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# Functional multisensory integration and plasticity of vestibular reflexes

Olga Kuldavletova

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Normandie Université

## THÈSE

**Pour obtenir le diplôme de doctorat**

**Spécialité PHYSIOLOGIE ET BIOLOGIE DES ORGANISMES - POPULATIONS -  
INTERACTIONS**

**Préparée au sein de l'Université de Caen Normandie**

**L'intégration multisensorielle fonctionnelle et la plasticité des  
réflexes vestibulaires**

**Présentée et soutenue par  
Olga KULDAVLETOVA**

**Thèse soutenue publiquement le 21/02/2020  
devant le jury composé de**

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Normandie de Biologie Intégrative,  
Santé, Environnement



COMETE  
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# **Functional multisensory integration and plasticity of vestibular reflexes**

PhD thesis



# Acknowledgements

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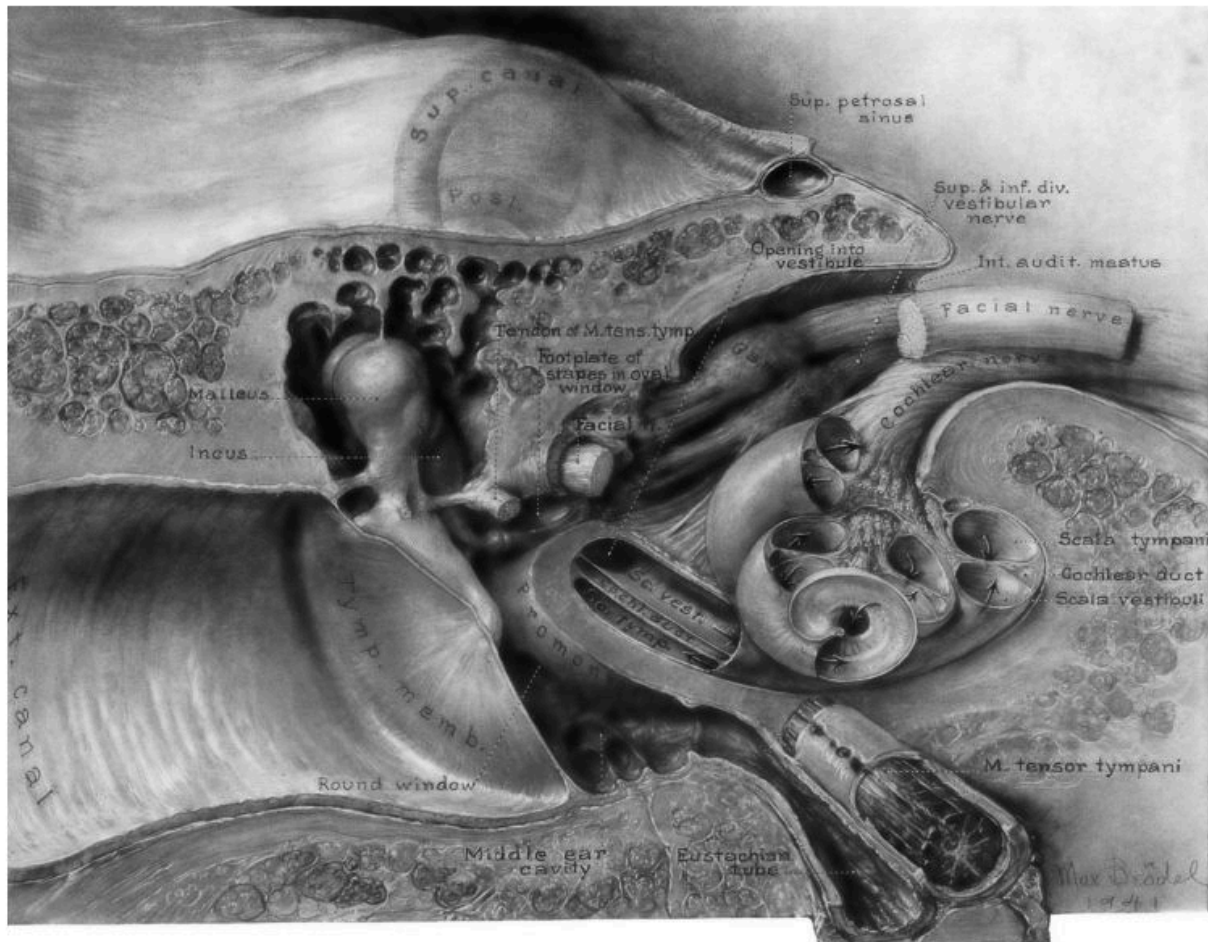
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I am the luckiest person in the world to know all of you.



**Illustration by Max Brödel, 1941.** A drawing of the temporal bone showing the relationships between the external ear canal with tympanic membrane, middle ear with ossicular chain, the cochlea and the internal auditory canal with vestibular, cochlear and facial nerves.

