structures including the vestibular nuclei [Fanardjian et al 1988], excitatory climbing fibre collaterals from the inferior olive and, finally, inhibitory Purkinje cell input from their respective cerebellar cortex zone above (zone "a" for fastigial nucleus) [Matsushita et al 1971(1), Armstrong 1978, Carleton 1983, Thach et al 1992, Voogd et al 1989 and 1998, Aizenman et al 1998 and 2000].

Numerous ipsilateral and bilateral spinocerebellar tracts to the cerebellar cortex emit collaterals to the fastigial nucleus [Matsushita et al 1971(2), Ito 1972 and 1984, Büttner et al 1991, Mori et al 2004, Thach et al 1992 and 2004] (Chapter 2.1.4).

Possible primary vestibular afferents to the fastigial nucleus were extensively discussed in the past. In some experiments, scarce afference was traced to the rostral fastigial tip [Carpenter 1967, Brodal 1972(1), Fukushima et al 1979, Korte 1979], while other authors strictly contradicted [Gardner et al 1975, Carleton et al 1984].

The secondary vestibular afferents from the vestibular nuclei mainly hail from the MVN [Brodal 1984, Mori et al 2004]. Anatomical studies on the origin of the secondary and higher-order vestibulo-fastigial projections are scarce, especially of those related to the rostral fastigial nucleus.

2.1.3.2.1.2 Fastigial output

Fibres from the fastigial nucleus target the vestibular nuclei, the reticular formation [Pompeiano et al 1997, Matsuyama et al 2004, Mori et al 2004, Thach et al 1992 and 2004], the inferior olive [Aizenman et al 1998 and 2000, De Zeeuw 1998, Voogd et al 1998, Thach et al 1992 and 2004] and the spinal cord. Non-oculomotor fastigial neurones target the contralateral "cerebellar thalamus "region around the ventro-lateral nucleus (VL) and oral lateral ventroposterior nucleus VPL_o [Batton et al 1977, Büttner et al 1979, Gdowski et al 1999, Thach et al 1992 and 2004], which receives almost exclusive cerebellar input [Thach et al 1992 and 2004]. Further projection targets the "vestibular cortex" (compare Chapter 2.1.2).

Fastigial neurons can be either inhibitory or excitatory. Inhibitory cells strictly project to the contralateral inferior olive; excitatory cells can project to any other of the structures mentioned above [Kistler et al 2000].

The rostral nucleus projects ipsilaterally [Ito 1972, Carleton et al 1983] through the inferior peduncule [Aizenman et al 1998 and 2000, De Zeeuw 1998, Voogd et al 1998] to the ipsilateral MVN, dorso-lateral LVN and dorso-medial IVN [Ito 1972, Gardner et al 1975, Carleton et al 1983, Pompeiano et al 1997, Matsuyama et al 2004]. There is also a direct spinal projection. All these targets give rise to individual vestibulo-spinal tracts (see Chapter 2.1.4 "neck and spine").

2.1.3.3 The inferior olive

The inferior olivary complex emits all climbing fibres to the contralateral cerebellar Purkinje cells [De Zeeuw et al 1998, Fanardjian et al 1988] and is supposed to be a key site for cerebellar circuitry [De Zeeuw et al 1998, Kistler et al 2000, Thach et al 1992 and 2004]. Input to the inferior olive targets its rostral part, whereas olivary output originates from the caudal compartment [Voogd 1989, De Zeeuw et al 1998, Manzoni et al 1999].

The rostral inferior olive receives vestibular input from the contralateral MVN, LVN and caudal IVN [Llinas et al 1972, Carleton et al 1983, Fanardjian et al 1988]. The medial accessory olive also receives primary ipsilateral vestibular afferents [Carleton et al 1984] and spinal input from spino-olivo-cerebellar relay fibres [Ekerot 1979].

The caudal inferior olive projects to contralateral longitudinal Purkinje cell layers [De Zeeuw et al 1998] with

collaterals to corresponding fastigial neurones [Voogd 1989], which in turn project back to the inferior olive. This unit consisting of inferior olive neuron, Purkinje cell in longitudinal zone "a" of Voogd [Voogd et al 1989 and 1998] and corresponding deep cerebellar nucleus cell is referred to as a "cerebellar module" [Matsushita et al 1971(2), Ito 1984, Büttner et al 1991, De Zeeuw et al 1998, Kistler et al 2000]. Implications on experimental findings are discussed in Chapter 5.6.

Different caudal olivary projections target longitudinal zone "b" of the cerebellar cortex [Voogd 1989], which is directly related to the lateral vestibular nucleus [Fanardjian et al 1988], thus forming another separate circuit.

An overview of the complex cerebellar and olivary connectivity is shown in Figure 10.

Figure 10

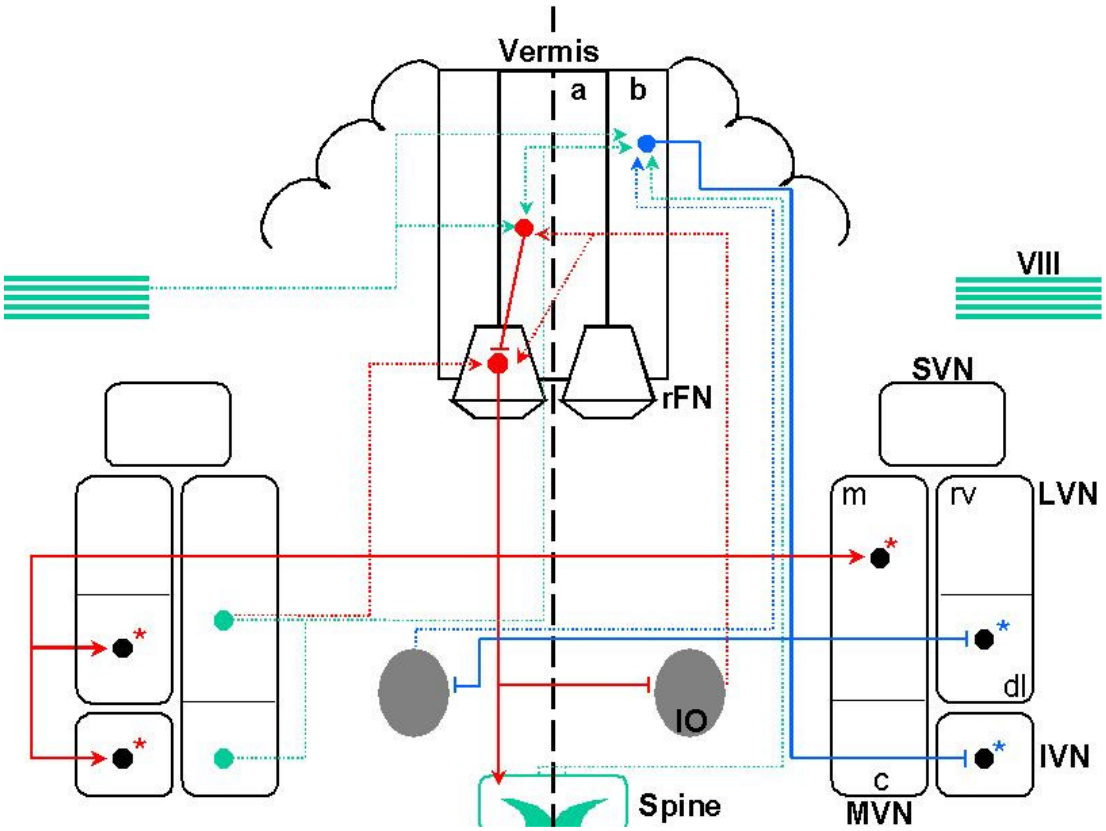


Figure 10:

This figure illustrates the connectivity of the two main vermal pathways. Frontal view on the brainstem with the cerebellum behind.
The left half of the midline depicts connectivity of the vermal longitudinal **zone "a"** and its corresponding rostral fastigial nucleus in **red**. Longitudinal **zone "b"** with its afferences and targets is shown on the right side of the midline (**blue**).
Bilateral afferents related to both pathways are coloured in **cyan**.

Abbreviations:
Medial vestibular nucleus (MVN) with medial (m) and caudal (c) part, lateral vestibular nucleus (LVN) with rostro-ventral (rv) and dorso-lateral (dl) part, inferior vestibular nucleus (IVN) and superior vestibular nucleus (SVN).
Other structures are the cerebellar vermis (Vermis) with longitudinal zones "a" and "b", the rostral fastigial nuclei (rFN), the vestibular nerve (VIII), inferior olive (IO) and the spinal cord (Spine).
Vestibulo-spinal **tract neurones** are marked with stars (*).
Connectivity is illustrated with " —| " for inhibitory and " —> " for unspecified synapses.

Image drawn with Microsoft Office © and Microsoft Paint ©

2.1.3.4 Cerebellar postural control – motor control and sensory coordination

The exact site of motor and sensory coordination for postural control inside the cerebellum has been subject to extensive research over the past decades. The anterior lobe vermis of the cerebellar cortex and the rostral fastigial nucleus have been under particular scrutiny.

Certain differences between direct cortico-vestibular and indirect cortico-fastigio-vestibular pathways were implied, but experimental findings could not differentiate functionally between different longitudinal zones, cortical and fastigial connectivity [Moruzzi et al 1957, Manzoni et al 1998, 1999 and 2004].

Just recently, the clinical impact of cortical and fastigial lesions have been studied, investigating the influence of fastigial nuclear resection on postural rehabilitation in children after posterior fossa tumor resection [Schoch et al 2006]. Fastigial involvement in resection was reconstructed from magnetic resonance imaging. An intact fastigial nucleus was found to be essential for the recovery of balance function.

Patients were exposed to tilting platforms, optic flow or combined stimuli. Correlation of fastigial nuclear intactness with posturography and clinical assessment revealed that resection of the fastigial nucleus had severe effects on rehabilitation of balance control. Postural control was especially impaired after superior cerebellar cortex lesions (involving the anterior lobe vermis) even though these effects lagged behind fastigial nucleus resection.

In summary, both the cortico-fastigial-vestibular and the cortico-vestibular pathway are probably essentially involved in postural motor control and coordination of vestibular and proprioceptive sensory modalities. Clinical findings indicate more severely impaired rehabilitation after fastigial lesions.

2.1.4 Neck and spine

2.1.4.1 Neck proprioception and spinal afference

Neck receptors are important for the coordination of postural control, by modulating vestibulo-spinal reflexes [Manzoni et al 1998, Kleine et al 2004]. Information on head-on-trunk position represents the relative position of the head-centred vestibular system to the trunk with its postural musculature. Responsible

proprioceptive receptors and related ascending spinal tracts are illustrated here.

The origin of the neck proprioceptive cues is discussed controversially. Dorsal-root-related receptors hail from the axial muscles or relate to the intervertebral joints [Hirai et al 1979]. Possible receptor candidates are the axial muscle spindles, the Golgi tendon organs positioned nearby, Pacini type bodies in the joints [Richmond et al 1979, Bakker et al 1980, Wilson 1988] and some free nerve endings in and around the intervertebral joints [Bakker et al 1980]. The most numerous receptors are muscle spindles and Golgi organs. The muscle spindles of the small intervertebral muscles were thought to be the main neck proprioceptors by many authors [Richmond et al 1977 and 1979, Bakker et al 1980, Wilson 1988, Kleine et al 2004]. A subset of these could be related to tonic head-on trunk-position [Richmond et al 1979], whereas Golgi tendon organs possibly relate to neck proprioception only at "extreme" neck positions with maximal muscle and tendon stretch [Richmond et al 1979, Bakker et al 1980].

We focus on the ascending proprioceptive tracts, targeting the vestibular nuclei, the inferior-olivary complex and the cerebellum as the "principal proprioceptive ganglion" [Mori et al 2004].

Generally, Golgi-organ-related activity is relayed separately from muscle spindle afferents and cutaneous receptors [Pompeiano 1972, Richmond 1977].

There are around 20 spinocerebellar pathways, which terminate as mossy fibres or climbing fibres (by the inferior olive) to the anterior lobe vermis [Ekerot et al 1979, Thach et al 1992]. The dorsal spinocerebellar tract and the cuneo-cerebellar tract project monosynaptically directly onto the ipsilateral anterior lobe vermis, coding for upper extremity and neck proprioception from muscle spindles, Golgi-organs, Ruffini joint receptors and cutaneous afferents [Ekerot et al 1979, Hirai et al 1979, Matsushita et al 1981]. The other spinocerebellar tracts project there polysynaptically, e.g. by inferior olive [Ekerot et al 1979] or external cuneate nucleus [Andre et al 2005].

The central cervical nucleus (CCN) and the external (accessory) cuneate nucleus only relate to neck-proprioception [Matsushita et al 1981, Carleton et al 1983, Hongo et al 1988, Kleine et al 2004] and project bilaterally [Hirai et al 1979, Matsushita et al 1981, Carleton et al 1983, Andjus et al 2005] to the longitudinal zone "a" of the cerebellar anterior lobe vermis [Hirai et al 1979, Matsushita et al 1981, Carleton et al 1983, Voogd et al 1989 and 1998]. These nuclei also receive secondary or even primary vestibular input [Carleton et al 1983, Hirai et al 1979], allowing for possible vestibular-proprioceptive interaction at these sites. The CCN targets the contralateral IVN [Hirai et al 1979, Carleton et al 1983].

In contrast, Clarke's column neurones from the lower body project to both cerebellar longitudinal zones"a" and "b" [Rexed 1952 and 1954, Matsushita et al 1985].

Apart from the cerebellum, the vestibular nuclei are a principal target of ascending spinal tracts. Neurones without primary vestibular input in the MVN, dorsal non-primary-vestibular LVN and IVN are preferred targets of spinal afferents [Fukushima et al 1979, Pompeiano 1972 and 1979, Carleton et al 1983, Brodal 1972(2) and 1984]. Projections are mostly ipsilateral collaterals of spino-cerebellar tracts [Pompeiano 1972, Ekerot et al 1979, Hirai et al 1979]. There might possibly be non-collateral, vestibular-nucleus-only ipsilateral spinal afferents from the lower extremity, but apparently not from the neck [Pompeiano 1972 Ekerot et al 1979, Hirai et al 1979].

2.1.4.2 Efferent spinal tracts and spinal circuitry

We focus on the two main descending spinal tracts related to postural control: the medial (MVST) and lateral vestibulo-spinal tracts (LVST).

The MVST from the MVN and closeby neurons [Fukushima et al 1979, Brodal 1984, Boyle et al 1992, Büttner-Ennever 1992, Uchino et al 1997] mostly crosses the midline to a contralateral spinal projection; a few fibres project ipsilaterally [Carleton et al 1983, Büttner-Ennever 1992, Uchino et al 1997]. Its excitatory and inhibitory fibres project to cervical and thoracic axial motoneurones, but not to limb motoneurones [Rexed et al 1952 and 1954, Carpenter 1967, Lund et al 1967, Brodal 1972(2), Ito 1972, Hongo et al 1975, Fukushima et al 1979, Carpenter 1988, Shinoda et al 1988, Uchino et al 1997, Gdowski et al 1999].

The most prominent efference of the LVN is the LVST, coursing down to ipsilateral spinal termination [Pompeiano 1972, Fukushima et al 1979, Carleton et al 1984, Fanardjian et al 1988, Raymond et al 1988, Boyle et al 1992, Büttner-Ennever 1992, Pompeiano et al 1997, Uchino et al 1997]. Ipsilateral limb-related and trunk-related postural control is under the influence of this somatotopically organized tract [Fukushima et al 1979, Matsuyama et al 2004]. Its rostro-ventral part projects cervically [Fukushima et al 1979, Uchino et al 1997] ("cervical lateral vestibulospinal tract"); the dorsocaudal "lumbosacral lateral vestibular tract" projects down to lumbar and sacral levels [Ito 1972, Fukushima et al 1979, Brodal 1972(2) and 1984, Carpenter 1967, 1983 and 1988, Raymond et al 1988, Boyle et al 1972(2) and 1992, Britton et al 1992, Pompeiano et al 1997, Matsuyama et al 2004]. It excites ipsilateral neck, axial and limb alpha- and gamma-motoneurones of physiological extensor muscles, i.e. those muscles operating against gravity, and inhibits the opposing flexors on the ventral side of the spine [Lund et al 1967, Hongo et al 1975, Brodal et al 1979(1), Fukushima et al 1979, Carleton et al 1983, Carpenter 1988, Shinoda et al 1988, Büttner-Ennever 1992, Pompeiano et al 1972 and 1997, Uchino et al 1997, Manzoni et al 1998, Matsuyama et al 2004].

Besides the vestibulo-spinal tracts, the reticular formation with its reticulo-spinal tracts has certain influence on postural control [Brodal 1972(1), Ito 1972, Pompeiano 1972, Batton et al 1977, Ekerot et al 1979, Fukushima et al 1979, Kubin et al 1981, Carleton et al 1983 and

1984, Carpenter 1988, Fanardjian et al 1988, Britton et al 1992, Uchino et al 1997, Kleine et al 2004, Manzoni et al 2004, probably on neck flexion Uchino et al 1997.

Little is known about a direct fastigio-spinal projection to the ipsilateral ventral horn of the upper cervical segments. It is the only direct spinal projection from a cerebellar deep nucleus Batton et al 1977, Thach et al 1992, Siebold et al 1997, Kleine et al 1999(1), Matsuyama et al 2004, Mori et al 2004.

2.1.5 Anatomical summary

The anatomical review has illustrated a series of anatomical structures, in which vestibular and neck-proprioceptive sensory information is involved – and probably also merged – for postural control.

In the cerebellar complex, two separate pathways exist: a “direct pathway” forming around longitudinal vermal zone “b” and an “indirect pathway”, involving vermal zone “a” and the rostral fastigial nucleus. Among the vestibular nuclei, especially the medial and the lateral vestibular nuclei with their corresponding vestibulo-spinal tracts are subject to both vestibular- and neck-proprioception-related input. Central nervous sites of vestibular and neck-proprioceptive sensory merging are probably anterior lobe vermis, rostral fastigial nucleus, the vestibular nuclei and possibly also the central cervical nucleus.

So far, there have been very few clinical attempts, to investigate the effect of lesions in the structures mentioned above and their effects of postural control. The study conducted here investigates lesions of the cerebellar complex and their clinical effects. Therefore, thorough understanding of the underlying anatomical circuitry is essential for the interpretation of experimental findings.

2.2 Galvanic vestibular stimulation and its postural effects

Galvanic vestibular stimulation is not a method of clinical routine examinations, although it has been well-established in clinical research over decades. We illustrate the theory of galvanic vestibular stimulation and its influences on postural control, with respect to the experimental setup of this study and related studies by other authors. Galvanic vestibular side-effects on oculomotor structures are not part of this work and will not be discussed further [Britton et al 1992, Cass et al 1996].

2.2.1 Fundamentals of galvanic vestibular stimulation

The electrophysiological term “galvanic stimulation” describes a continuous application of electric current, following the discovery of Luigi Galvani 1780 in a metallurgic context. This name is given in dissociation of “faradic stimulation”, which describes an “on-off” application of electric current.

Cathodal currents can artificially excite neurones like vestibular afferents, whereas anodal currents are inhibitory [Goldberg et al 1982, Day et al 1997, Iles et al 2007] down to zero-activity as a kind of “functional ablation” [Bacsi et al 2003(1)]. Galvanic vestibular stimulation (GVS) can thus either excite or inhibit vestibular nerve fibres, depending on its stimulus polarity.

GVS is believed to influence the vestibular nerve activity mainly at the unmyelinated postsynaptic transduction site, but not presynaptically at the labyrinthine hair cells [Dohlman 1935, Britton et al 1992, Goldberg et al 1982 and 1984, Cass et al 1996, Bacsi et al 2003(2), Balter et al 2004(1) and (2), Fitzpatrick et al 2004]. This short segment of 10 to 50 micrometres spans from the synaptic contacts with the hair-cells down to the basilar membrane [Goldberg et al 1984] (Chapter 2.1.1.3). Some galvanic effects may possibly also influence the nerve at Scarpa’s Ganglion and the entry zone into the vestibular nuclear complex [Balter et al 2004(1)]. In general, irregularly discharging vestibular fibres appear to be more sensitive to GVS than regular fibres, probably because of differences in their membrane potential recovery [Britton et al 1992, Goldberg et al 1982 and 1984, Bacsi et al 2003(1), Fitzpatrick et al 2004].