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# Abbreviations

## Anatomy

Amb – nucleus ambiguous [brainstem]  
AOS – accessory optic system [brainstem]  
CNS – central nervous system  
CVLM – caudal ventrolateral medulla  
DRG – dorsal respiratory group [brainstem]  
DVN – descending vestibular nucleus = IVN  
IL – intralaminar nuclei [thalamus]  
IO – inferior olive [brainstem]  
IVN – inferior vestibular nucleus [brainstem]  
LC – locus coeruleus [brainstem]  
LD – lateral dorsal nucleus [thalamus]  
LGN – lateral geniculate nucleus [thalamus]  
LP – lateral posterior nucleus [thalamus]  
LVN – lateral vestibular nucleus [brainstem]  
MGN – medial geniculate nucleus [brainstem]  
MIP – medial intraparietal area [cortex]  
MLF – medial longitudinal fasciculus [brainstem]  
MST – medial superior temporal area [cortex]  
MVN – medial vestibular nucleus [brainstem]  
NOT – nucleus of optic tract [midbrain/brainstem]  
NTS – nucleus tractus solitarius [brainstem]

NPH – nucleus prepositus hypoglossi [brainstem]  
NRTP – nucleus reticularis tegmenti pontis [brainstem]  
OMN – oculomotor nuclei [brainstem]  
PIVC – parieto-insular vestibular cortex [cortex]  
PNS – parasympathetic nervous system  
Psol – parasolitary nucleus [brainstem]  
RFN – rostral fastigial nuclei [cerebellum]  
RVLM – rostral ventrolateral medulla [brainstem]  
SCC – semicircular canals  
SNS – sympathetic nervous system  
SVN – superior vestibular nucleus [brainstem]  
VA – ventroanterior nucleus [thalamus]  
VI – ventral intermediate [thalamus]  
Vim – nucleus ventralis intermedius [thalamus]  
VIP – ventral intaparietal area [cortex]  
VL – ventrolateral nucleus [thalamus]  
VN – vestibular nuclei [brainstem]  
VNC – vestibular nuclear complex [brainstem]  
VP – ventral posterior nucleus [thalamus]  
VPI – ventral posterior inferior nucleus [thalamus]  
VPL – ventral posterior lateral nucleus [thalamus]



VPM – ventral posterior medial nucleus [thalamus]  
VRG – ventral respiratory group [brainstem]

## **Methods, materials, protocols, variables**

ANOVA – analysis of variance  
AP – arterial pressure  
BF – breathing frequency  
BVL – bilateral vestibular loss  
CBF – calf blood flow  
CCW – counter-clockwise  
CO – cardiac output  
COR – canal-ocular reflex  
cVEMP – cervical vestibular evoked myogenic potential  
CVR – calf vascular resistance  
CW – clockwise  
DAP – diastolic arterial pressure  
ECG – electrocardiography / electrocardiogram  
EtCO<sub>2</sub> – end-tidal volume (of CO<sub>2</sub>) [respiration]  
EVAR – Earth-vertical axis rotation  
FRC – functional residual capacity [respiration]  
GIA – gravito-inertial acceleration  
GVS – galvanic vestibular stimulation  
HD – head-down  
HDNE – head-down neck extension  
HDNF – head-down neck flexion  
HPF – high-pass filter  
HR – heart rate

HTOT – head-turn-on-trunk  
HU – head-up  
I-E (transition) – Inspiration - Expiration transition [respiration]  
LED – left ear down  
LP – lateral position  
LPF – low-pass filter  
IVOR – linear VOR  
MAP – mean arterial pressure  
MS – motion sickness  
MSNA – muscle sympathetic nerve activity  
MSSQ – motion sickness susceptibility questionnaire  
ND – nose-down  
NU – nose-up  
OOR – otolith-ocular reflex  
OVAR – off-vertical axis rotation  
RC – rotational comparator  
RED – right ear down  
RFT – rod-and-frame test  
RNI – rotational neural integrator  
SD – standard deviation  
SEM – standard error of the mean  
SPV – slow phase velocity  
SSNA – skin sympathetic nerve activity  
SV – stroke volume  
TC – time constant  
Ti – inspiratory time  
tVOR – translational VOR  
UVL – unilateral vestibular loss  
VCR – vestibulo-collic reflex  
VHIT – video head impulse test  
VOR – vestibulo-ocular reflex  
VP – ventral position  
VR – virtual reality  
VSR – vestibulo-spinal reflex  
Vti – inspiratory tidal volume

# Introduction

The text of this thesis contains a large view on the problematic of vestibular-driven responses. A functional approach is used in the studies of the thesis, trying to reveal the underlying mechanisms of processing of vestibular information within a “black box” that receives sensory inputs and generates responses for outputs. Nevertheless, the underlying neural structures are reviewed in the Background section in order to illustrate a highly complex, distributed and multisensory character of the network transmitting and processing vestibular afference. Rather than considering just the peripheral vestibular apparatus and its functions in isolation, the vestibular function is viewed as the overall structure, which includes multiple sensory sources and their integrations. We will show that this circuitry is multisensory, individually tuned and plastic.