Galvanic vestibular stimulation is able to modulate peripheral vestibular activity. This is perceived like an adequate stimulus for the vestibular system: movement of the individual in space.

2.2.2 Perceived movement and postural reactions

GVS modulates vestibular nerve fibres of both semicircular canals and otolith organs, of which semicircular canal modulation is generally supposed responsible for the observed postural effects.

The otolith organs have been described anatomically and physiologically in chapter 2.1.1.2. Otolith-related postural reactions were found to be dominant during faradic stimulation [Britton et al 1992, Hlavacka et al 1993, Fransson et al 2000, Fitzpatrick et al 2004, Cathers et al 2005, Iles et al 2007, Schneider et al 2009] (on-off). During galvanic vestibular stimulation, their effects are probably negligible [Tokita et al 1989, Britton et al 1992, Hlavacka et al 1993, Kleine et al 1999(2), Angelaki et al 2004, Balter et al 2004(1), Fitzpatrick et al 1994 and 2004, Tribukait et al 2001 and 2005, Cathers et al 2005, Iles et al 2007, Schneider et al 2009] and can only become manifest in very specific experimental conditions [Schneider et al 2009].

As shown in chapter 2.1.1.1, the semicircular canals of each side are orthogonally oriented with respect to each other, and can be stimulated by head angular acceleration. The entire vestibulo-cochlear system, defined by a common plane of the horizontal canals, is tilted backwards about 30 degrees from the head horizontal plane [Pompeiano et al 1997, Fitzpatrick et al 2004, Manzoni et al 1998, and 2004]. The two horizontal canals share the same plane; each anterior canal, however, shares a common plane with its contralateral posterior counterpart, shifted by a few centimetres.

Figure 11

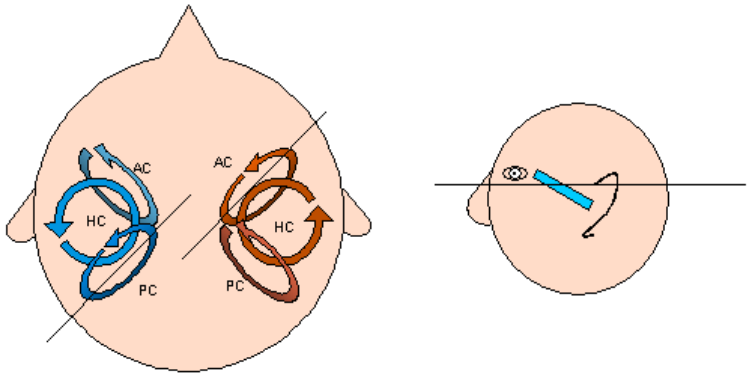


Figure 11:

Left: on-top view of the head with the semicircular canals (AC = anterior, HC = horizontal, PC = posterior canal).The horizontal canals are in the same plane. Each anterior and contralateral posterior canal shares a common plane with a small shift, indicated here for the right anterior and left posterior canals. Coloured arrows indicate the direction of excitatory (blue, left) and inhibitory head movements for the individual canals (red, right). The right figure indicates the plane of the horizontal canals tilted backwards about 30 degrees. (Schematic images drawn with Microsoft Office © and Microsoft Paint ©)

There appears to be a close relation between the optimal physical stimulation directions of the individual semicircular canals and the observed postural effects of GVS [Cass et al 1996]:
Cass and colleagues exposed a patient with an incomplete vestibular nerve transsection (only the left posterior canal left intact) to unilateral left galvanic stimulation. Cathodal excitatory stimulation evoked a perceived backward and leftward movement illusion, with concomiatant postural forward and rightward body movement. Opposite effects were achieved during inhibitory anodal stimulation. After complete left vestibular surgical resection, left unilateral GVS could no longer evoke motion illusions or postural effects. This experiment can be seen in support of the above assumption.

The effect of GVS is apparently interpreted as an unplanned passive movement in space and treated like any other perturbation by a natural vestibular stimulus. Accordingly, postural control mechanisms induce a compensatory movement in an opposite direction to the perceived stimulus.
In a static surrounding, the induced compensatory postural reactions result in galvanically induced body sway [Day et al 1997, Bense et al 2001, Fitzpatrick et al 1994 and 2004, Iles et al 2007].

It remains unknown, whether the "vestibular cortex" [Büttner et al 1979, Guldin et al 1998, Fitzpatrick et al 2004] (Chapter 2.1.2) is actively involved in the interpretation of the galvanic stimulus, or whether it is only informed after decisive postural counter-measures have already been taken on a brainstem level [Guerraz et al 2005, Day et al 2007].

In this study, a bipolar sinusoidal galvanic stimulus is applied. To understand its effects, we illustrate the effects of bipolar stimulation at one defined moment, before we describe the time course of these effects during sinusoidal stimulation:
During GVS of an intact vestibular system on either side, fibres related to all three semicircular canals are either activated or inhibited, depending on stimulus polarity. According to observations of movement illusions and body movements during GVS, the combined signal of all three canals of one side is interpreted as a "rolling" movement around head-sagittal axis. This cumulative effect can be explained by vector addition using the right hand rule, as shown in Figure 12 [Fitzpatrick et al 2004, Cathers et al 2005]. The "right hand rule", as commonly used in electrodynamics, can be used to unambiguously co-relate directed circular fields to vectors – and vice versa: the fingers of the right hand enclose a circular field

with the fingertips pointing in the same direction as the field direction; the stretched-out thumb then indicates the direction of a vector orthogonal to the field plane. Field intensity is vector length.

Figure 12

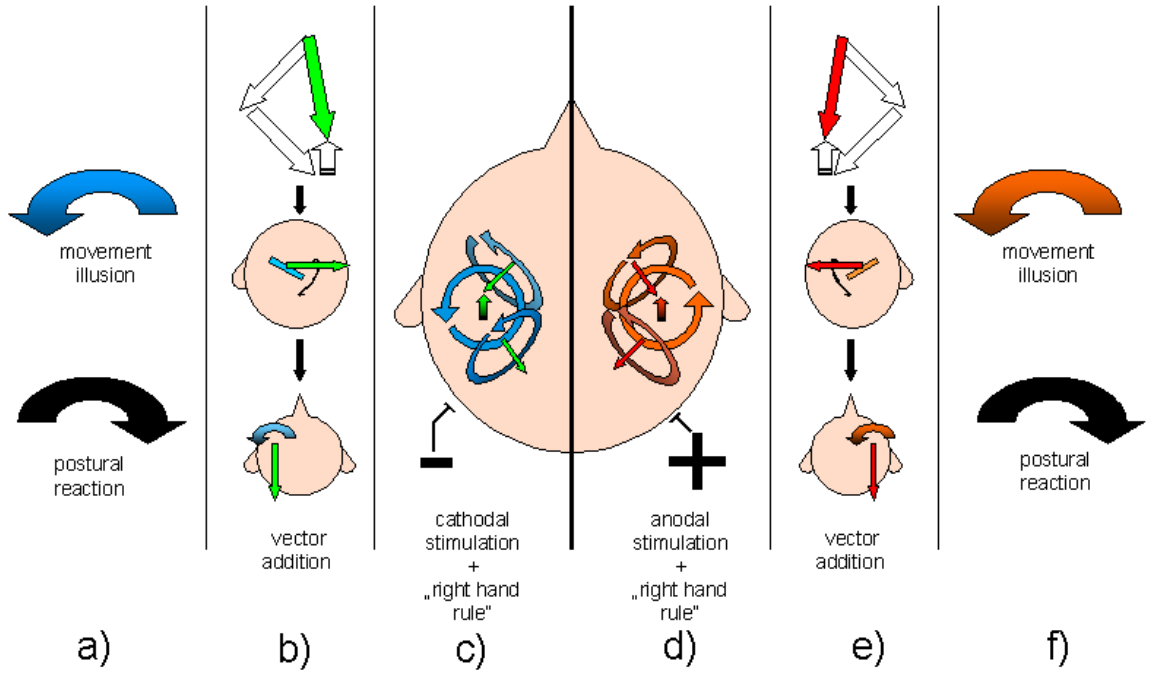


Figure 12:

This figure is based on the schematic semicircular canals in Figure 11. The figure splits in half for the effects of cathodal GVS on the left, and of anodal stimulation on the right side.
Cathodal stimulation (left) excites vestibular canal fibres, simulating movement in the directions indicated by the blue circular arrows in 12c. To encode this into a summable vector, we use the “right hand rule” (the fingers of the right hand enclose the circular arrow with the fingertips pointing in the same direction as indicated; then the stretched-out thumb indicates the direction of the encoding vector).
Vector addition results in a sum vector pointing backwards in the head-horizontal plane, taking into account the –30° backward tilt of the horizontal canal plane (12b). Coding this vector back with the “right hand rule” gives the perceived movement illusion of all three excited canals of the left side: a “roll” around a head-sagittal axis. The opposingly directed postural reaction is a rightward roll (12a).

In analogy to the left side, we encode inhibition on the right side by anodal stimulation with the “right hand rule” again (12d). Adding these vectors into a sum vector (12e) and then un-coding it again with the “right hand rule”, gives a movement illusion directed leftwards, and a postural counter-roll reaction to the right (12f).

Combined galvanic vestibular stimulation results in a total perceived “roll” sensation and an opposingly directed postural counter-roll reaction, depending on the polarity of the stimulus.

Simultaneous bi-polar stimulation (i.e. for example cathodal excitation of the left canals and anodal inhibition of the right canals as shown in the image above) evokes congruently directed movement sensations for both canal systems.

Schematic image drawn with Microsoft Office © and Microsoft Paint ©

As shown in Figure 12 above, the vestibular sensation evoked by GVS can be explained by vector addition. Studies to refine this basic theory of GVS effects have taken into account the relative length of the semicircular canals with respect to each other and the exact backward tilt of the horizontal canal

plane. Calculations suggested an additional small rotation around the head vertical axis [Ishizaki et al 1991, Hlavacka et al 1993] (head horizontal plane “yaw”). This small component can probably be regarded negligible.

It has been shown that galvanically-induced body sway cannot be opposed voluntarily, but instead only be attenuated, irrespective of whether the galvanic stimuli are unpredictable, predictable or even self-triggered [Guerraz et al 2005].

Binaural bipolar sinusoidal galvanic vestibular stimulation refers to GVS with electrodes placed over the mastoid bones bilaterally. During continuous electric stimulation of the peripheral vestibular systems, one electrode is always opposingly polarized (“bipolar”) to the other.

As shown in Figure 12, bipolar stimulation evokes congruent motion sensations in both sets of semicircular canals. In contrast to unilateral stimulation, bipolar stimulation leaves no un-influenced canals to send contradictory vestibular input: an un-influenced canal system would record the actual body movements in disaccordance with the stimulated canals. Inconsistent vestibular input is generally known to evoke discomfort and nausea more easily than congruent binaural and bipolar stimulation.

Furthermore, galvanic current applied to both vestibular systems simulataneously allows to decrease stimulus amplitude at the individual stimulation site for an identical postural reaction. Stimulation in the dark or with eyes closed further increases effectiveness, because of cancelling out incongruent visual cues [Britton et al 1992, Fitzpatrick et al 1994, Trouillas et al 1997, Latt et al 2003, Guerraz et al 2005, Day et al 2007, Iles et al 2007].

A reduction of proprioceptive sensory input, e.g. sensory polyneuropathy, is also known to increase galvanically induced body sway [Day et al 2007].

In summary, binaural and bipolar GVS is more compatible with a comfortable experimental situation for subjects than unilateral GVS, causing less ambivalent vestibular cues and less skin-irritating and possibly painful stimulation.

It can be applied sinusoidally, with alternating increasing and decreasing stimulus amplitudes at a given frequency. Consecutively, binaural bipolar sinusoidal galvanic vestibular stimulation gives the movement illusion of a constant rolling to the left and right, as if the subject was standing on a rolling boat in the sea (see Figure 13).

Figure 13

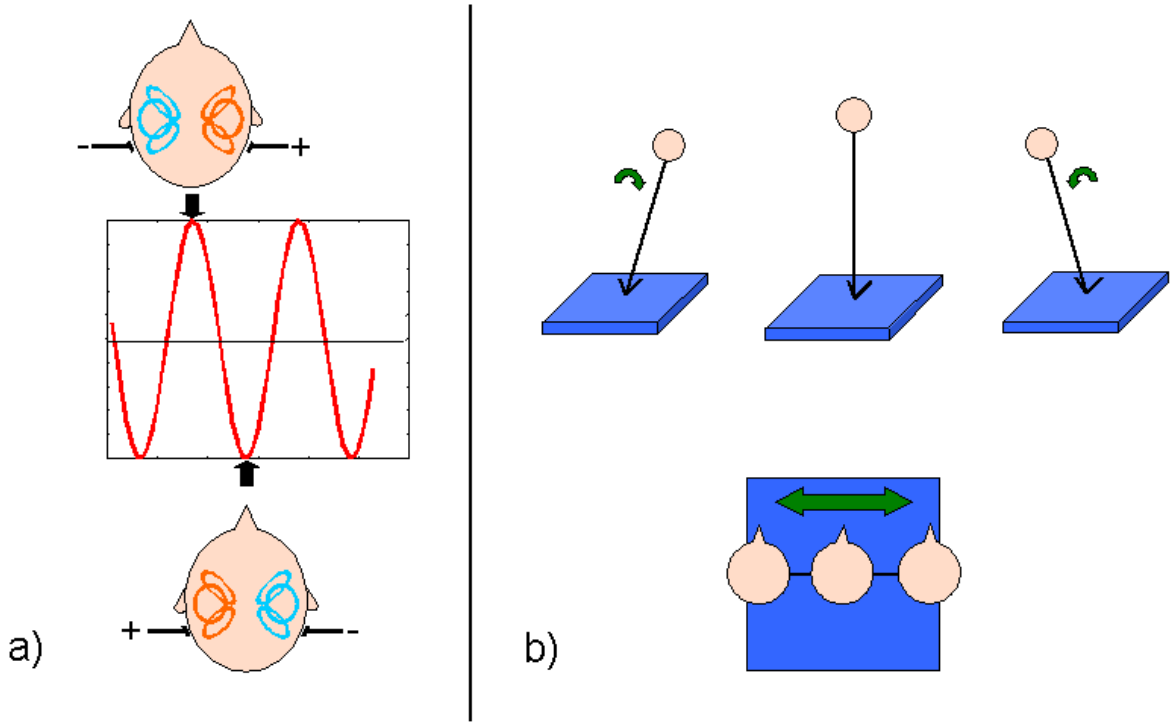


Figure 13:

a) Illustration of binaural bipolar sinusoidal galvanic vestibular stimulation. The sets of semicircular canals on both sides are alternatingly excited and inhibited, as shown by “blue” for excitation and “orange” for inhibition.
b) According to the vector summation theory (compare Figure 12), sinusoidal stimulation evokes alternating “roll” illusions in the head lateral direction. Compensatory postural reactions are opposingly directed, resulting in alternating “rolling” body movements to the side, as if the individual was trying to keep upright on a rolling ship.

Schematic image drawn with Microsoft Office © and Microsoft Paint ©

The postural reactions evoked by binaural bipolar sinusoidal GVS can be understood as a protective manoeuvre against falling, keeping the movement range of the “centre of body mass” projecting down on the ground as “centre of foot pressure” (CoP) well away from the borders of support, i.e. the area on the ground delineated by the feet [Day et al 1997, Hlavacka et al 1999, Latt et al 2003].

The galvanically induced response extends all across the “leaning and bending” body [Day et al 1997, Hlavacka et al 1999]. This body sway can be measured, for example, by the surrogate “centre of foot pressure” (CoP) moving across a static recording platform. During stimulation, this CoP keeps moving towards the side of the anodally stimulated ear [Tokita et al 1989, Britton et al 1992, Hlavacka et al 1993, Cass et al 1996, Day et al 1997, Pavlik et al 1999, Bacsi et al 2003(1), Fitzpatrick et al 1994 and 2004, Cathers et al 2005, Iles et al 2007] at the same frequency as the imposed sinusoidal galvanic stimulus between 0.1 and 0.2 Hz [Coats 1972, Dichgans et al 1976, Pavlik et al 1999, Kleine et al 1999(2), Latt et al 2003, Krafczyk et al 1999 and 2006]. At higher frequencies the postural response finally suspend, whereas oculomotor effects increase [Coats 1972].

In summary, binaural bipolar sinusoidal galvanic vestibular stimulation at a given frequency is a simple but effective method to evoke a standardized vestibular illusion of a “rolling” in space and consecutive “leaning and bending” postural reactions in the standing human. This effect can be explained by semicircular canal vector addition. Otolith organs probably do not contribute significantly.

2.2.3 Galvanic vestibular stimulation and head position

Bipolar sinusoidal GVS evokes a specific vestibular illusion. As stated in the introduction of this work, the relative position of the head against the trunk is essential for the adequate interpretation of vestibular inputs. So how does head position influence postural effects of vestibular stimulation?

The combination of GVS and horizontal head turns has been shown to alter the GVS postural reaction in animals and healthy human subjects: the lateral swaying keeps aligned to the head-frontal plane [Lund et al 1983, Tokita et al 1989, Hlavacka et al 1993, Day et al 1997, Pompeiano et al 1997, Fransson et al 2000, Latt et al 2003, Fitzpatrick et al 2004, Manzoni et al 1998, 1999 and 2004, Cathers et al. 2005] (see Figure 14)

Figure 14

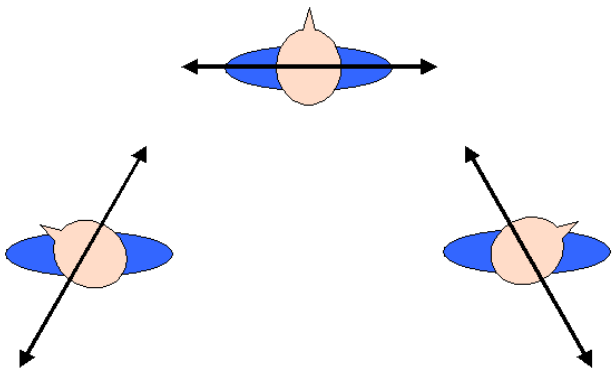


Figure 14:

On-top view of three subjects under binaural, bipolar sinusoidal GVS. Depending on their horizontal head-on-trunk position, i.e. by turning their heads either left or right, the evoked postural “rolling” is always in the head-frontal plane (head-centred reference frame).

Schematic image drawn with Microsoft Office © and Microsoft Paint ©

In this study, patients with cerebellar lesions and healthy controls are exposed to binaural bipolar sinusoidal GVS during simultaneous static head-on-trunk turns.

Will functional deficiency in the presumed cerebellar vestibular-neck interaction sites alter the modulation of galvanically evoked body sway, or will it keep aligned to the head-frontal plane in a centrally re-computed body-centred reference frame?

3 Materials and Methods

Twelve healthy subjects aged 30 to 64 (average 48) and twenty patients with cerebellar impairment (age 30 to 73, average 59) were included in this study. All subjects gave their written informed consent and received financial compensation for their participation effort. The experiment was performed in accordance to the 1975 Helsinki Declaration and was approved by the University's ethics committee.

3.1.1 Inclusion and exclusion criteria for control subjects

Twelve healthy control subjects were recruited from personnel of the Munich University Clinic and their relatives. None had a medical history of any disease related to the central nervous system, the peripheral vestibular system including peripheral neuropathy, by testing for ≥6/8 pallesthesia on both medial ankles with a standard 128Hz Rydell-Seiffer tuning fork. No disabilities or impairments of the motor system were known. No alcoholic beverages, medication affecting the central nervous system or other drugs had been consumed for the past 24 hours before the experiment. Controls were either under their regular medication or under none at all. The authors of this study did not participate as controls.

3.1.2 Inclusion and exclusion criteria for patients

Patients with exclusive cerebellar disease have been recruited from the in-house neurological wards and ambulance from the past 7 years. No non-cerebellar focal neurological deficit was accepted. In all patients, peripheral neuropathy had been clinically excluded, like in control subjects, with a Rydell-Seiffer tuning fork. None of the patients had any orthopaedic disorders, or history of alcohol or drug abuse. There was a variety of cerebellar disorders: idiopathic cerebellar degeneration without other clinical central nervous manifestations (n = 8, cerebellar syndrome for >1 year, cerebellar atrophy in tomographic imaging, no concurrent aetiology by the date of publishing), spinocerebellar ataxia (SCA, n = 3), multi-system atrophy of cerebellar type (MSA-C, n = 2), ischemic or hemorragic cerebellar stroke (n = 5), paraneoplastic vermal atrophy (n = 1) and episodic ataxia type II (EA II) during an atactic episode [Strupp et al 2007] (n = 1). All patient data was pseudonominized for this study, using a random 3-letter code and a number, as can be seen from Table 15.

Table 15

Code		Etiology	Age	Gender (m/f)
Veh01		Stroke	71	m
Jel02		Idiopathic	72	m
Sit03		Stroke	67	m
Ele04		Idiopathic	30	m
Mah05		Stroke	73	m
Lel06		SCA	50	m
Ach07		Idiopathic	69	m
Cah08		SCA	57	f
Azi09		Idiopathic	63	f
Ala10		MSA-C	68	f
Lau11		Idiopathic	40	m
Hah12		Stroke	44	f
Iez13		MSA-C	59	f
Meb14		Stroke	68	f
Har15		Idiopathic	57	f
Hak16		Paraneo	49	f
Lav17		Idiopathic	44	f
Cal18		SCA	68	m
Leu19		EA II	57	m
Pah20		Idiopathic	70	f

Table 15:
Summary of the patients included in this study. Etiology of cerebellar disease: Stroke = ischemic or hemorrhagic insult, Idiopathic = idiopathic cerebellar atrophy, not attributable to a specific type disease by the date of publishing, SCA = spino-cerebellar atrophy, Paraneo = paraneoplastic cerebellar atrophy, EA II = episodic ataxia type II; m / male, f / female
Data sheet created with Microsoft Excel®

3.2 Clinical assessment

All patients included in this study were specifically examined to record the degree of cerebellar deficiency for later correlation with experimental results. Their proprioceptive [Day et al 2007] and their peripheral vestibular system [Halmagyi 2003 and 2005] were tested to detect possible exclusion criteria.

The level of impairment was assessed by experienced clinicians using the cerebellar score according to Klockgether and colleagues [Klockgether et al 1990, Masur et al 2003]: seven cerebellum-specific signs of impairment are evaluated using standard clinical examination techniques: gait ataxia, stance ataxia, dysmetria and decomposition of movements in upper limb as well as lower limb, dysdiadochokinesis, intention tremor and dysarthria [Diener et al 1992]. Depending on the degree of impairment, zero (normal) to five points (worst performance) is given (see Figure 16). The individual levels of cerebellar impairment are clearly delineated and allow little or no inter-rater variability [Masur et al 2003]. Beyond the original Klockgether scoring, gaze-evoked nystagmus, saccadic pursuit and the vestibule-ocular reflex (VOR) along with visual VOR suppression were recorded. The clinical assessment sheet is illustrated in Figure 16.

Additionally, a specific clinical trial for vestibular-neck interaction was performed:
Patients and control subjects had to assume an active head turn horizontally as far as possible to one side (approximately 60-70°). They were asked to stand upright and then walk a straight line. This trial was tested with open and closed eyes and for either side subsequently in comparison to trials with neutral head position. Increases of gait and stance instability in the head-turned condition versus neutral head position were recorded independently by subject and clinical observer. If a side difference was present, the worst performance was used for evaluation and the direction of lateralization was noted.

Testing of the peripheral vestibular system was achieved using the Halmagyi head impulse test for the vestibulo-ocular reflex (VOR) [Aw et al 1996 (1) and (2), Cremer et al 1998, Halmagyi 2003 and 2005].

Figure 16

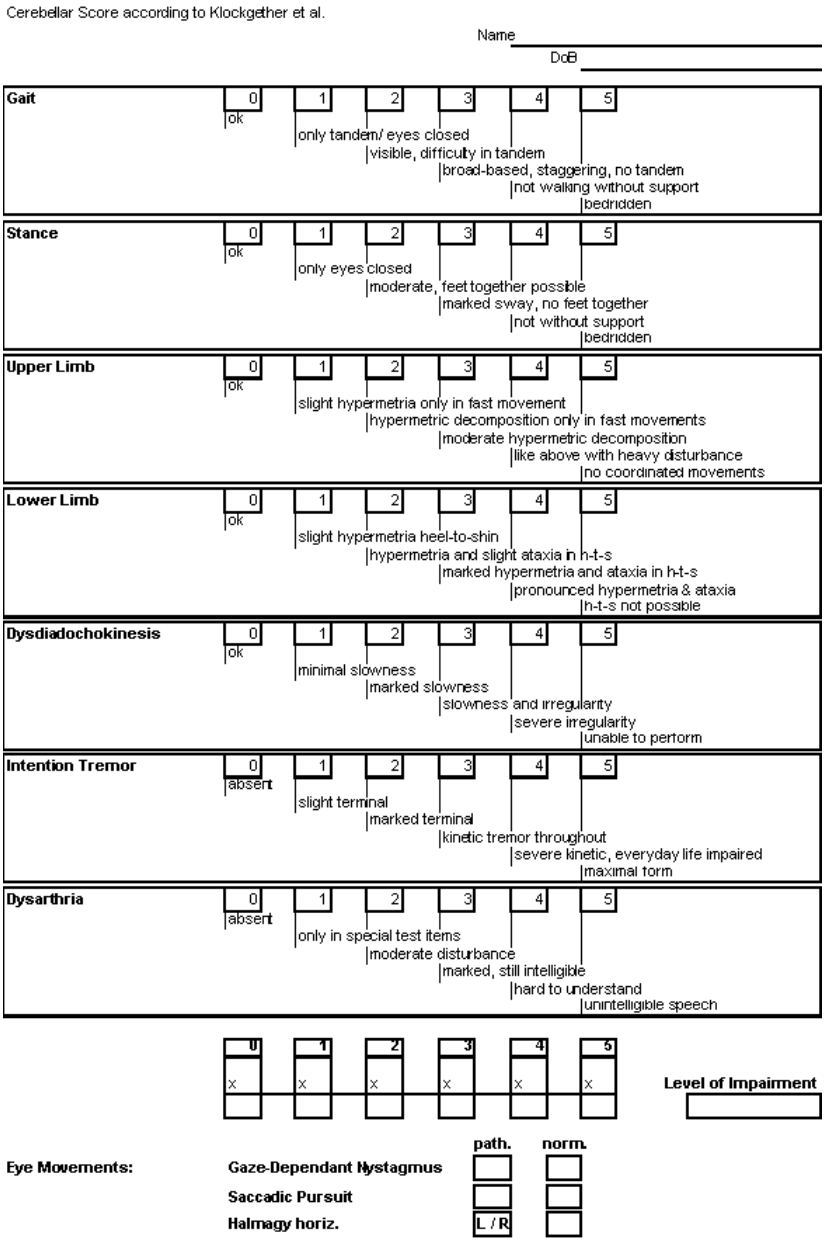


Figure 16:

Cerebellar score according to Klockgether and colleagues, as used in this study. Gaze-evoked nystagmus, saccadic pursuit and head-impulse test of Halmagyi are not part of the original Klockgether score, but were recorded separately.

Table created with Microsoft Excel®

Intact neck proprioception was tested as follows:

Patients were asked to actively reproduce passive head excursions in the horizontal plane. Patients were asked to close their eyes. Then their heads were passively turned to one of the horizontal head positions later used in the experiment: 30°, 45° and 60° in a random order. Patients were told to remember this position and then the head was guided back to the 0° position. The position had to be

reproduced actively on a verbal signal given. No deviations larger than 5° from the indicated position were found in any patient, thus assuming their neck proprioception intact.

Computer tomography or magnetic resonance imaging had been performed before recruitment to exclude extra-cerebellar lesions. Because most patients recruited for this subject were affected by degenerative cerebellar disorders (14 of 20), in which a precise delineation of involved cerebellar structures would have been questionable, high-resolution MRT imaging for 3D-volumetry was not deemed useful, and thus omitted.

3.3 Experimental setup

3.3.1 Force transducer platform

Subjects were asked to stand on a force platform (Type 9281A Mehrkomponenten Messplattform mit Ladungsausgang, Kistler Instrumente AG, Winterthur, Switzerland) in an erect, but relaxed position [Guerraz et al 2005], with their arms hanging down loosely by their sides. Data from the Piezo force transducers in the platform were transmitted to a personal computer (Pentium IV 2,80 GHz 512 MB Ram, featuring Windows XP Professional 2002, Service Pack SP 2) by an amplifier unit (Type 9261A 8-Channel Electronic Unit, Kistler Instrumente AG, Winterthur, Switzerland). This platform can record the centre of foot pressure (CoP) in antero-posterior ("y") and in lateral direction ("x"), as well as the weight of the person standing on top (measured as force, "z") at a sampling rate of 40Hz [Krafczyk et al 1999 and 2006].
The weight was checked to agree with the subject's body mass. If differences exceeding 5 kilograms were obtained from the platform, the subject had to step off and the platform was recalibrated. For data evaluation only axes "x" and "y" were used (for illustration see Figure 17, page 47).

To ensure a relatively small base of support, granting for enhanced body sway, the subject's feet were positioned heels together and the tips turned apart 30° [Fransson et al 2003, Krafczyk et al 1999 and 2006].

Custom-programmed recording software, written in MatLab (MatLab 7, The Math Works Inc., Natick, Massachusetts, U.S.A.) was used for on-line data analysis and recording [Krafczyk et al. 1999 and 2006].

3.3.2 Head restraining and posture

Subjects wore a head restraint device, based on a trekking backpack with massive metal framework [Kammermeier et al 2009] (Classic Air 25, Deuter Sport & Leder GmbH, Gersthofen, Germany), featuring a horizontal wooden ring, adjusted around the neck just below the atlanto-occipital plane. Angles from zero to ninety degrees from the head straight ahead position (0°) were inscribed on the "halo" (Figure 17). The backpack was firmly attached to the subject's chest and the axial bolts of the backpack frame aligned over the median spinal axis. The horizontal ring could be individually adjusted to subject physiognomy to centre on the atlanto-occipital axis with the "0°"-mark pointing straight ahead.

An individual mould of the subject's teeth was formed, using a single-use dental mould kit (TripleTray Anterior, Premier, Plymouth Meeting, Pennsylvania, U.S.A. and Provil novo Monophase c.d. fast set Vinyl Polysiloxane, Heraeus Kulzer GmbH, Dormagen, Germany). It was attached to the ring by a multidirectionally adjustable interface constructed from plastic by a computerized numerical control (CNC) milling machine.

The dental mould with its attachment to the horizontal ring was designed not to allow for unwanted movement of the head against the trunk in the horizontal plane. In the vertical plane, the flexibility of the dental mould handle required certain active muscular head holding, unlike the passive head restrainer used by Fransson and colleagues [Fransson et al 2000, Kammermeier et al 2009]. Here, no resting of the chin in the restraining device with relaxed neck muscles was possible.

It has been suggested that active head holding, as required in our setup, might allow for better neck proprioception than passive resting of the head in a specific position, possibly due to higher activity in neck muscle spindles. This assumption will be detailed in the discussion chapter of this work.

Figure 17

Figure 17:

The experimental setup of this study requires the subject to stand on the Kistler-type piezo platform as indicated in the two images on the left: toes spread 30° and heels together within a pattern drawn on the platform.
A custom-built head restraining device is attached to the chest with a horizontal ring encircling the neck in the atlanto-occipital plane (left and bottom right). The head is fixed against the restraining ring using a dental mold (bottom right) and a multi-directionally adjustable interface (top right).

Images taken during a mock setup, using a Sony DSC500 digital camera.

During the whole experiment, an assistant was positioned behind the subject to prevent possible falling. Subjects were asked to stand upright, relaxed and comfortably on the platform, adjusting their balance as they felt to [Guerraz et al 2005]. This advice was given to prevent subjects from fighting the galvanically imposed sensation with high-frequency corrective posture adjustments [Ishizaki et al 1991, Fitzpatrick et al 2004, Guerraz et al 2005], which would have superimposed the galvanically-evoked postural reactions. They were asked not to perform voluntary movements of head, arms or legs [Ishizaki et al 1991, Krafczyk et al 1999 and 2006].

3.3.3 Galvanic stimulation

Bipolar, binaural sinusoidal galvanic vestibular stimulation was applied by a custom-built current generator [Kleine et al. 1999(2)], allowing to transform voltage input from an external waveform generator (hp 33120A 15MHz Function / Arbitrary Waveform Generator, Hewlett-Packard Corporation, Palo Alto, California, U.S.A.) into a galvanically isolated, current-controlled stimulus over a wide range of conductancies; the frequency of stimulation was set to 0.16 Hz across all experiments performed.
As illustrated in the introduction to galvanic vestibular stimulation and its postural effects (Chapter 2.2), galvanic stimulus frequency and the frequency of the evoked body sway were effectively identical.

The galvanically evoked sinusoidal body sway, evoked by GVS of the same frequency, had to correspond optimally to the platform recording characteristics. The force transducer platform recorded at a sampling frequency of 40 Hz. The period length of 40 Hz is 0.025 s. According to Coats [Coats 1972], the ideal stimulation frequencies for postural effects can be found between 0.1 and 0.2 Hz. 256 data points per expected body sway sinusoid were chosen. At a resolution of 256 data points, the optimal period length is 256 • 0.025 s = 6.4s. The corresponding frequency to this period length is 0.16 Hz. Other optimal distributions of data points would have moved the stimulation frequency out of the range of the optimal postural response range tested by Coats. In the pre-testing phase of this study, this stimulation frequency was found to evoke subjectively well-tolerable body sway of high amplitude among the authors of this study.

The stimulator was connected to the mastoid bones behind both ears with child-sized ECG-electrodes (Skintact ECG-Electrodes F 40, Leonhard Lang GmbH, Innsbruck, Austria; see Figure 17) after skin preparation with a mild detergent and abrasive gel for better adhesion and conductivity.

In a first trial without galvanic stimulation, the subject was asked to stand on the platform, wearing the entire experimental gear. Thirty seconds of neutral body sway were recorded.

Subsequent to this pre-testing, the individual GVS amplitude for optimal body sway within safe limits was determined. Subjects were asked to stand upright and relaxed in the position specified in Figure 17. With eyes closed, GVS was gradually increased up to 4mA. The applied amplitude was controlled

using an oscilloscope (TDS 220 Two-Channel Digital Real-Time Oscilloscope, Tektronix, Beaverton, Oregon, U.S.A.).

As detailed in chapters 2.2.1 and 2.2.2, rising stimulus amplitude resulted in increasingly visible sinusoidal body sway in the head frontal plane. Individual stimulus amplitude was chosen to evoke a good amount of body sway without reaching the dangerous borders of foot support.

Latt and colleagues proposed a possible saturation effect of sinusoidal galvanic vestibular stimulation in close vicinity of the stability margin [Latt et al 2003]. To avoid such possible nonlinearity and to avoid falling, the stimulus intensity was set to evoke body sway well within safe limits.

Across all trials, stimulation amplitudes were well tolerated by all subjects due to the relatively large area of conductance and good skin preparation. Regularly, minor “prickling” on the stimulation site was perceived, due to cutaneous nerve stimulation, but no painful cutaneous sensations were reported. Occasionally a metallic taste on the tongue was reported, probably due to co-stimulation of the facial nerve [Johansson et al 1995]. When co-stimulation or discomforting cutaneous sensations were experienced, the electrodes were re-checked for positioning or the skin preparation was repeated.

Individual stimulus amplitudes ranged from 1 to 4 mA with a median of 2 mA in both control and patient groups. Because of well-known large inter-individual variability, this individual approach to the ideal individual stimulus ampitude had to be performed [Coats 1972, Fransson et al 2000, Fitzpatrick et al 2004, Cathers et al 2005, Iles et al 2007].

After determining the optimal stimulus intensity, the dental mould was inserted and attached to the horizontal ring. In seven subsequent trials, each lasting 30 seconds, the subject’s body sway was recorded during exposure to bipolar binaural sinusoidal GVS at 0.16 Hz and the previously determined stimulus amplitude. Patients had to close their eyes and a pair of blackened swimming goggles was put on (as seen in Figure 17). The visual indicator of the backpack dorsal axis helped the experimentator with manually aligning the spinal axis, legs and feet to the “y” axis of the piezo platform with a probable error of less than 5 degrees [Lund et al 1983, Hlavacka et al 1993]. The alignment of the feet was controlled by checking whether the backpack longitudinal axis formed a line running in between the subject’s heels. An involuntary turning away from the adjusted body axis was consequently controlled by the assistant standing behind the subject.

The observation that the main body sway effect was found one to three seconds after stimulus onset was considered in the experimental procedure: after the onset of GVS, 5 seconds were given to establish a steady state of body sway. Then the examiner manually started the recording of the force platform [Fitzpatrick et al 1994, Fransson et al 2000 and 2003, Latt et al 2003].

In between the trials, the galvanic stimulus was turned off and the subject was allowed to hold on to the gangway surrounding the platform for at least 30 seconds, in order to avoid a possible habituation to the stimulus on the timescale of several minutes [Gurfinkel et al 1989, Hlavacka et al 1993].

The initial trial was always at 0° horizontal head position, the following trials were 30°, 45° and 60°, both left and right, in a computer-determined random order, to avoid systematic errors.

The entire procedure lasted approximately 30 to 45 minutes per subject, with a total of 3 to 4 minutes of actual galvanic stimulation.

3.4 Data analysis and statistics

The data sets acquired in the experiments were stored on a personal computer hard disk for later off-line analysis. For every subject, seven 30-second files including lateral (“x”) and antero-posterior (“y”) centre of foot pressure (CoP) were available, one for the “head 0°” paradigm and the others for 30, 45 and 60 degrees both left and right. Each file featured centre of foot pressure position signals in two axes at 40 Hz recording rate for 30 seconds (1200 data points for each axis). A representative data set of one control in the head straight paradigm is shown in Figure 18.

For on-line visualisation of postural responses, a custom program imbedded into the recording software was used. An individual recording trial was represented in a graph over 30 seconds with the CoP moving in “x” and “y” directions. Body sway excursions away from the resting centre were summed in 24 bins over 30 seconds, each representing a 15° slice of the total 360°. Movement amplitudes were coded for by vector length (see Figure 18). An “envelope” line around the 24 vector tips originating from the coordinate centre was marked with a blue encircling line and displayed on-

screen, as a surrogate for overall body sway effort. The coordinate centre was obtained by averaging "x" and "y" position signals. This display method was not used for further data analysis; it only served to visualize body sway performance [Krafczyk et al 1999 and 2006].

Figure 18

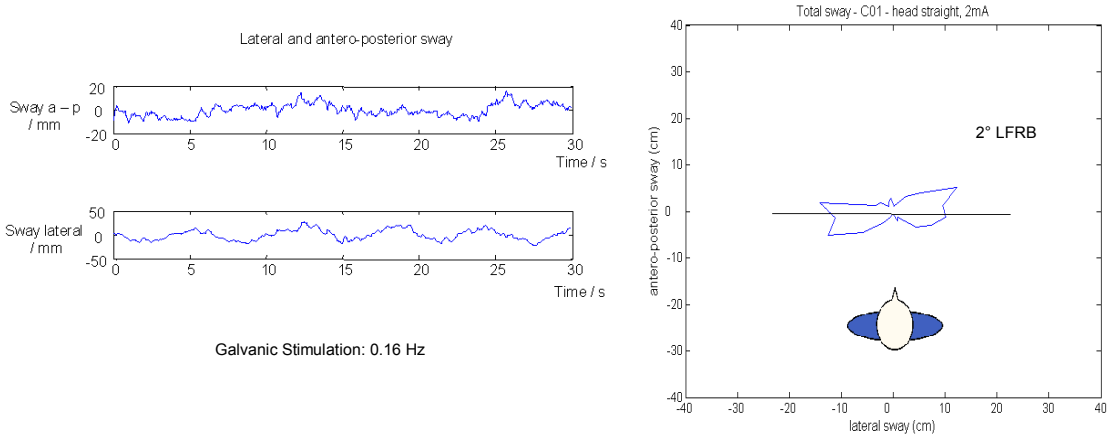


Figure 18:
The left figure shows raw data from control C09 in the head straight paradigm. The centre of foot pressure course is shown over 30 seconds in the "y" antero-posterior (top; positive values represent anterior movements) and lateral "x" axes (bottom, positive values represent leftward movements) The bottom graph shows slow sinusoidal movement (0.16 Hz) in the lateral direction, corresponding to GVS-evoked lateral sway at 0.16 Hz. Antero-posterior sway shows no clear sinusoid.
Right figure: Visualisations of the overall body sway of C09. CoP excursions are summed in 24 direction bins across 360°, with 15° in each bin. The blue line marks the "envelope" around all 24 sum vector tips.

Figures created with MatLab©

To analyze the direction of the galvanically-evoked sway component, amplitude and phase of the body sway components in the "x" and "y" directions were computed for the 0.16 Hz stimulus. These two sinusoids unambiguously defined the shape, direction and clockwise or counter-clockwise orientation of an ellipse in the piezo platform plane. The direction of the body sway corresponded to the longitudinal axis of this ellipse.

The angles of sway directions were related to a Cartesian coordinate system originating at the centre of the platform plane (0° right, 180° left and 90° forward for unidirectional movements). The centre of the Cartesian coordinate system was re-defined for every trial by the average of the 1200 CoP data points in x and y coordinates. This measure was required to eliminate possible body offsets after the head-on-trunk re-alignment for the next trial.

Alternating sway movements were called either "right-forward-left-backward" (positive RFLB for alternating sway between the 0-90° and 180-270° quadrants; in the following given as angles between 0° (horizontal) to +90°) and "left-forward-right-backward" (negative LFRB for alternating movements

between the 90°-180° and 270°-360° quadrants; given as angles between 0° (horizontal) to -90°). Sinusoidal body sway at 0° is termed “lateral” and sway at 90° “antero-posterior” (see Figure 19).

This definition of sway directions (LFRB – RFLB) is not to be mistaken for the commonly used definitions of “left anterior-right posterior” (LARP) and “right-anterior-left posterior” (RALP) planes for the vertical semicircular canals relative to the head.

This ellipse-based computation procedure was repeated for all seven trials of an individual and for all subjects included in this study.

In the given data example in Figure 18, the computed longitudinal axis of the ellipse is -2° “left forward right backward” (LFRB), which means alternating laterally-directed body sway.

Figure 19

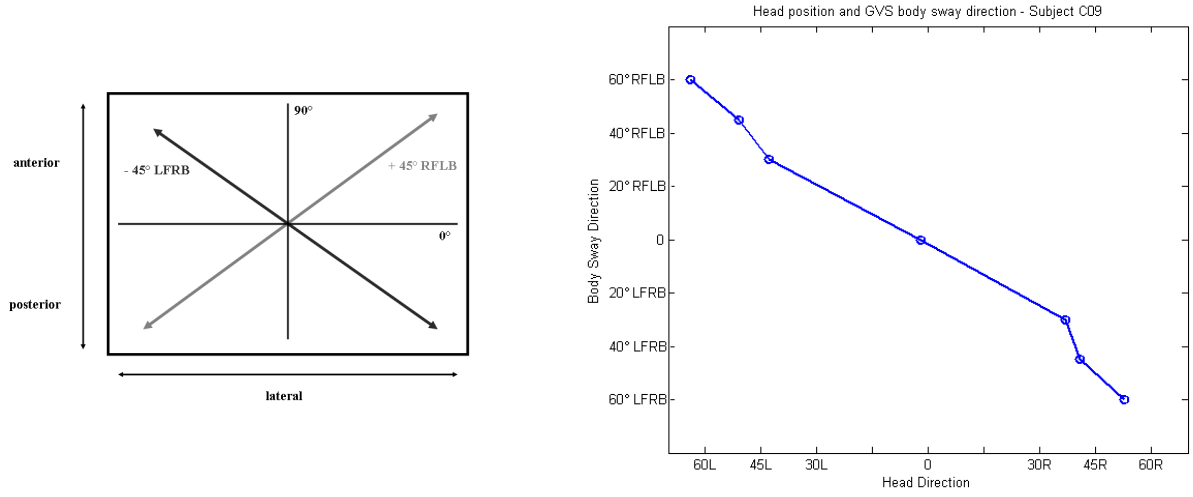


Figure 19:

The left schematic image displays the definition of “body sway direction” as used in this study. On-top view of the piezo platform. The longitudinal axis inclination of the body sway ellipse is described relative to a two-dimensional Cartesian coordinate system in the piezo platform plane. The inclination angle is given in absolute numbers <90°, non-ambiguously describing body sway direction in the physiological context: “RFLB” describes a subject’s postural reaction directed alternatingly right forward and left backward, whereas “LFRB” describes the mirror image situation. LFRB angles are deliberately defined as negative, RFLB angles are defined positive.
The “centre” of the coordinate system was re-defined for every trial, by averaging all positional “x” and “y” coordinates of one individual trial. This measure eliminated possible changes in stance after an individual trial.

In the right figure the body sway directions of the control subject (as already seen in Figure 18) across all 7 trials is shown: head direction (abscissa) is centred on 0° head pointing straight ahead, with 30, 45 and 60 degrees both left (L) and right (R). According to the definition of directions used, the ordinate gives the computed body sway direction in RFLB (right forward – left backward) and LFRB (left forward – right backward). This basic pattern is used throughout this study to illustrate the directions of galvanically induced body sway.

Left figure: drawn with Microsoft Office©, Right figure: data taken from the original data sets, figures created with MatLab©

Experimental data of controls and patients was compiled with age, sex, stimulus amplitude, disease aetiology and the outcome of patients' clinical assessment for further analysis with MatLab and Statistica software (STATISTICA 5.1, StatSoft Inc., Tulsa, Oklahoma, U.S.A.) and Microsoft Excel (Microsoft Office, Microsoft Corporation, Redmond, Washington, U.S.A.). Graphic illustration was programmed in MatLab and Microsoft Office.

Statistical methods included the "multivariate approach to repeated measures analysis of variation", Welch's t-test and the Wilcoxon rank sum test. Data sphericity for multivariate analysis was investigated with Mauchley's test; Gaussian Normal Distribution was tested for with the Kolmogornov-Smirnov-test.

The independent variables in this study were patient or control group affiliation, age, sex, disease aetiology and clinical cerebellar impairment (Klockgether score with its sub-scales). Galvanically-evoked body sway directions recorded in 7 different head on trunk positions for each subject formed 7 dependent variables, which could assume any number between –90° LFRB and +90° RFLB. The dependent variables were submitted to multivariate analysis of variation with one between-subjects factor with two (control/patient affiliation) or more (age, sex, Klockgether score, etc.) levels and one repeated within-subjects factor with 7 levels (head-on-trunk position). The null hypothesis was no statistical interaction between independent variables with expewrimental sway direction results, i.e. sway directions were irrespective of control/patient group affiliation, age, sex, etc. The p value describes the probability of erroneous rejection of the null hypothesis (statistical α error).

4 Results

All data obtained from control subjects and patients was included for data analysis. We successively describe the results of clinical examination, postural reactions without galvanic stimulation, changes in postural control with galvanic vestibular stimulation and horizontal head turns. Different sub-groups of patients are identified and analyzed statistically in comparison to control subjects.

4.1 Clinical examination

The Klockgether cerebellar score was used to assess the overall amount of cerebellar impairment in our patient group. Clinical cerebellar impairment ranged from mild (4 points) to severe (17 of 35) with a median of 10 points (n = 20).

Gait and stance ataxia (anterior lobe vermis syndrome) and other cerebellar symptoms were rated in patients. The vestibulo-ocular reflex was tested with the Halmagyi head impulse test in all patients. No patient had any signs of peripheral vestibular dysfunction. Two patients had additionally been tested with caloric irrigation during their hospital stay. Saccadic pursuit and VOR suppression deficits were common in cerebellar patients. No expressed gaze-dependant nystagmus was found.

Table 20 (continued on next page)

Code		Etiology	Age	Gender		**Klockgether**	Gait	Stance	Arm	Leg	Dia	Tremor	Dysarthria
Veh01		Stroke	71	m		**8**	3	2	2	1	0	0	0
Jel02		Idiopathic	72	m		**11**	3	2	2	0	2	0	2
Sit03		Stroke	67	m		**7**	2	2	2	0	0	1	0
Ele04		Idiopathic	30	m		**9**	3	3	2	0	0	0	1
Mah05		Stroke	73	m		**4**	3	1	0	0	0	0	0
Lel06		SCA	50	m		**13**	3	3	1	1	2	1	2
Ach07		Idiopathic	69	m		**4**	0	0	2	0	2	0	0
Cah08		SCA	57	f		**11**	2	1	1	1	3	1	2
Azi09		Idiopathic	63	f		**13**	2	2	1	1	2	2	3
Ala10		MSA-C	68	f		**13**	4	3	0	0	2	2	2
Lau11		Idiopathic	40	m		**17**	2	2	3	3	3	1	3
Hah12		Stroke	44	f		**6**	3	3	0	0	0	0	0
Iez13		MSA-C	59	f		**17**	4	3	1	2	2	2	3
Meb14		Stroke	68	f		**13**	2	2	3	2	4	0	0
Har15		Idiopathic	57	f		**4**	1	0	1	1	0	0	1

Hak16	Paraneo	49	f		**11**	3	3	2	2	1	0	0
Lav17	Idiopathic	44	f		**13**	2	2	2	2	2	1	2
Cal18	SCA	68	m		**7**	2	1	1	1	0	1	1
Leu19	EA II	57	m		**8**	2	2	2	1	1	0	0
Pah20	Idiopathic	70	f		**8**	3	1	2	2	0	0	0

Table 20:

All 20 patients (compare Table 15) with the total Klockgether score ranging from 0 to 35 points. Each sub-scale has 0 to 5 points (see Figure 16): Gait and stance ataxia, upper limb ("Arm") and lower limb ("Leg") ataxia, dysdiadochokinesis ("Dia"), intention tremor ("Tremor") and dysarthria. Etiology of cerebellar disease is shown as compared to Table 15: Stroke = ischemic or hemorrhagic insult, Idiopathic = idiopathic cerebellar atrophy, not attributable to a specific type disease by the date of publishing, SCA = spino-cerebellar atrophy, Paraneo = paraneoplastic cerebellar atrophy, EA II = episodic ataxia type II; m / male, f / female

Table created with Microsoft Excel©.

In our experiment, we had both patients and controls stand and walk with additional lateral head turns in extreme positions at both sides. This test was to assess the performance of vestibular-neck interaction on a clinical level, as has been described in Chapter 3.2.

All controls could manage to stand and walk with their eyes closed without difficulty. Additional extreme lateral head turns did not prove to result in increased postural instability.

Patients with Klockgether scoring below 8 points had some difficulty with walking and standing, according to their degree of cerebellar deficiency. These mildly affected patients however had no increased postural instability in any extreme lateral head position.

Patients with cerebellar deficits rated above 8 Klockgether points showed considerable additional gait and stance ataxia, when they turned their heads to either side for standing upright or walking with their eyes closed. This effect added to their individual gait and stance ataxia present in "head-neutral" standing and walking, without a lateral head turn. Several patients, who could walk with eyes closed and their heads straight, were no longer able to do so, when an additional lateral head turn was imposed. The relation of the clinical trial to GVS sway performance is described in Chapter 4.3.3 for the different patient sub-groups.

4.2 Body sway without galvanic vestibular stimulation

Prior to the galvanic vestibular stimulation trials, body sway was recorded in controls and patients without galvanic vestibular stimulation in a head straight paradigm.

Cerebellar patients exhibited considerably increased total sway path, i.e. the total distance covered in 30 seconds and an increased root-mean-square-path, a surrogate for the muscular effort used to cover the corresponding sway distance [Krafczyk et al 1999 and 2006]. With known high variance in the patient group for both variables, there was highly significant difference between controls and patients in total sway path ($p < 0.001$) and sway effort ($p< 0.001$), tested for with the Wilcoxon rank sum test for unpaired samples.

Comparison between controls and cerebellar patients from the database established by Krafczyk and colleagues [Krafczyk et al 1999 and 2006] revealed that controls and patients in our study populations performed no different from their counterparts in the database during the head straight paradigm.

4.3 Body sway under galvanic vestibular stimulation

At first, we show one patient and one control in comparison, in order to illustrate basic effects and differences in body sway found among patients and controls, followed by statistical analysis of both subject groups. Finally, the different qualities of postural compensation mechanisms and correlation with clinical vestibular-ointeraction among patient sub-populations are described in detail.

4.3.1 Individual effects

Figure 21 depicts the centre of foot pressure movements in one selected control (C01).

In accordance with functional considerations (see Chapter 2.2) and previous experiments [Fransson et al 2000], the direction of body sway turned in alignment with the head frontal plane across all 7 head-on-trunk positions. Two representative head-on-trunk positions are shown here: = “0°” (head straight ahead) and “60° right”.

Figure 21

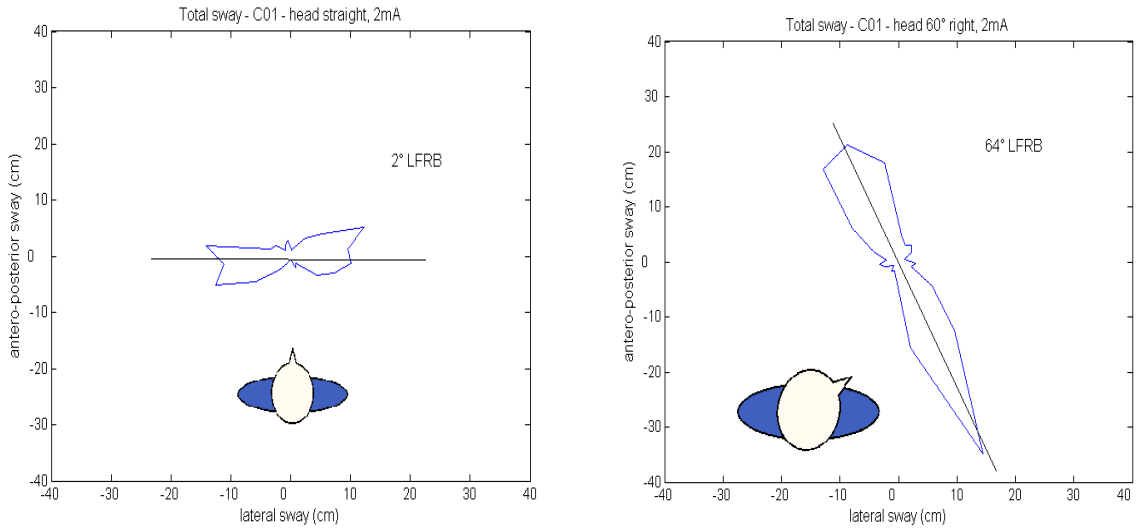


Figure 21:

The diagrams show the centre of foot pressure movements away from the average centre of movement over 30 seconds in all directions, by the "envelope" visualisation described in chapter 3.4. The body sway direction calculated with the elliptic approximation method is given separately.
Galvanic stimulation evoked lateral body sway in the head straight condition (left). With the 60° head right turn, body sway direction kept aligned with the head-frontal plane, as expected functionally (compare Chapter 2.2.3).

Figures created with MatLab© and Microsoft Office for the pictograms.

In comparison to the control subject in Figure 21, Figure 22 shows galvanically evoked body sway in patient "Lau11" under identical experimental conditions: head straight (0°) and 60° right. The direction of galvanically induced body sway does not turn in alignment with head position in between the two conditions. "Lau11" is a 40-year old male suffering from idiopathic cerebellar degeneration with pronounced clinical impairment (17 of 35 points in Klockgether score) with moderate gait- (2 of 5 points) and stance ataxia (2 of 5 points).

Considering the total amount of body sway excursions, this patient shows more body sway than the control shown above, as it could generally be found in our controls and patients, in full accordance with previous results [Krafczyk et al 1999 and 2006]. In both subjects, the relative amount of body sway at 0° is lower than in the extreme head-on-trunk position at 60°.

Figure 22

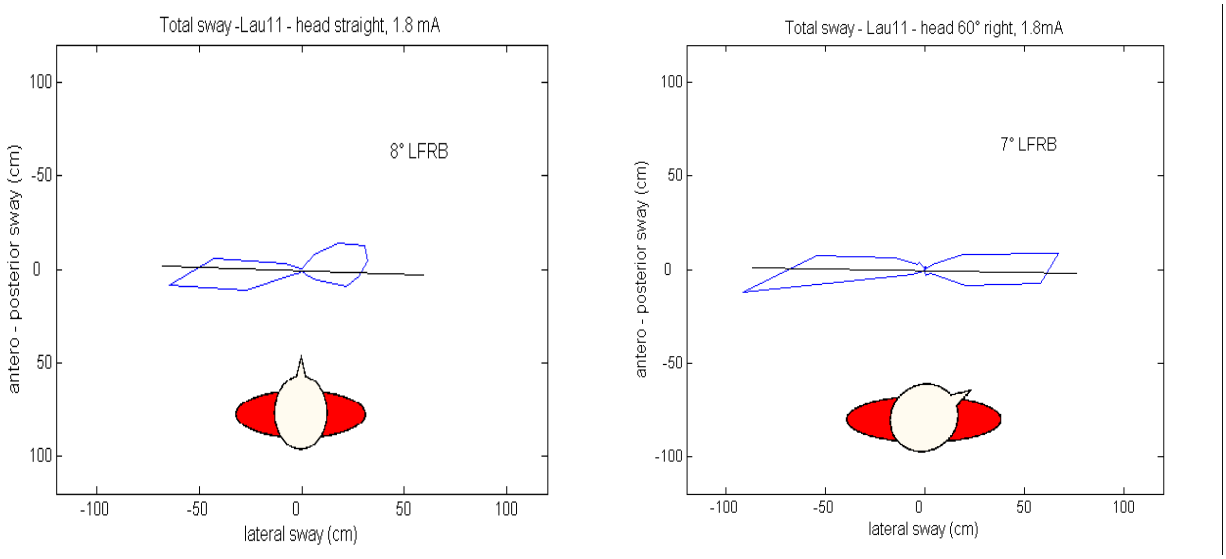


Figure 22:

In analogy to Figure 21, these diagrams show the envelope around the sway direction sum vectors for patient Lau11 (40yo, idiopathic degeneration, 17 Klockgether points). Body sway direction does not alter in accordance with head-on-trunk position. Note that the amount of body sway at 0° in Lau11 is greater than in control C01 at 60° (Figure 21).

Figures created with MatLab© and Microsoft Office for the pictograms.

This lack of sufficient turning of the body sway direction could be found in all 7 trials for this patient (Lau11, Figure 23, next page). The direction of galvanically evoked body sway remained at an angle comparable to the angle found at a neutral, straight head-on-trunk position.

Turning of the body sway direction in-tune with horizontal head-on-trunk position was generally attributed to intact coordination of vestibular and neck-proprioceptive sensory signals, as proposed in Chapters 1, 2.1.3 and 2.2.3. This patient apparently could not change his galvanically induced body sway direction in-tune with head-on-trunk position, suggesting an alteration in the central vestibular-neck interaction mechanisms [Kammermeier et al 2009].

Figures 21 and 22 have illustrated body sway for only two of 7 head-on-trunk positions. Figure 23 depicts all seven directions of GVS-evoked sway, for both selected subjects “C01” and “Lau11”.

Figure 23

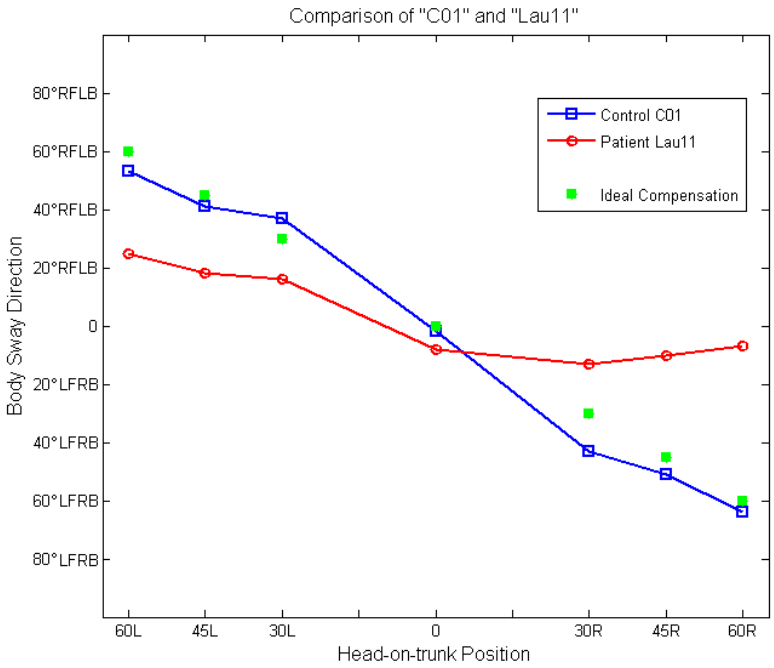


Figure 23:

Body sway direction in all 7 head-on-trunk positions is shown for control subject C01 and patient Lau11. Ideal compensation, i.e. body sway aligned exactly in the head frontal plane for each head position, is marked with a green square for the respective head-on-trunk position, e.g. - 60° LFRB sway in the “head 60° right” paradigm. Fully compensatory sway directions across all head on trunk positions are all on a line with an inclination of -1 (y = -x).
In C01, body sway direction turns along with head-on-trunk position close to “ideal compensation”. Patient Lau11, in comparison, cannot compensate for head lateral excursions as well as the control subject.

Figures created with MatLab©

In contrast to control “C01”, patient “Lau11” cannot compensate for head-on-trunk position adequately: “C01” exhibits body sway in alignment with the head frontal plane, close to the ideal “full compensation” line. In the “head straight” and “60° right” conditions, “Lau11” showed no compensation during rightward turns and very little compensation (up to 25° instead of 60°) during head turns to the left. This patient’s general cerebellar impairment had no clinically preferred lateralization.

In summary, there are major differences in body sway compensation for the imposed head-on-trunk position for the one control subject and the patient [Kammermeier et al 2009]. The patient cannot compensate for head-on-trunk position, whereas the control subject is able to keep body sway direction aligned to the head frontal plane.

4.3.2 Group analysis

In the following, patients and control subjects are compared statistically, based on their clinical and experimental characteristics. Analysis also revealed a number of sub-groups among the patients: Patients with Klockgether scores of 8 points and lower were not found to differ from control subjects in their GVS-evoked sway directions. Patients with 8 points and higher were clearly distinct from controls with respect to their postural reactions.

In the following section, three sub-groups of patients will be discussed in detail, with respect to a linear fit to their sway directions across all 7 head-on-trunk positions ("slope", see below) in comparison to control subjects:

I) Patients scoring <8 points; no difference from control subjects

II) Patients scoring ≥ 8 points, body sway "slopes" within 95% confidence intervals of controls

III) Patients scoring ≥ 8 points, body sway "slopes" outside confidence intervals of controls

4.3.2.1 Group effects in multivariate analysis

Head position had decisive influence on the direction of galvanically evoked body sway in the 12 control subjects and all 20 patients, i.e. head-on-trunk position could generally influence the direction of GVS-evoked body sway (each $p < 0.001$; multivariate analysis of sway directions versus head-on-trunk positions, tested individually for both groups).

For statistical group analysis of sway directions in-between controls and patients, the repeated within-subjects factor (GVS-evoked sway directions across all 7 head-on-trunk positions) was related to the within-subjects factor "group affiliation". This required information about data distribution: GVS-evoked sway directions showed statistically spherical distribution in controls, but not among patients (violated Mauchley's Sphericity Test). Consecutively, the appropriate statistical means was the "multivariate approach to repeated measures analysis of variation" (compare Chapter 3.4).

Patients with a Klockgether rating of 8 points and higher (n= 14) showed expressed and highly significant differences in sway direction (n = 14), compared to those found in control subjects and the ideal full compensation to head-on-trunk position (each $p < 0.001$).

Patients with Klockgether rating of less than 8 points (n = 6) exhibited sway direction alignment to the head frontal plane no different from control subjects and the ideal "full compensation" (each $p >> 0.05$, compare Figure 23). In this study a clinical cut-off value at 8 Klockgether points was therefore introduced, distinguishing between patients with clearly abnormal sway directions and clinically mildly affected patients with normal postural during simultaneous GVS and horizontal head excursions.
In the following, only patients with scores ≥ 8 points will be considered for statistical group analysis.

Controls could modulate their GVS-evoked body sway directions in a narrow band around full head-on-trunk angle compensation. The body sway median of the whole control group was at the ideal compensation to head-on-trunk position with an inclination of -1 ($y = -x$, see Figure 24) with no statistical difference from the ideal 7 sway directions ($p >> 0.05$).

Figure 24 illustrates the median body sway directions across all 7 head-on-trunk positions for patients with Klockgether rating of ≥ 8 points in comparison to control subjects.

Figure 24

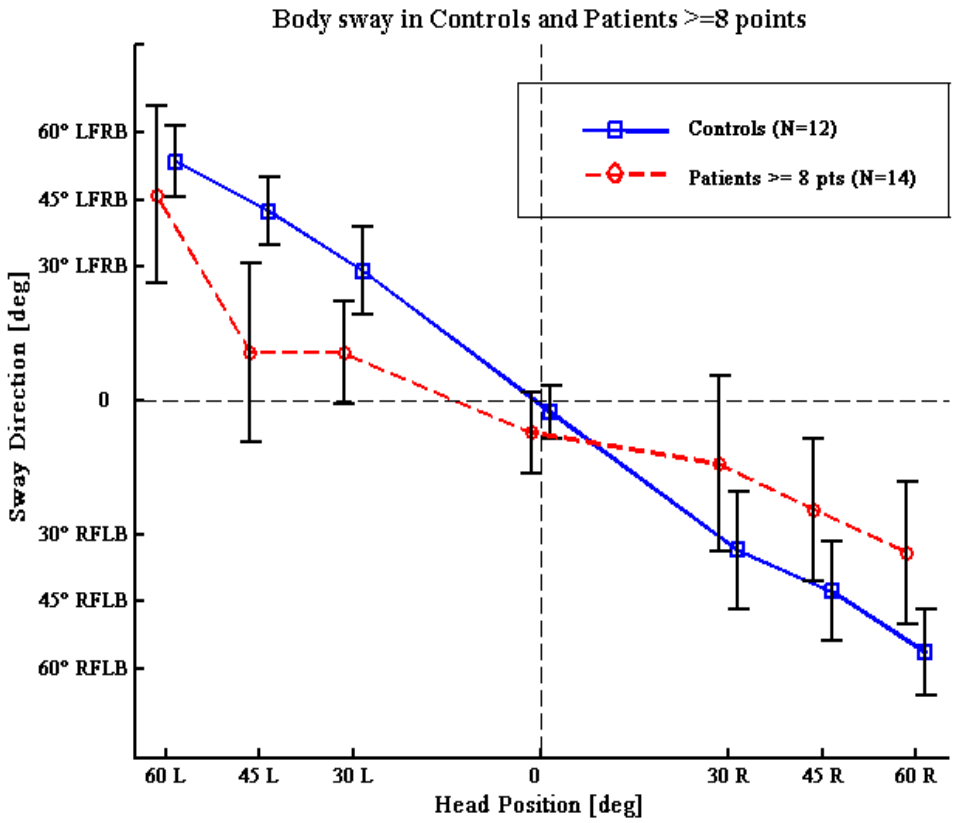


Figure 24:

Body sway direction across all seven head-on-trunk positions is shown for controls and patients with ≥ 8 Klockgether points. 95% confidence intervals are depicted for each head-on-trunk-position. In controls, body sway direction was in close alignment to the ideal compensation for head excursion, i.e. GVS at a 60° right head turn resulted in body sway around 60° LFRB. In patients, a wider range of directions was found, ranging from sway within confidence intervals of controls up to excessive under-compensation.
There was highly significant difference in statistical interaction between group affiliations (controls versus patients scoring ≥ 8 points) for their respective sway directions at individual head-on-trunk positions ($p < 0.001$, multivariate analysis).

Figure created with MatLab©

4.3.2.2 Slopes and overall compensation ability

Multivariate analysis allowed explaining for variance in sway direction at individual head-on-trunk positions and their two-way interaction. This complex type of analysis, however, could not directly take into account a possible linear interaction Fransson et al 2000 between head-on-trunk position and the corresponding GVS-evoked sway direction. Therefore, a robust slope fitting to an individual subject's sway responses across all 7 head positions was investigated as a surrogate for the overall vestibular-neck compensation (dis)-ability.

Previous studies have discussed possible non-linearities between the head-on-trunk position and the GVS-evoked sway direction [Pavlik et al 1999, Fransson et al 2000]. A linear least-square fit was found the best match to the actual raw data, rather than any exponential or hyperbolic non-linear fit across all 7 positions.

After calculating a least-squares linear fit to all 7 head-on-trunk conditions for each individual, data points with a distance away more than two standard deviations (2 σ) from the fitted line were defined as outliers and subsequently eliminated. This applied for a total of 11 data points of 224 (20 patients plus 12 controls, each with 7 trials).

The inclination of the least-squares fit through the remaining data points, i.e. “s” of the general line equation $y = s \cdot x + t$, was taken for further analysis. In the following, this inclination “s” will be termed “slope”. The slope will be used as a surrogate for the overall proprioceptive compensation (dis)-ability across all 7 head-on-trunk positions.

Full compensation to head-on-trunk position (compare Figure 23) is represented by $y = - x$, a line with an inclination of -1 (slope = -1).

Lateral body sway across all 7 head-on-trunk positions in the frontal plane of the trunk is represented by a slope of 0, i.e. a line described by $y = 0$. A zero-slope implies a complete lack of any compensatory action to head-on-trunk excursions: at “zero-slope”, there would be galvanically evoked, laterally directed body sway in the frontal plane of the trunk, instead of the head frontal plane.

Figure 25 shows the slopes for all control and patient subjects, along with 95% confidence intervals. Patients with less than 8 Klockgether points are not shown.

Figure 25

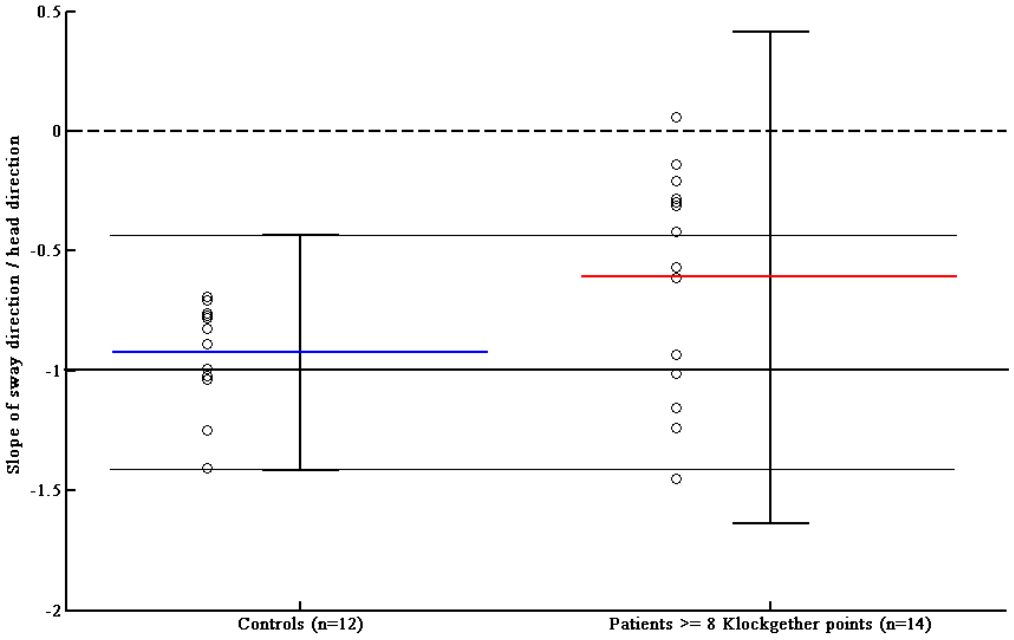


Figure 25:

Slopes of body sway behaviour for controls and patients (i.e. amount of body sway turn relative to head-on-trunk position). The coloured bars show the median along with the 95% confidence intervals. The small circles depict the individual slopes.

In controls, slopes form a narrow band around the fully compensatory slope of –1. Two controls and 2-3 patients showed mild over-compensation (see Discussion; considered individual variance rather than pathology).

In patients with Klockgether higher than 8 points, by contrast, a wider range of body sway slopes could be found, ranging from sway behaviour similar to controls, down to non-compensatory sway. 7 of 14 patients had a body sway slope outside the confidence intervals of control subjects: their overall vestibulo-proprioceptive interaction was clearly hypo-compensatory.

Figures created with MatLab©

Seven of 14 patients with a Klockgether score higher than 8 points had clearly insufficient vestibulo-proprioceptive interaction abilities: their slopes were outside the lower 95% confidence intervals of control subjects and significantly different from the control group ($p < 0.05$, Welch's t-test for unequal sample size and unequal, but Gaussian variance, as confirmed by the Kolmogornov-Smirnov test). These seven patients with significantly hypo-compensatory slopes had slopes ranging from -0.42 to +0.10. Their overall vestibular-neck interaction was massively perturbed in the GVS experiment. This finding correlated to clinical vestibular-neck disorders (Chapter 4.3.3).

For the seven other patients (≥ 8 Klockgether points, GVS slopes within controls' confidence intervals), multivariate analysis revealed significantly different interaction between head position and body sway direction against controls, alone due to the sway response angles at -45° and -30° (left) head position:

sway angles at these sub-maximal head positions were lower than in controls, indicating a lateralized, asymmetric group effect.

Four patients were alone responsible for the asymmetric nonlinearity to the left side. They had expressed ataxia symptoms towards the left side. Only for the left side in these four patients, sway directions were best described by an exponential rather than a linear function. During rightward head turns in these four, sway directions were in regular linear relation to head positions with a normal slope, like in controls. Clinically, four of these 7 patients had more expressed cerebellar symptoms on the left side (see Chapter 4.3.3). Small amounts of head excursions were not sufficiently compensated for, whereas near-maximal head turns evoked sufficient compensation (unilateral “exponential” vestibular-neck interaction).

The other three patients with slopes within normal limits, but without symptom lateralization, had no different sway directions compared to controls ($p = 0.07$, multivariate analysis). These three patients and the four patients with sway direction asymmetry shared two common features: slopes within normal limits and common deficits in clinical vestibular-neck testing (see Chapter 4.3.3).

It was a remarkable finding to see two of the control subjects and 3 patients with clinical scoring ≥ 8 points exhibit over-compensatory slopes exceeding $y = -1$. It has to be remarked that this mild over-compensation can easily be obtained by just minimal amounts of slope variance, and may probably be part of normal variance (see Discussion).

4.3.2.3 Influence of sex, age and disease aetiology

Both groups had a wide range of subject ages: 30 to 64 (average 48, mean 47) for controls and 30 to 72 (average 59, median 61) for patients. Because of the relatively small number of subjects included in this study (12 controls, 20 patients), not all age classes could be represented equally. Age did not influence the slope of body sway direction in controls or patients (Figure 26); neither had subject sex any significant influence on body sway performance (both $p >> 0.05$). Also for individual sway directions in multivariate analysis, neither age nor sex showed statistically significant interaction (both $p >> 0.05$). Disease aetiology (e.g. idiopathic degeneration) was not related to sway directions or slopes ($p >> 0.05$, multivariate analysis).

Figure 26

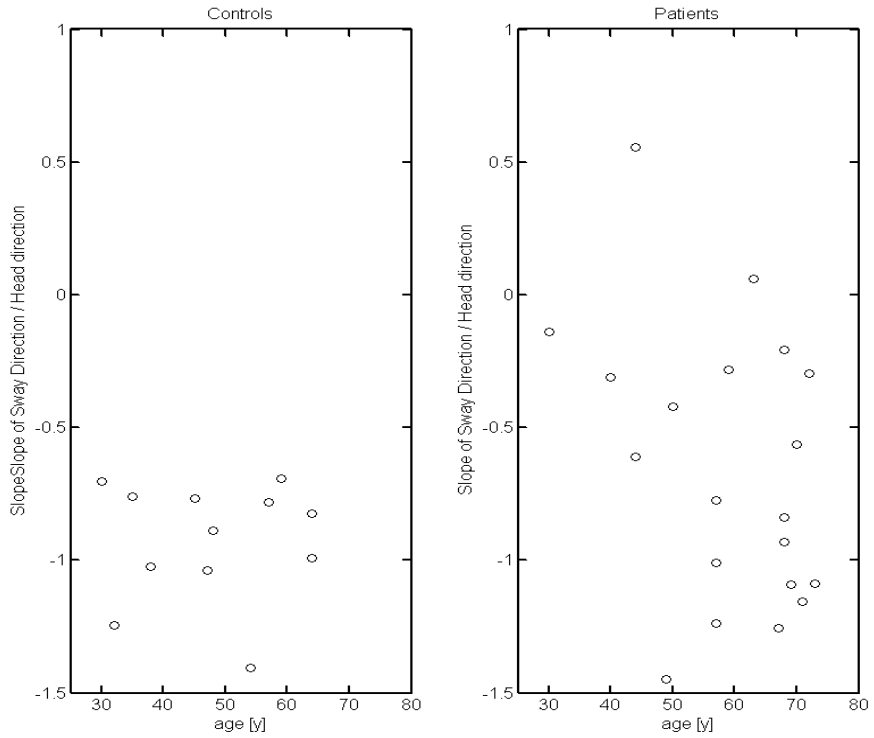


Figure 26:

The slopes of body sway behaviour relative to subject age for controls and all patients are shown, including also those patients with Klockgether scoring <8 points. There was no correlation with age ($p >> 0.05$).

Figures created with MatLab©

4.3.2.4 Influence of stimulus amplitude

Stimulus amplitude might possibly have influenced body sway performance. As proposed in Chapter 2.2, there is generally tremendous inter-individual variance in susceptibility to galvanic vestibular stimulation. In the proposed study, stimulus amplitude was adjusted individually to evoke visible sway well inside the borders of stability. Stimulus amplitude ranged from 1 to 4 mA with both a median and average at 2mA in both groups. There was no detectable influence on the body sway directions and slopes in either group ($p >> 0.05$ in multivariate analysis and Welch's t-test for both controls and patients). Influence on the body sway amplitude is self-explanatory.

4.3.3 Clinical head-on-trunk interaction deficits

The following section details the three main patient sub-groups and shows correlation with the Klockgether score and clinical vestibular-neck interaction testing.

4.3.3.1 Patients with slopes outside control confidence intervals

Among the 20 patients, 7 showed clear mal-compensation to head-on-trunk excursions. Their body sway slopes were outside the 95% confidence intervals of control subjects (Figure 25). Klockgether scores ranged from 9 to 17 (average 13). Two of these patients are illustrated in Figure 27: “Ele04” is a 30 year-old male with idiopathic cerebellar degeneration (9 points in Klockgether score, 3 points in gait ataxia, 3 for stance ataxia); “Iez13”, a 59 year-old female prone to multi-system atrophy of cerebellar type, was rated 17 points (gait ataxia 4, stance ataxia 3 points). Patient “Lau 11”, who also exhibited distinct hypo-compensation, has already been depicted in Figure 23. All patients with hypo-compensatory sway outside the 95%-boundaries of “normal” are shown in Table 28.

Their body sway directions were aligned to the frontal plane of the trunk rather than turning along with the frontal plane of the head. Ataxia was uniformly distributed on both sides among these patients.

Figure 27

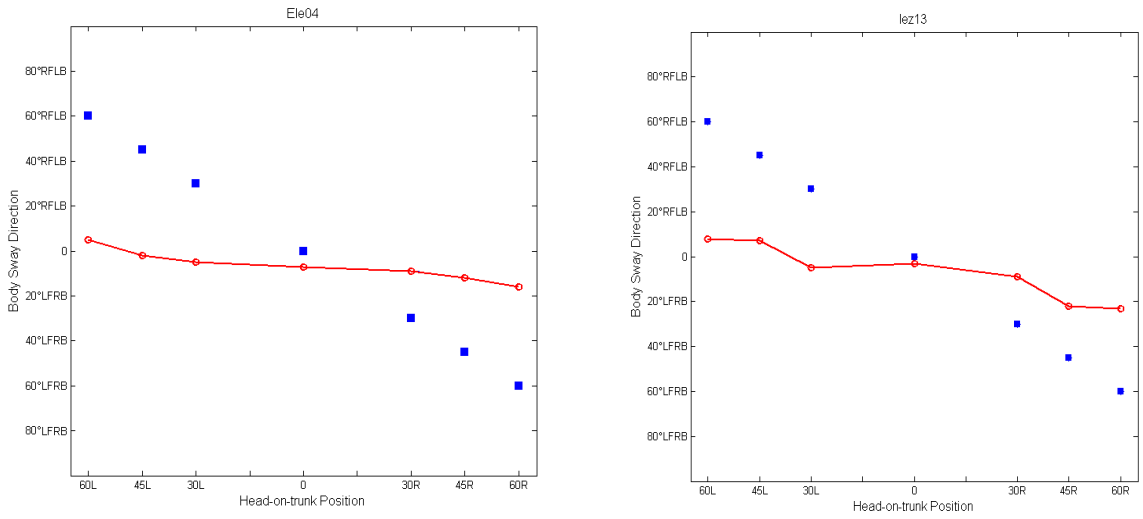


Figure 27:

Patients “Ele04” and “Iez13”: body sway remains below 20° in the correct direction. Blue squares mark ideal full compensation. Figures created with MatLab©

Table 28

Code		Etiology	Age	Gender		**Klockgether**	Gait	Stance
Jel02		Idiopathic	72	m		**11**	3	2
Ele04		Idiopathic	30	m		**9**	3	3
Lel06		SCA	50	m		**13**	3	3
Ala10		MSA-C	68	f		**13**	4	3
Lau11		Idiopathic	40	m		**17**	2	2
Iez13		MSA-C	59	f		**17**	4	3
Lav17		Idiopathic	44	f		**13**	2	2

Table 28:
In these 7 patients a clear body sway alignment deficit was found. Higher overall Klockgether rating, as well as high gait and stance ataxia scales were a common feature. Table created with Microsoft Excel©

With increasing lateral head excursions, compensation for head excursion massively lagged behind controls, although the minimal remaining compensation reaction was in the correct direction: a head turn 60° to the right only resulted in a body sway turn at e.g. -20° in the LFRB direction.

4.3.3.2 Patients with slopes within controls' confidence intervals

Another seven patients showed intermediate effects in-between statistically control-like sway directions and excessively reduced vestibular-neck compensation. These subjects performed no different from the 95% confidence intervals of control subject variability with respect to their slopes. There was pronounced gait and stance ataxia, similar to those patients with distinct hypo-compensation of vestibular-proprioceptive interaction (Table 29).

Table 29

Code		Etiology	Age	Gender		**Klockgether**	Gait	Stance
Veh01	*	Stroke	71	m		**8**	3	2
Cah08	*	SCA	57	f		**11**	2	1
Azi09	*	Idiopathic	63	f		**13**	2	2
Meb14		Stroke	68	f		**13**	2	2
Hak16		Paraneo	49	f		**11**	3	3
Leu19		EA II	57	m		**8**	2	2
Pah20	*	Idiopathic	70	f		**8**	3	1

Table 29:
Seven patients showed intermediate defects in body sway alignment with the head frontal plane. They show gait and stance ataxia comparable to patients with clear mal-alignment deficits. Four patients marked with (*) clinically exhibited pronounced ataxia lateralization to the left side. Table created with Microsoft Excel©

Four of the 7 patients had predominantly left-sided cerebellar symptoms in upper-limb, lower-limb and diadochokinesis tasks: one had cerebellar embolic stroke, another 3 suffered from general cerebellar atrophy with lateralized left-sided limb ataxia.

The other three patients showed equally expressed ataxia on both sides with moderate gait and stance ataxia and an overall Klockgether score ≥ 8 points.

4.3.3.3 Patients scoring below the 8-point Klockgether cutoff

Six other patients did not exhibit any vestibular-neck mal-compensation. Their slopes and individual sway directions were indistinct from those of control subjects. Their ataxia was expressed equally on both sides. Table 30 shows the six patients with body sway directions fully within normal limits:

Table 30

Code		Etiology	Age	Gender		**Klockgether**	Gait	Stance
Sit03		Stroke	67	m		**7**	2	2
Mah05		Stroke	73	m		**4**	3	1
Ach07		Idiopathic	69	m		**4**	0	0
Hah12		Stroke	44	f		**6**	3	3
Har15		Idiopathic	57	f		**4**	1	0
Cal18		SCA	68	m		**7**	2	1

Table 30:

In these 6 patients no significant difference could be found relative to healthy controls. Relatively low rating in the overall Klockgether score is a common feature. Gait and stance ataxia scales are variable from mild or no impairment to ataxia grades comparable to patients showing mal-alignment of body sway.

Table created with Microsoft Excel©

4.3.3.4 Clinical vestibular-neck interaction testing

Gait and stance ataxia were rated subjectively and by an experienced clinician during lateral head excursion in stance and walking, allowing for a descriptive division of the investigated patients. Clinical performance is summarized in Table 31 (p. 71).

All patients with abnormal slopes outside controls' confidence intervals reported massively increased

subjective instability during the clinical gait and stance trials with the head turned aside. They exhibited an objective considerable increase in gait and stance ataxia during lateral head turns in comparison to the same tasks with straight head-on-trunk position. “Jel02” and “Ele04” were able to walk with their eyes closed and extreme lateral head turns, but only during constant assistance by the clinical observer. This task was completely impossible to the other patients in this sub-group. By contrast, they could all walk with closed eyes and only little assistance during neutral head position.
The corresponding stance task with closed eyes was around the border of stability and required considerable assistance. When tested with open eyes, gait and stance ataxia increased with horizontal head excursion, but testing was possible in all of these patients.

Patients with Klockgether scores ≥ 8, who had slopes within controls’ confidence intervals, generally showed an increase in ataxia during head turns in the clinical vestibular-neck interaction task compared to neutral head position, irrespective of ataxia lateralization. This was objectively most consistent in the gait and stance tasks with eyes closed.
The four patients with left-lateral ataxia (marked with * in Table 31), exhibited a more prominent increase of gait and stance ataxia during leftward head excursions than during rightward turns.
The other three patients without ataxia lateralization and ≥ 8 points clinically performed like lateralized patients with an increase of head-turned ataxia in either head direction, in contrast to the mildly affected patients scoring <8 points without any increase in ataxia versus head neutral position. Independent from possible lateralization, patients in this group could exhibit objectively increased stance ataxia either with eyes closed or already with open eyes.

None of the patients scoring <8 Klockgether points reported increased subjective instability during stance and walking with the head turned aside in either direction. In clinical gait analysis, no increased gait or stance ataxia could objectively be observed with additionally imposed extreme lateral head turns. The same applied for testing with open eyes.

Controls neither reported nor exhibited any difficulty in the clinical vestibular-neck interaction trial.

Table 31

		Subjective Rating					Objective Rating			
		Eyes open		Eyes closed			Eyes open		Eyes closed	
		Stance	Gait	Stance	Gait		Stance	Gait	Stance	Gait
Sit03		0	0	0	0		0	0	0	0
Mah05		0	0	0	0		0	0	0	0
Ach07		0	0	0	0		0	0	0	0
Hah12		0	0	0	0		0	0	0	0
Har15		0	0	0	0		0	0	0	0
Cal18		0	0	0	0		0	0	0	0
Veh01	*	0	1	1	1		0	1	1	1
Cah08	*	0	1	1	1		1	1	1	1
Azi09	*	0	1	1	1		1	1	1	1
Meb14		0	1	1	1		0	1	1	1
Hak16		0	1	1	1		0	1	1	1
Leu19		0	0	0	0		1	1	1	1
Pah20	*	0	1	1	1		0	1	1	1
Jel02		0	1	1	2*		0	1	1	2*
Ele04		0	1	1	2*		0	1	1	2*
Lel06		1	1	1	2		1	1	1	2
Ala10		1	1	1	2		1	1	1	2
Lau11		1	1	1	2		1	1	1	2
Iez13		1	1	1	2		1	1	1	2
Lav17		1	1	1	2		1	1	1	2

Table 31

Clinical trial in patients: gait and stance ataxia were rated subjectively and objectively with eyes open and eyes closed.
White spaces define patients scoring < 8 points. They had no increased ataxia in the clinical task.
Grey spaces mark patients with ≥ 8 points and slopes within controls' confidence intervals, with a moderate increase of head-turn induced ataxia. The stance - eyes open condition could be performed with no or little increased ataxia. Those patients with lateralized cerebellar symptoms towards the left side are marked with (*). Note, that both patients with and without lateralization could exhibit an objective increase of stance ataxia in the eyes open task (compare Chapter 5.8 and Table 33)
Black spaces indicate patients with ≥ 8 points, slopes outside controls' confidence intervals and considerable increase in head-turn induced ataxia. The gait - eyes closed condition was only possible with permanent aid (marked with 2*) or was not possible at all.

"0" no increased ataxia in this task
"1" increased ataxia in this task
"2" gait and stance tasks possible, but impossible with lateral head turns
"2*" only possible with constant assistance

Table created with Microsoft Excel©

4.3.3.5 Correlation of GVS sway with Klockgether scores

There was a near-significant tendency towards higher Klockgether scores in patients with ≥ 8 points and abnormal slopes ($p = 0.06$ both in Welch's t-test for slope (Figure 32) and in multivariate analysis

for individual head positions). In this study with a total of 20 patients, neither the total Klockgether score nor the gait and stance ataxia scales alone could serve as statistically sufficient characterization predictors for experimental or clinical vestibular-neck deficits for ≥ 8 Klockgether points (all $p > 0.05$ in both Welch's t for slopes and multivariate analysis for individual sway directions). The seven affected patients with slopes outside controls' confidence intervals had total scores ranging from 9 to 17 (average 13), whereas the 7 patients with slopes within these limits ranged from 8 to 13 (average 10).

Below 8 points, the Klockgether score provided a clear cut-off value for 6 patients without any deficits in GVS or clinical vestibular-neck testing, in accordance with slope and clinical vestibular-neck testing.

In summary, the Klockgether score only provided weak correlation with vestibular-neck interaction deficits found in GVS and specific clinical testing for patients scoring ≥ 8 Klockgether points, but a cut-off value at 8 Klockgether points was well able to distinguish between cerebellar patients with any degree of vestibular-neck interaction deficits and those without.

Figure 32

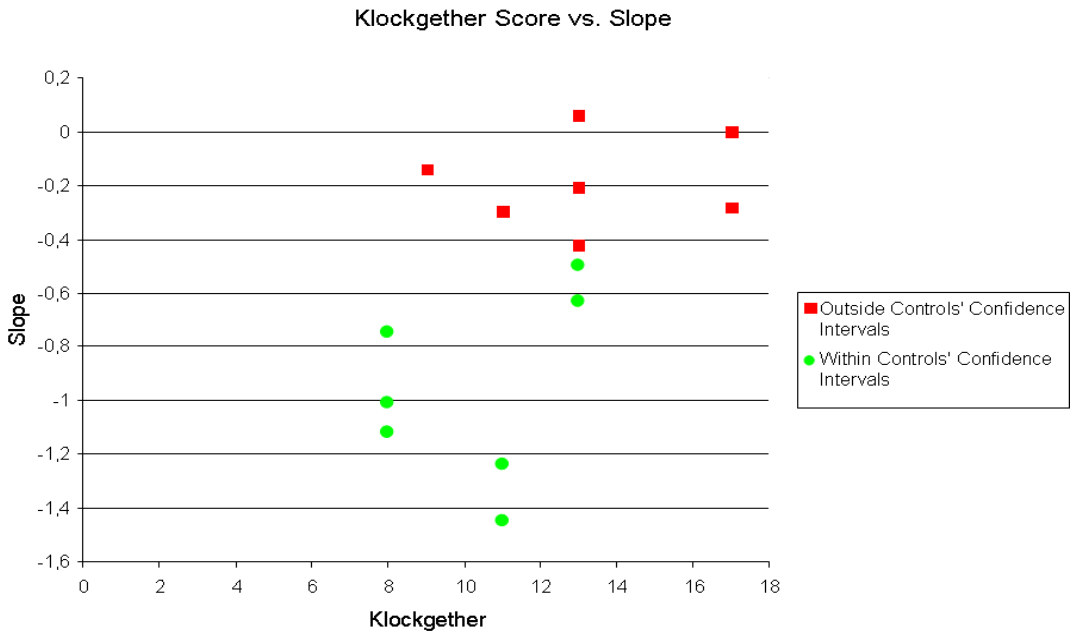


Figure 32:

Correlation between the total Klockgether score and the slope for all patients scoring at least 8 points. The seven patients with slopes within controls' 95% confidence intervals are marked with green circles; the seven patients outside these limits are red squares. Welch's t-test for slopes found near-significant difference between groups at $p = 0.06$, suggesting a trend towards higher scores in patients with abnormal vestibular-neck interaction and slopes outside normal boundaries.
Figures created with Excel©

4.4 Summary of Results

Controls could keep their GVS-evoked body sway aligned to the head-frontal plane during horizontal head turns. Their sway directions linearly compensated for the imposed head turn. There was an increase in sway amplitude during head excursion compared to neutral head position, like it was in patients. Controls experienced no difficulty in the clinical vestibular-neck interaction test.

Twenty patients were divided into four groups, by their sway direction slopes, the clinical vestibular-neck test and the Klockgether score cut-off at 8 points:

- Seven patients with slopes outside controls' confidence intervals and a Klockgether score ≥ 8. In the clinical test for vestibular-neck interaction walking with closed eyes was possible in neutral head position, but (near-)impossible with head turns.
- Four patients with (left-) lateralized ataxia and a Klockgether score ≥ 8. Vestibular-neck interaction ipsilateral to the more affected side was hypo-compensatory and non-linear; towards the contralateral side there was linear vestibular-neck interaction and a normal slope. In clinical vestibular-neck testing, there was an increase of ataxia during lateral head turns (preferred towards the more affected side) versus neutral head position.
- Three patients with a Klockgether score ≥ 8 and slopes within normal limits. Clinical vestibular-neck testing revealed an increase of ataxia during lateral head versus neutral head position, like in lateralized patients, despite normal slopes.
- In six patients with Klockgether scores < 8 points and sway directions, slopes and clinical vestibular-neck interaction was fully within normal limits.

5 Discussion

Our results have uncovered relations between the vestibular system, neck proprioceptors and the cerebellar complex in a human model. We debate our experimental findings with respect to other studies and propose a basic human model of cerebellar vestibular-proprioceptive interaction in health and cerebellar disease. Clinical implications of our findings on trunk ataxia theory are suggested.

5.1 Experimental groundwork for this study

Our experiments were based on cerebellar vestibular-neck interaction theories developed from clinical observation, clinical electrophysiology and single cell recordings in animal studies.
Key studies were single cell recordings from the anterior lobe vermis [Manzoni et al 1998, 1999 and 2004] and the fastigial nuclei [Kleine et al 2004]. These structures connect to the descending vestibulo-spinal tracts for postural control [Mori et al 2004]. These studies, however, had been performed in animals like macaque monkeys or cats. It was unclear, whether and to what extent these experimental findings could be generalized into a theory of human vestibular-neck interaction.

Galvanic vestibular stimulation (GVS) has been used in posture research for decades, even though not as a routine method. Continuous, sinusoidal, binaural galvanic vestibular stimulation induces well-reproducible, alternating lateral body sway reactions, aligned to the head frontal plane at the same frequency as the imposed stimulus [Coats 1972, Hlavacka et al 1993, Day et al 1997, Pompeiano et al 1997, Fransson et al 2000, Bense et al 2001, Fitzpatrick et al 1994 and 2004, Manzoni et al 1998, and 2004, Cathers et al 2005, Iles et al 2007] (compare Chapter 2.2.3). The GVS effects can be modulated by lateral head excursions in animals and healthy human subjects [Lund et al 1983, Tokita et al 1989, Hlavacka et al 1993, Day et al 1997, Pompeiano et al 1997, Fransson et al 2000, Latt et al 2003, Fitzpatrick et al 2004, Manzoni et al 1998, 1999 and 2004, Cathers et al. 2005].

Cerebellar patients and healthy controls were exposed to GVS with different head-on-trunk positions and a clinical testing condition with lateral head excursion in comparison to neutral head position. With no other differences in-between groups than cerebellar impairment, experimental and clinical deficits in vestibular-neck interaction were solely attributable to cerebellar structures, probably including those identified in the animal single cell studies mentioned above.

5.2 Vestibular-neck interaction in control subjects

In controls, GVS-evoked body sway at our applied stimulus frequency of 0.16 Hz was found to keep aligned to the head frontal plane at the imposed frequency [Coats 1972], irrespective of the individual's galvanic susceptiblility and applied stimulus amplitude, in accordance with previous studies [Coats 1972, Fransson et al 2000, Fitzpatrick et al 2004, Cathers et al 2005, Iles et al 2007].

Regarding the body sway amplitude, lateral head turns increased the postural compensation effort in controls and patients, as reflected by increased sway amplitude ("sway path") and effort ("root mean square sway", compare Chapter 4.3.1). In comparison to postural compensation with the head straight, postural compensation efforts during horizontal head turns appeared to be more demanding on central nervous activity, which was manifest in the observed higher sway, even in control subjects.

Previously discussed nonlinearities in vestibular-neck interaction under galvanic vestibular stimulation, as proposed by some authors [Pavlik et al 1999, Fransson et al 2000], could not be observed in our control subjects and cerebellar patients, except for patients with ataxia lateralization (see below). The best possible fit model, to describe the evoked body sway slopes, was a linear least-squares fit, not any type of exponential function (compare Chapter 4.3.2). This is in accordance with the idea of vestibular-neck interaction fully compensating for lateral head turns in healthy subjects.

Small over-compensatory slopes for GVS-evoked sway were found in two healthy controls and three patients, i.e. their vestibular-neck interaction was best represented by a linear model with an inclination exceeding s = -1 [Pavlik et al 1999, Fransson et al 2000]. Such slopes were probably within normal variance above and below the fully compensatory slope at -1, rather than defining specific pathology. Possible future studies may investigate hints at inter-individual variability of head-neck interaction in a considerably larger number of healthy subjects.

Altogether, our experimental results obtained by GVS in healthy subjects fully confirmed findings by other authors. Translating this electrophysiological experiment into a clinical context, by having subjects walk and stand with full lateral head turns, led to no considerably increased dysbasia and dystasia in controls, as expected.

5.3 Vestibular-neck interaction deficits in cerebellar patients

Patients' clinical impairment was assessed with the clinical ataxia rating score proposed by Klockgether and colleagues [Klockgether et al 1990], which has proven to be an objective and reliable clinical test [Masur et al 2003]. In comparison, the more widespread International Cooperative Ataxia Rating Scale [Trouillas et al 1997, Schmitz-Hübsch et al 2006 (2)] (ICARS), which has proven to be objective and reliable as well, takes considerably longer time to assess (30-45 min.versus 5-10 min. for the Klockgether score). Several test items are redundant, differently weighted and not sufficiently valid [Schmitz-Hübsch et al 2006 (1) and (2)], instead of giving an overall grading of a clinically specific cerebellar symptom like the Klockgether score. Thus, the ICARS was deemed inferior to the Klockgether score for our specific experimental context: a general, non-weighted score, accounting for all established clinical cerebellar symptoms equally, allowed for easier cross-correlation of cerebellar symptoms with experimental performance.

The featured large number of patients with atrophic cerebellar disease, aquired over a long period of time, had been preferred over the more numerous patients with small focal cerebellar lesions in study design for a number of reasons:

For this pilot study on the general role of cerebellar circuitry in human vestibular-neck interaction, the cerebellum as a whole unit had to be considered as a knock-out. Patients with large cerebellar lesions, such as those with atrophy, could potentially provide better evidence for cerebellar involvement in a functional context. Patients with general atrophy were preferentially recruited. Due to supposed functional co-localization with gait and stance ataxia (anatomically in the vermis), also one patient with paraneoplastic cerebellar atrophy with pronounced vermal atrophy was included.

Patients with a specific left-sided preference of their ataxia symptoms were included more by coincidence rather than intent. If patients with progressed right-sided ataxia would have been included as well, the lateralization effect found in this study would potentially have escaped scrutiny. The four lateralized patients all had bilateral cerebellar disease, either due to embolic bilateral stroke (n = 1) or due to asymmetric cerebellar atrophy (n = 3), but their ataxia symptoms were more expressed towards the left side.

A wide range of cerebellar impairment was found in patients, with scores ranging from mildly affected 4 points to considerable deficits at 17 points. All patients were ambulatory. More severely affected

non-ambulatory patients, with Klockgether scores up to the full 35 points, could not be included in this study, because our experimental setup required free stance in an eyes-closed paradigm under additional vestibular perturbation. This difficult task could be performed by all patients, including those with 17 Klockgether points.

This selection bias excluded wheelchair-bound and bedridden patients with end-stage cerebellar disease. Our present findings and implications are thus restricted to ambulatory cerebellar impairment. Patients with more extreme deficits would have to be investigated under an experimental setup which does not require upright stance, like GVS plus surface electromyography in a lying subject [Tokita et al 1989, Britton et al 1993, Fitzpatrick et al 1994, Bacsi et al 2003, Cathers et al 2005]. Such experimental setup will be subject to future research, possibly expanding the field of vision on cerebellar vestibular-neck interaction deficits. A portable device for functional cerebellar bedside-testing for patients after acute cerebellar stroke or hemorrhage should be introduced – possibly for use even on intensive care units.

Three-dimensional magnetic resonance tomography of cerebellar lesions had been considered but refuted, because most patients in this study (14 of 20) had atrophic cerebellar disease, which would have made valid border delineation of functionally dysfunctional structures near-impossible.

Investigating vestibular-neck interaction in patients with precisely circumscribed lesions and superimposing the anatomical lesion sites – such as by three-dimensional magnetic resonance imaging – might provide deeper insight into the anatomical structures involved in this sensory interaction mechanism in further studies. Such approach would require larger subject quantities and restriction to patients with cerebellar ischemia or hemorrhage.

5.4 Body sway and compensation for head turns in cerebellar disease

Generally, cerebellar patients with trunk ataxia suffer from postural imbalance and dyscoordinate movements in gait and stance.

A specific phenomenon of vestibular-interaction deficits was explicitly reported by some patients with progressed cerebellar disease upon recuiting for the study: they experienced severely increased motor instability during walking with their heads aside, so that some of them were forced to keep their heads straight all the time during walking. For a head turn to the side, e.g. for a look into a display window on

a shopping tour, they had to stop first and only then could look to the side.

Patients with low-grade clinical manifestations of their cerebellar disease still could fully compensate for horizontal head excursions, indiscernible from postural compensation effects in control subjects. The range of asymptomatic patients with normal vestibular-neck compensation (6 of 20) was below 8 points in the clinical Klockgether ataxia rating score for the patients in this particular study. In clinical observation they had no additional functional deficits in gait and stance examinations during additional head turns: whatever lateral head turn was imposed during gait and stance, no additional instability could be evoked.

This threshold for vestibular-neck interaction deficits could sharply discern between normal and clearly abnormal sway directions ($p < 0.001$) in multivariate analysis. These findings suggest that below the defined threshold of cerebellar damage, the complex mechanism of vestibular-neck interaction is very unlikely to bear functionally relevant damage. If this study was to be repeated with another set of patients, this cut-off might possibly be higher or lower by a few points in clinical rating. Nevertheless, any other selection of patients rated with the Klockgether score, or any other objective and reliable clinical assessment tool, might probably show a similar cut-off phenomenon.

Above a certain amount of cerebellar structural damage, the vestibular-neck interaction mechanism is more likely to be impaired. From anatomical studies, the neural circuitry of vestibular neck coordination (see chapter 2.1.3) is supposed to lie in regions, which are associated with vestibular-neck interaction. Lesions there are known to result also in gait and stance ataxia.

Findings suggest that below a certain amount of cerebellar circuitry degeneration or destruction, the relevant mechanisms for vestibular-neck interaction apparently remain unaffected – or affected without functional relevance in our experimental and clinical trials. However, even below 8 points in clinical scoring, there are still considerable subjective and objective symptoms of the underlying cerebellar disease, accompanied with considerable impairment in acivities of everyday life.

Above the Klockgether cut-off defined at ≥ 8 points, vestibular neck interaction in the remaining 14 subjects was considerably different from control subjects ($p < 0{,}001$, multivariate analyisis).

Seven of these 14 patients showed pronounced slope under-compensation to the imposed head turns, outside the 95% confidence intervals of healthy control subjects under GVS. Cerebellar damage decisively impaired their mechanisms for vestibular-neck coordination. Walking with closed eyes plus head excursion was impossible or near-impossible to them. Walking with neutral head position was possible, even with eyes closed.
The slopes were massively reduced in these patients as a surrogate for massive overall vestibular-neck interaction deficits. To either side, the relation of head position to sway direction was linear with low inclination; clinically, ataxia was equally expressed on either side in these patients.

The other seven of the 14 patients scoring ≥ 8 points had vestibular-neck interaction within the confidence boundaries of normal. However, they all showed an increase in clinical atactic symptoms during walking and stance with additional head turns.
Among these 7 patients were four with bilateral cerebellar disease, but predominant left-sided ataxia, and three patients with bilaterally equal distribution of ataxia symptoms. All seven showed abnormal clinical vestibular-neck interaction deficits; lateralized patients more towards their predominant left side.

The four with ataxia lateralization had an expressed asymmetry in GVS-evoked sway directions, which correlated to a more expressed increase of gait and stance ataxia in head excursions towards the left side versus neutral head position, in comparison to the smaller increase of ataxia during rightward head turns. Lateralized vestibular-neck interaction deficits were therefore consistently manifesting in non-linear GVS-evoked sway directions to the left and in lateralized vestibular-neck interaction in the clinical test. This may possibly be seen as an indication of dissociate side-specific central mechanisms for vestibular-neck interaction, also based on data obtained from clinical testing. Little amounts of head turn did not induce sufficient sway direction turns, whereas near-maximal head excursion could still induce a sufficient directional compensation. Possibly, intense neck-proprioceptive input is required to drive sufficient compensation, whereas small amounts of proprioceptive stimulation are insufficiently processed in the damaged ipsilateral vestibular-neck circuit.

The three patients with equilateral ataxia and Klockgether scores ≥ 8 points were statistically within normal limits ($p > 0.05$), regarding sway directions in multivariate analysis and slopes in Welch's t-test.

In the clinical test however, they exhibited a clear increase in ataxia with lateral head turns to either side versus neutral head position. Therefore, it may be suggested that these three patients still have a certain amount of vestibular-neck interaction deficits, manifest in clinical testing, but only to a small extent in GVS-evoked sway directions. Due to the very small number in this sub-group as well as a probably small-extent vestibular-neck deficit, differences to patients with Klockgether scores < 8 may probably have evaded multivariate statistical scrutiny in this study. There should be a focus on these patients with moderate cerebellar disease around 8 Klockgether points in future studies.

The walking task with closed eyes and full lateral head turn could be seen as a surprisingly striking clinical correlate to the impaired response under galvanic stimulation. “Vestibular-neck ataxia” was both an experimentally observed deficit in postural control adjustments to head turn under GVS as well as manifest in increased visible gait and stance ataxia upon lateral head turn in a clinical trial.

The Klockgether and its sub-scales, by contrast, could not sufficiently explain for whether a patient with high clinical rating above the “cut-off” at 8 points was predictably outside the limits of normal slope or within. The Klockgether score was only near-significantly correlated to abnormal slopes ($p = 0.06$, Welch’s t-test) and individual sway directions ($p = 0.06$, multivariate analysis); the scales for gait and stance ataxia completely failed as statistical predictors for GVS sway direction and slope outcomes.
Clinical vestibular-neck testing in comparison formed a superior predictor, even with the given subject numbers.

5.5 Vestibular, proprioceptive and visual interaction

The vestibular organ alone, without additional information on the relative position of neck to trunk, cannot determine in which direction it has been stimulated, relative to the body [Jones et al 1972, Pompeiano et al 1972, Lund et al 1983, Manzoni et al 1998, Angelaki et al 2004]. Without this additional information, purposeful postural compensation is impossible. Additional information is required to solve this “vestibular-alone information ambiguity”, to measure the position of the peripheral vestibular system against the trunk [Gdowski et al 1999, Kleine et al 2004] through the proprioceptors of the neck [Fransson et al 2000], as shown in this study.
The central integration of sensory inputs from three sensory systems allows the brain to create a

concept of “position and movement in space”: the vestibular system with semicircular canals and otolith organs; the proprioceptive sensors in muscles and joints and finally, the visual system. Elimination of one or more systems leads to increasing postural instability [Krafczyk et al 1999 and 2006]. In this study, the visual system was functionally eliminated by having subjects close their eyes, in order to test vestibular-proprioceptive interaction.

The visual system is one decisive contributor to body stability. Its influence on postural control is subject of a whole research field [Day et al 2007]. In subjects with intact vestibular-neck interaction in our experimental setup, additional visual input accords to the perceived vestibular stimulation. No inter-sensory conflict occurs. In subjects with vestibular-neck interaction deficits however, a vestibular-visual conflict would appear: GVS evokes the vestibular sensation of swaying in the head frontal plane. If the head of a subject with this interaction deficit is turned e.g. 60° to the left during GVS with consecutive sway in the body-frontal plane (due to cerebellar deficits), visual and vestibular input would not be congruent, as illustrated in Figure 33:

Figure 33

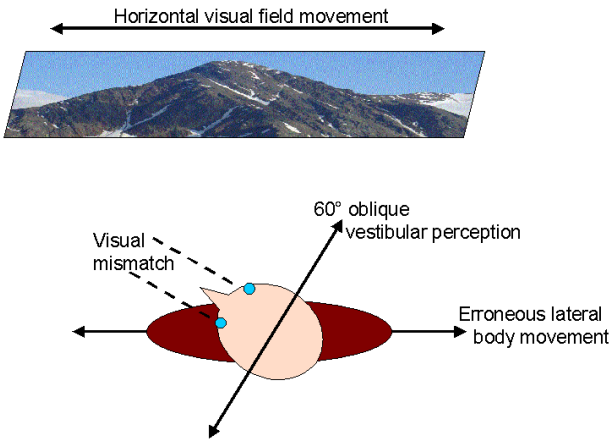


Figure 33:

Visual-vestibular mismatch in a patient with vestibular-neck interaction deficits: The vestibular system perceives rolling relative to the head. The body, however, is erroneously tilted left and right because of faulty intersensory interaction, resulting in a mismatch between visual field and vestibular sensation. Figures created with Microsoft Office©, included picture taken by the author.

During such visual-vestibular mismatch, one of the conflicting sensory modalities is known to be disregarded in favour of the other, as could be shown for the visual and vestibular systems by Dieterich, Brandt and colleagues in functional magnetic resonance tomography [Bucher et al 1998, deWaele et al 2001, Brandt et al 1998, 1999 and 2002, Marx et al 2004, Dieterich et al 2007 and 2008, Bense et al 2000, 2004 and 2009, Deutschländer et al 2009]. This conflict had to be

avoided in this study, in order to investigate vestibular-neck interaction alone. By having subjects close their eyes, no visual-vestibular conflict could occur in those subjects with erroneous vestibular-neck interaction; otherwise their vestibular-neck deficits would probably have been attenuated (and consecutively underestimated) in comparison to subjects with intact vestibular-neck interaction. In this context, the visual system plays a corrective, antagonistic role in the visual-vestibular-proprioceptive system. Future co-operation studies will further investigate these relations between sensory and motor systems [Brandt et al 1998, 1999 and 2002, Dieterich et al 2007 and 2008, Bense et al 2000, 2004 and 2009, Deutschländer et al 2009, Schneider et al 2009].

5.6 General theories on cerebellar function revisited

The function of the cerebellum has originally been described by the deficits upon its lesion [Ito 1984, Diener et al 1992, Trouillas et al 1997, Mori et al 2004, Thach et al 2004].

The true mechanism of the cerebellar circuitry remains unknown to the present date, although several models have been developed to explain its inner workings. Early models were proposed by Marr, Albus and Ito [Ito 1984, Thach et al 1992 and 2004] and by Miles and Lisberger; both were systematically reviewed by Boyden and colleagues [Boyden et al 2004]. Each model is based on cerebellar microarchitecture and clinical observations in vestibulo-ocular reflex pathology.

Computational neuroscience has brought forth new approaches to the problem, suggesting more comprehensive models of cerebellar control [De et al 2000, Kistler et al 2000]: the cerebellum, the deep cerebellar nuclei and the inferior olive are considered as a functional unit in present opinion [Kistler et al 2000, Boyden et al 2004, Mori et al 2004, Thach et al 1992 and 2004]. Several reverberating circuits and time window control for “pseudo-digitalisation” in these structures [Batton et al 1977, Aizenman et al 1998 and 2000, De et al 2000, Kistler et al 2000, Karakossian et al 2004] allow cerebellar signals to be processed – instead of the usual millisecond-range of neuronal activity – on a large timescale of several hundreds of milliseconds [Kistler et al 2000] or even seconds [Karakossian et al 2004]. These timescales may probably correspond to timescales relevant in postural control and during long-lasting vestibular modulation by our galvanic vestibular stimuli and physical stimuli on a similar timescale.

The midline cerebellar region, including the anterior lobe vermis and the rostral fastigial nucleus with its “cerebellar locomotor region” [Mori et al 2004], are key structures for the coordination of stance and gait

Matsushita et al 1971(1), Diener et al 1992, Thach et al 1992, Siebold et al 1997, Trouillas et al 1997, Büttner et al 1991 and 2003, Mori et al 2004, Thach et al 1992 and 2004, Ilg et al 2007. The more lateral structures are not considered here Thach et al 1992.

Studies with focus on gait analysis in cerebellar patients Mori et al 2004, Thach et al 2004, Ilg et al 2007 revealed highly variable step width, stride length, speed, periods of ground contact and a characteristic increase of temporal movement variability across joint segments. Across the multi-joint model of the walking human, cerebellar deficiency could be seen as a "lack of active oscillation damping" Thach et al 1992 and 2004, resulting in "asynergia" of the individual body segments, speaking in the terms of the aforementioned cerebellar reverberating circuit theory.

Similar in-detail studies on possible similar deficits in stance "synergia" of the multi-segment human have not been performed yet, but probably quite similar restrictions in postural compensation to physical perturbance could apply.

Can the deficits in vestibular-neck interaction found in our experiments also be subsumed under "multi-segment asyergia", as described in the cerebellar gait studies? Or could this effect be a completely different type of central processing deficit?

5.7 A separate entity of the anterior lobe syndrome?

The total Klockgether score was only very weakly related to vestibular-neck interaction deficits, while the trunk-specific ataxia symptoms "gait and stance ataxia" were not. As a consequence, vestibular-proprioceptive interaction may possibly be independent from the entities of "gait ataxia" and "stance ataxia", as tested in clinical routine by having patients stand and walk under visual observation. So the question is, whether this "vestibular-neck ataxia" might be a fully independent sub-type of trunk ataxia.

Studies defining "multi-joint asynergia" Mori et al 2004, Thach et al 2004, Ilg et al 2007 primarily referred this term to deficits in joint movements. The cerebellar deficit approached by our study, in comparison, refers to mal-adaptive re-alignment of sensory reference frames.

Thus, we propose the following theory:

In a neutral head-on-trunk position, the underlying amount of trunk ataxia manifests in the cerebellar

patient. Once the head is turned away from the centre, however, mal-adaptive coordinate re-alignment can come into play with increased dystasia: the “basic” gait and stance ataxia results in stance full of unplanned small excursions. Additionally, natural small body excursions due to breathing and short-loop spinal reflexes constantly disturb balance.

During a head turn away from the neutral position, unplanned movements of the body cannot be sufficiently compensated for by postural reflex arcs, as would be normally. When the compensation to these atactic unplanned movements is wrongly directed, due to the supposed coordinate mal-alignment, additional unplanned movements are added to the basic stance ataxia, multiplying its effect. Analogous mechanisms would also apply for gait ataxia.

This theory would form a probable explanation to the clinically observable increase in gait and stance ataxia during lateral head excursions, as seen in our patients with vestibular-neck-interaction deficiency.

We suggest there may be “vestibular-neck ataxia” next to – and possibly also independent from – the two types of classic joint asynergia called “gait ataxia” and “stance ataxia”. The possible independence from the other ataxia entities might relate to the missing statistical correlation between the clinical vestibular neck testing and the clinical assessment of gait and stance ataxia, as well as the weak correlation with the overall Klockgether score.

Figure 33 illustrates the proposed concept of gait-, stance- and vestibular-neck ataxia resulting from cerebellar disease: vestibular-neck ataxia can appear in severe cerebellar deficits, additional to gait- and stance ataxia. It was not observed without considerable other deficits in palaeo-cerebellar function in this study, possibly because vestibular-neck interaction is a more robust function, or its circuits are more redundantly (and possibly also bilaterally) imprinted. Its primary manifestation is mal-compensatory postural control during lateral head excursions.

Figure 33

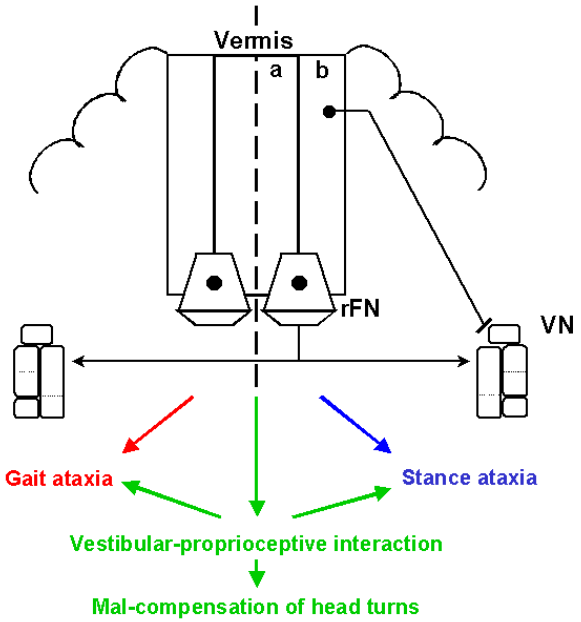


Figure 33:

This figure illustrates the proposed concept of different anterior lobe syndrome entities. Vestibular-proprioceptive interaction mechanisms may exist independently from those manifesting with gait- and stance ataxia upon lesion. Deficits in inter-sensory interaction however can aggravate symptoms of the two forms of multi-joint coordination “gait ataxia” and “stance ataxia”. The illustration of cerebellar circuitry is based on figures 8 (p. 21) and 10 (p. 29).

Figure created with Microsoft Office©

Whether the Purkinje cells of the anterior lobe vermis [Manzoni et al 1998, 1999 and 2004] or the vestibular-only-cells of the rostral fastigial nucleus [Kleine et al 2004] are responsible for vestibular-neck interaction individually or as a whole functional unit, could not be distinguished by the mode of this study, due to the predominance of general cerebellar atrophy.

Anatomical and physiological data suggest that the circuitry including the cerebellar cortex, its nuclei, the inferior olive and the brainstem vestibular nuclei form such a functionally tightly-knit unit, that damage to one part would inadvertably influence or take out the mechanism as a whole. Computational Neuroscience with its neural modelling capabilities, incorporating data from clinical and neurophysiological trials, could provide striking answers. This topic will be subject to future research.

We conclude that in humans vestibular-neck interaction is probably a paramount feature of the cerebellar functional complex [Mori et al 2004]. In analogy to animal single cell recordings, structures like the anterior lobe vermis and the rostral fastigial nuclei in man may be decisively involved.

This proposed concept may explain for bilateral attenuation of the postural vestibular-neck interaction

response in patients with severe bilateral cerebellar disease.

However, it could not yet account for findings in the lateralized cerebellar syndrome. In patients with left-predominant ataxia, a change from linear vestibular-neck interaction to non-linear interaction was found in the more affected left side, but not in the less affected right side. This specific non-linear asymmetry has not been reported before.

The dissociation in non-linear vestibular-neck interaction towards the more affected side and the constant linear interaction towards the other might speculatively indicate two cerebellar circuits, computing vestibular-neck interaction for each side. However, why lateralization manifests in an exponential relation between head-on-trunk position and sway direction, instead of a unilaterally attenuated linear relation across all head positions of one side, remains entirely unknown.

Further research in lateralized cerebellar syndromes in coordination with Computational Neuroscience approaches might possibly construct mathematical models of unilaterally defect cerebellar circuitry, possibly identifying the computational source and functional nature of this novel finding.

5.8 Suggested clinical implications

The idea of a separate type of ataxia next to gait and stance ataxia and the other manifestations of cerebellar deficits like dysdiadochokinesis, limb ataxia, intention tremor, dysarthria and oculomotor deficits suggests an amendment to the clinical rating score according to Klockgether and colleagues [Klockgether et al 1990, Masur et al 2003]: we propose a 5-grade range of vestibular-neck interaction, to reflect the different amounts of vestibulo-proprioceptive interaction deficits encountered in our patients, both experimentally and clinically (see Table 33).

This score amendment allows clinical stratification with respect to head-neck interaction based on the experimental findings of our study. It can be easily used together with the established Klockgether clinical score as part of everyday clinical examination to appraise a previously neglected, but clinically important component of the cerebellar syndrome.

The proposed amendment is easy to assess and can be performed in less than one minute.

Table 33

Head-Neck Dyssyergia	
0	none
1	increased gait ataxia with head turn, eyes closed
2	increased stance ataxia with head turn, eyes open gait with head turn and eyes closed only with permanent assistance;
3	gait in neutral head position possible gait with head turn and eyes closed not possible at all;
4	gait in neutral head position possible
5	Not able to perform any gait or stance tasks.

Table 33:

The proposed amendment to the Klockgether clinical ataxia rating score allows to objectively measure head-neck coordinate re-alignment deficits. In case of a side preference, the worst performance is evaluated.
According to experimental results in this study, patients scoring <8 points in the present score would score no additional points here; patients with ≥8 points within controls' slope confidence intervals would score 1-2 additional points (independent from a possible lateralization) and patients in this study outside the slope confidence intervals would be rated with 3-4 additional points.
Non-ambulatory patients, who cannot perform any of the above tasks, are rated with 5 points each for "gait" and stance" in the original Klockgether score and would be given another 5 points for vestibular-neck interaction deficits. Such patients could not participate here by study design.

Table created with Microsoft Excel©

Patients with a total clinical score lower than 8 points in the original Klockgether score would not get additional points. Patients in our study with more than 8 points in the original score and body sway slopes within 95% confidence intervals of control subjects would get a rating between 1 and 2 in this amendment scale, irrespective of cerebellar ataxia lateralization; those with slopes outside of controls' confidence intervals would score 3-4 points. Bedridden patients were not considered in this study. The overall possible score would increase from a total of 35 to 40 points.

The stratification between 1 and 2 points in particular, applying for patients with slopes within controls' confidence intervals, was introduced because an increase in stance ataxia with open eyes during head turns compared to head neutral position was found in 4 of the 7 patients, but irrespective of ataxia lateralization. Clinically describing a possibly distinct symptom, it might allow for patient stratification in future studies. In the present study, it could not yet be correlated to ataxia lateralization or other patient characteristics.

Future research will have to evaluate this proposed amendment with respect to objectivity and test-retest- and inter-rater-reliability. Validity may be tested in relation to GVS sway directions in a large collective.

Currently, none of the present ataxia scores specifically relates to lateralization.

5.9 Prospectus

Subsequent studies will have to validate the proposed amendment to the Klockgether scoring system in a clinical and electrophysiological context.

The present study could only investigate ambulatory cerebellar patients by design; therefore studies on severely affected bedridden cerebellar patients, either due to progression of their atrophic disease or due to acute neurological disease like ischemic stroke or hemorrhage should be performed. Galvanic vestibular stimulation in combination with surface electromyography of early and late myogenic responses with respect to head-on-trunk position may be a promising setup in bedridden patients. Such an experimental setting may be established as a portable device, being able to be carried to patients at intensive care units or in ambulatory care.

The novel finding of ipsilateral asymmetric non-linear vestibular-neck interaction in lateralized cerebellar syndromes will pose questions to Computational Neuroscience, asking for mathematical models explaining for the observed unilateral nonlinearity.

Also the question of cerebellar cortical and/or deep nuclear involvement has not yet been solved.

Visual influence forms decisive interaction with vestibular and proprioceptive systems. Cerebellar involvement in this circuitry will be under future scientific scrutiny. Other brainstem structures than the cerebellum are supposedly also involved in vestibular-neck interaction, based on anatomical data. Different patient groups with brainstem pathology might enlighten the view on vestibular-neck interaction.

The present study has provided a small step in multi-sensory interaction research.

6 Summary

6.1 Summary in English

This study investigated patients suffering from cerebellar disease with respect to their ability to merge vestibular and neck-proprioceptive sensory information in the central nervous system, given indication from animal studies, that the cerebellar midline structures anterior vermis and rostral fastigial nucleus are decisively involved in this form of inter-sensory interaction.

The vestibular system in the head detects external perturbation on upright posture. Such perturbation must be counter-acted by trunk and leg muscles, in order to maintain stability. The head with the detecting vestibular sensors is highly mobile against the trunk. Therefore, information from the neck proprioceptors must re-aligned centrally in order to elicit adequate postural reactions, despite the changed reference frame of the vestibular organs against the trunk.

20 cerebellar patients and 12 healthy control subjects were investigated clinically with respect to the effects of static horizontal head-on-trunk excursions on posture control in a clinical trial with specific gait and stance tests and in an experimental trial under sinusoidal, binaural, bipolar galvanic vestibular stimulation at 0.16 Hz, a method known to evoke a defined vestibular illusion. Their static head-on-trunk position was systematically altered in the head-horizontal plane: 0° straight ahead and 30°, 45°, 60°, each left and right. Postural compensation reactions to galvanic stimulation were recorded by a Kistler-type force-transducer platform. The clinical trial for vestibular-neck interaction was walking and stance with open and closed eyes during lateral head excursions versus neutral head position.

The overall amount of cerebellar disease in patients was clinically assessed by the ataxia rating score according to Klockgether and colleagues.

Patients were grouped, depending on the experimentally obtained vestibular-neck interaction ability, clinical vestibular-neck testing and a clinical cut-off at 8 Klockgether points:

Cerebellar patients with pronounced GVS-evoked vestibular-neck interaction deficits across all 7 head-on trunk positions and at least 8 of 35 Klockgether points could not account for clinical and experimental vestibular perturbations with adequate directions of postural adjustments during lateral head turns. Multi-variate repeated measures analysis of variation of experimental data suggested highly-significant difference ($p < 0.001$) between these patients' and control subjects' body sway directions. Irrespecive of their head-on-trunk position, these severely affected patients maintained the direction of the defined galvanically-induced body sway, as if the head would have remained in the straight-looking position. Clinically, these patients were not able to walk during lateral static head-on-trunk excursions, whereas it was possible to all of them with neutral head position.

Patients with scores ≥ 8 and lateralized cerebellar symptoms (n = 4) exhibited a previously unreported asymmetric, hypo-compensatory, non-linear vestibular-neck interaction to head excursions ipsilateral to the predominant side, whereas vestibular-neck interaction to the less affected side remained linear and fully compensatory.

Both patients scoring < 8 Klockgether points and control subjects were able to fully account for head-excursions by adjusted postural reflex directions; their galvanically evoked body sway turned in alignment with the degree of lateral head excursion, keeping it aligned with a head-centred reference frame. This intact compensation allowed these mildly affected patients to walk and stand with turned heads just like healthy controls.

Analysis with respect to the clinical gait and stance ataxia sub-scales of the Klockgether score suggested, that the observed deficit in vestibular-neck interaction appears to be an independent cerebellar ataxia symptome. The deficit provides striking evidence of a previously neglected, but decisive component of the cerebellar syndrome. The authors suggested an amendment to the established Klockgether clinical rating score, obtaining a surrogate marker for this newly observed deficit.

Review of anatomical and physiological literature implies that the closely-knit circuitry of the cerebellar midline structures and brainstem nuclei (like the vestibular nuclei and the inferior olive) provide the

central interaction site for vestibular and neck-proprioceptive interaction not only in animals, but also in humans. The presented study has given evidence that the cerebellum, as part of this functional circuitry, leaves certain patients with mal-adaptive vestibular and proprioceptive intersensory interaction upon its lesion.

Future studies will focus on other parts of this functional circuitry and the influence of visual cues on this network. Refined clinical scoring and cerebellar functional assessment applications will be in focus, possibly even after acute cerebellar lesions in an intensive care unit setting.

The novel finding of asymmetric nonlinearities in vestibular-neck interaction among patients with lateralized cerebellar syndromes will be of particular interest, due to given hints at central vestibular-proprioceptive circuitry for individual sides.

6.2 Zusammenfassung auf Deutsch

Hinweisen aus tierexperimentellen Studien folgend, dass die Mittellinien-Strukturen des Kleinhirns (anteriorer Vermis und rostraler Nucleus fastigii) entscheidend an der inter-sensorischen Verschaltung von Gleichgewicht und Hals-Lagesinn beteiligt sind, untersuchte die hier dargelegte Studie Patienten mit Kleinhirnerkrankungen, ob diese die genannten Sinneseindrücke im zentralen Nervensystem adäquat miteinander verschalten können.

Das Gleichgewichtsorgan im Schädel erkennt von außen einwirkende Störungen, die zur Stabilisierung des Körpers von Muskeln in Rumpf und Beinen ausgeglichen werden müssen. Der Kopf mit den innenliegenden Gleichgewichtssensoren hat einen erheblichen Bewegungs-Spielraum gegenüber dem Rumpf. Während solcher Kopfauslenkungen müssen deshalb Informationen aus den Lagesensoren des Halses zentral miteinbezogen werden, um trotz der veränderten Lagebeziehung der Gleichgewichtsorgane zum Rumpf sinnvolle Haltungsstellreaktionen gewährleisten zu können.

20 Patienten mit Kleinhirnerkrankungen, vor Allem Kleinhirndegeneration, wurden hinsichtlich der Auswirkungen von konstanten, horizontalen Kopfauslenkungen auf die Haltungskontrolle untersucht: klinisch durch spezielle Geh- und Standversuche, experimentell durch sinusoidale, binaurale, bipolare galvanisch-vestibuläre Stimulation mit einer Frequenz von 0,16 Hz, welche für die Auslösung einer definierten Scheinwahrnehmung des Gleichgewichtssinns bekannt ist. Ihr Kopf wurde dabei seitlich ausgelenkt gehalten (0°, sowie 30°, 45° und 60°, jeweils nach links und rechts). Ihre Haltungsstellreaktionen wurden mittels einer piezoelektrischen Plattform vom Kistler-Typ aufgezeichnet. Die klinische Untersuchung der vestibulär – halspropriozeptiven Interaktion fand durch Stand- und Gangprüfung mit geschlossenen bzw. offenen Augen unter horizontaler Kopfauslenkung im Vergleich zu neutraler Kopfposition statt.

Das Ausmaß der klinischen Beeinträchtigung der Patienten wurde gemäß dem klinischen Bewertungsschema für Ataxie nach Klockgether eingestuft. Eine Kontrollgruppe aus 12 gesunden Individuen diente dem Vergleich.

Die Ergebnisse der Studie weisen auf eine Unterteilung der Kleinhirnpatienten hin, die anhand der Fähigkeit zur Verschaltung von Gleichgewicht und Lagesinn über alle 7 Kopfpositionen, ihres

Verhaltens im klinischen Test zu Kopf-Rumpf-Interaktion sowie einem Schwellenwert bei 8 Punkten im klinischen Beurteilungssystem nach Klockgether vorgenommen werden kann:

Patienten mit erheblichen klinischen Defiziten über alle 7 Kopfpositionen hinweg sowie mindestens 8 von maximal 35 Punkten nach Klockgether boten keine richtungs-adäquaten Haltungs-Stellreaktionen während seitlicher Kopfauslenkungen, sowohl unter klinisch wie experimentell beigebrachten Gleichgewichts-Störreizen. Eine mehrfaktorielle Varianzanalyse der experimentellen Daten deutete auf hoch signifikante Unterschiede ($p < 0{,}001$) zwischen der Richtung der Körperschwankungen dieser schwer betroffenen Patienten und Kontrollpersonen hin. Unabhängig von der Position ihres Kopfes auf dem Rumpf behielten sie die durch die galvanische Stimulation definierten Körperschwankungen so bei, als wäre ihr Kopf weiterhin in Neutralposition auf dem Rumpf. Klinisch war es ihnen unmöglich, mit geschlossenen Augen und mit seitlich ausgelenktem Kopf zu gehen, während sie dies mit neutraler Kopfposition sehr wohl konnten.

Erstmals konnte über eine asymmetrische, nicht-lineare und unterkompensatorische Beziehung zwischen Kopfposition und der Richtung der galvanisch evozierten Stellreaktionen ipsilateral zur vorherrschend betroffenen Seite bei Kleinhirnpatienten mit seitendominanter Ataxie und mindestens 8 Klockgether-Punkten berichtet werden ($n = 4$). Die vestibulär – halspropriozeptive Interaktion auf der weniger betroffenen Seite blieb dagegen voll kompensatorisch in einer linearen Beziehung zur horizontalen Kopfauslenkung.

Patienten mit weniger als 8 Punkten nach Klockgether zeigten – wie Kontrollpersonen – eine vollständig adäquate Anpassung ihrer Stellreaktionen im Bezug auf die Kopfauslenkungen: die galvanisch ausgelösten Schwankungen drehten sich abhängig von der Kopfdrehung, so dass ihre Richtung stets im Bezugssystem des Kopfes blieb. Klinisch konnten diese leicht betroffenen Patienten mit seitlichen Kopfauslenkungen genau so unbeeinträchtigt gehen und stehen wie gesunde Kontrollpersonen.

In Bezug auf die Klockgether'sche Einteilung von Gang- und Standataxie zeigte sich, dass es sich bei dem beobachteten Defizit von Gleichgewicht-Hals-Interaktion wohl um ein eigenes, unabhängiges Symptom der Kleinhirnataxie handeln könnte. Es wird deshalb eine Ergänzung des Klockgether-

Beurteilungsschemas vorgeschlagen, um ein klinisches Surrogat für dieses Defizit bestimmen zu können.

In Zusammenschau der zur Verfügung stehenden anatomischen und physiologischen Literatur stellt sich ein eng verknüpfter zentralnervöser Schaltkreis von Gleichgewicht und Lagesinn des Halses dar, bestehend aus den Mittellinien-Strukturen des Kleinhirns und Hirnstammkernen, wie den Vestibulariskernen und der Oliva inferior. Diese Verschaltung existiert wohl analog zu tierexperimentellen Daten auch beim Menschen. Die vorgestellte Studie hat gezeigt, dass Defekte des Kleinhirns – als Teil dieser Verschaltung – bei bestimmten Patienten zu einem Verlust oder einer Einschränkung der Transformation von kopf-bezogenen vestibulären Koordinaten zum Referenzsystem des Rumpfes führen können.

Zukünftige Studien werden sich mit anderen Teilen dieses funktionellen Schaltkreises und mit dem Einfluss visueller Stimuli auf dieses Netzwerk befassen. Wir werden uns verfeinerten klinischen Bewertungsschemata und neurophysiologischen Anwendungen zur Beurteilung der Kleinhirnfunktion widmen, auch nach akuten Kleinhirninsulten unter möglicherweise sogar intensivmedizinischen Bedingungen.

Die Entdeckung asymmetrischer nichtlinearer vestibulär-halspropriozeptiver Interaktion bei lateralisierter Ataxie ist von besonderem Interesse, zumal sich dadurch Hinweise auf seitenspezifische neuronale Schaltkreise für die Verschaltung vestibulärer und propriozeptiver Reize ergeben haben.

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8 Acknowledgements

Sincere thanks to the subjects who participated in the experiments, for their time and effort.

I am deeply indebted to my supervisor, Professor Dr. med. Ulrich Büttner for his outstanding mentorship and excellent support; I express whole-hearted thanks for his guidance and supervision throughout my training. He taught me to enjoy clinical medicine, both as a profession and a vocation.
Thanks to Dr. med. Justus F. Kleine for providing the idea to this study and his tremendous support with knowledge and technology. Despite his compulsive and trying ICU labour, he has always found time to provide help and constructive criticism of my work. Without him, this work would not have been possible.
Professor Dr. rer. nat. Jean A. Büttner-Ennever PhD encouraged me to undertake research at an early stage in my career. I deeply acknowledge her steadfast support and continuous kind guidance. Great thanks for having taught me the many things, which cannot be learnt from neuroscience texts.

Dr. rer. nat. Siegbert Krafczyk has established the posturography setting and provided unmatched technological expertise in the field. His much-needed assistance with data acquisition, analysis and his great equanimity with healing equipment (which had suffered tremendously at my hands) have more than just once saved the day.
Hans Hintermaier's construction of the experimental setup, his patience with a young medical student and his kind way quite literally formed the backbone of this work.
Dr. ing. Thomas Eggert provided immense patience with teaching me the principles of MatLab programming. His unmatched expertise in data analysis and statistics were indeed a much needed quality. His constructive criticism provided key elements to this study. Great thanks for his contribution.

Especially to Sigrid Langer and all colleagues of the Neurologische Klinik und Poliklinik and the Neurologische Forschung, technicians, researchers, past and present, I sincerely thank for their expert assistance, valued kindness and immense tolerance for research clutter.

The "Bernstein Centers for Computational Neuroscience" (BCCN) and the "Graduiertenkolleg 1091: Orientation and Motion in Space" provided financial support for this research. Tremendous thanks also to Professor Dr. med. Dr. h.c. Thomas Brandt FRCP, who provided excellent pre-conditions for productive research at the LMU University Hospital Großhadern.

Thanks to my parents, Luise and Rolf Kammermeier, and to Paul Doberauer, Catherine Conradty, Peter Bell, Bettina Schwarz and Alexa Arnoldi for words of encouragement in trying times and help to attain happiness in its many guises. I thank them for their love and guidance at the example of their own lives.

I dedicate this thesis to Paul Doberauer (1944 – 2008).

9 Curriculum Vitae and Declaration of Originality

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Declaration of Originality

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any other degree or diploma at the Ludwig-Maximilans-Universität München (LMU) or any other educational institution, except where due acknowledgement is made in this thesis. Any contribution made to the research by others, with whom I have worked at LMU or elsewhere, is explicitly acknowledged in this thesis.
I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

Munich, (Date) ..... (Signed) .....

10 Publications

10.1 Periodicals

Vestibular-neck interaction in cerebellar patients, S. Kammermeier, J.F. Kleine, U. Büttner, Annals of the New York Academy of Sciences; 1164 (2009) 394-399

Vestibular and neck proprioceptive interaction in cerebellar disease, J.F. Kleine*, S. Kammermeier*, U. Büttner; article in communication (* equal contribution)

10.2 Conference Abstracts

Impaired vestibular-neck interaction in cerebellar patients, S. Kammermeier, U. Büttner and J. F. Kleine, Proceedings of the Seventh Göttingen Meeting of the German Neuroscience Society and 31st Göttingen Neurobiology Conference 2007, Neuroforum Supplement 1 (2007), Vol. XIII, #T23-3B, ISSN 0947-0875

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10.3 Conference Plenary Lectures

TüMüZü Oculomotor Meeting, Tübingen, 2006

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2007 Neuroscience Meeting, San Diego, CA, USA

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