In the Background part of the text, we will describe the anatomy and physiology of the vestibular apparatus and the central organization of the processing of vestibular signals and their integration with other sensory signals at every step of processing. Then we describe the main responses driven by the vestibular system, focusing first on the stabilization reflexes, the Vestibulo-Ocular, Vestibulo -Spinal and -Collic and Vestibulo-Sympathetic Reflexes, and after on some higher functions such as estimation of the gravity vector. Then we describe what reactions might occur when the vestibular stimulus is out of the natural range and causes the conflict in the sensory processing. These include perceptual illusions and motion sickness. The conflict, occurring persistently, can be a signal for the brain to review the previous sensory processing strategies, so in the next part we are focusing on the plasticity of vestibular responses. Finally, the last part of the Background section would be a brief list of the natural (e.g. induced by motion or orientation) and non-invasive methods used in the research for vestibular stimulation in Human.

In the Experimental part of the text, four experimental studies of the thesis are presented. Three studies are presented as texts of papers, published in peer-reviewed journals. One study that has not yet been published is described with the preliminary, though incomplete results. Study I (published) contains the publication on the vestibulo-sympathetic reflex in patients with bilateral vestibular

loss, assessed with the help of the Head-Down-Neck-Flexion (HDNF) protocol. The results indicate that BVL patients present the same cardio-vascular response to changes in head position with respect to gravity as normal subjects. Two possible explanations of this finding are discussed. Additionally, the significance of the vestibulo-sympathetic reflex in Human is questioned. Study II (published) assesses the influence of graviceptors stimulation initiated by off-vertical axis rotation on ventilation. In this study, the effect of trunk graviceptors and otolithic graviceptors is switched in phase with the Head-Turn-On-Trunk (HTOT) protocol. The phases of the respiratory synchronization to Off-Vertical-Axis-Rotation (OVAR) were analysed in order to find a dominant source of graviceptor information for respiratory synchronization. The portions of the vestibular and graviceptor impact were found to be individually weighted. Study III uses the OVAR stimulation combined with Virtual Reality visual stimulation to assess the effect of visual stimulation, driving self-motion perception, on autonomic control. The mean levels and modulation of the cardio-vascular and respiratory responses are analysed through different stimulation combinations. The significant effect of OVAR in comparison to non-OVAR (visual-only) stimulation was found for the mean values of cardio-vascular and respiratory parameters. Also, the sustainable and variable between individuals neural effect on the modulation of arterial pressure is observed. Further analysis is required for this study. Study IV (accepted for publication) assesses the vestibulo-ocular responses, visual field dependence and motion sickness in a population submitted to vestibular stimulation out of the normal range (aerobatic pilots) in comparison to control subjects. Contrary to what was expected, the aerobatic pilots did not present clear vestibular habituation. The mechanisms of plastic changes are discussed in attempt to find a possible explanation of the finding.

Finally, in the General Discussion part, the results of all the four studies of the thesis are discussed within a general context.

# **Part I: Background**



# Vestibular system

The vestibular system is one of the earliest sensory systems developed in living organisms during evolution. However, it is still present and important in almost any life form.

In humans, the sense of balance is represented primarily, but not solely by the vestibular system. Anatomically simple and small, a few millimeters in size, the vestibular organ is linked in human with a complex neural interactions network, that has been drawing attention of researchers for many decades. Indeed, the vestibular system has been shown to be involved in control of numerous motor, autonomic and cognitive functions, and the importance of its understanding is hard to overestimate, especially in the era of the intensive development of transport systems.

## 1. Introduction

The vestibular apparatus is an important part of spatial orientation system. This small and simple organ detects accelerations of one's head. Linear acceleration and angular velocity are coded by the sensory organs of the vestibular system and transmitted by the vestibular nerve to the vestibular nuclei in the brainstem. By multiple pathways and in different combinations the vestibular information is redistributed into numerous brain zones to affect multiple functions, from maintaining clear vision during movement to cardiovascular control during postural changes.

Just as this sense is involved into a variety of operations, many other inputs are involved into processing of vestibular information. Unlike other sensory systems that have major pathways and cortical zones, the vestibular system forms a fine neural web that distributes and integrates sensory information at all levels from brainstem to cortex. This integrative and distributed character makes the vestibular research challenging. We can close our eyes, we can plug ears, but we cannot naturally abolish the vestibular sensory signal. All the possible natural

stimulations delivered with movement or the orientation changes would inevitably affect other sensors in addition to the vestibular ones. Somatosensation, vision, cognition add to the vestibular sense. Therefore, the choice of an adequate stimulation and examination technique is crucial.

Basically, vestibular function is often reduced to the reflexive control of posture and gaze. However, the spectrum of vestibular activity is much larger.

Here, we describe the main pathways that transfer the vestibular information in different brain zones. Vestibular information does not travel alone, so we describe the sensory integration that happens at every step of processing.

Then, we present different functions, in which the vestibular information is involved. We describe the reflexes, such as vestibulo-spinal and the vestibulo-ocular reflexes. We demonstrate that the sense of gravity direction requires a complex processing and estimation. We also present the link existing between the vestibular inputs and autonomic control.

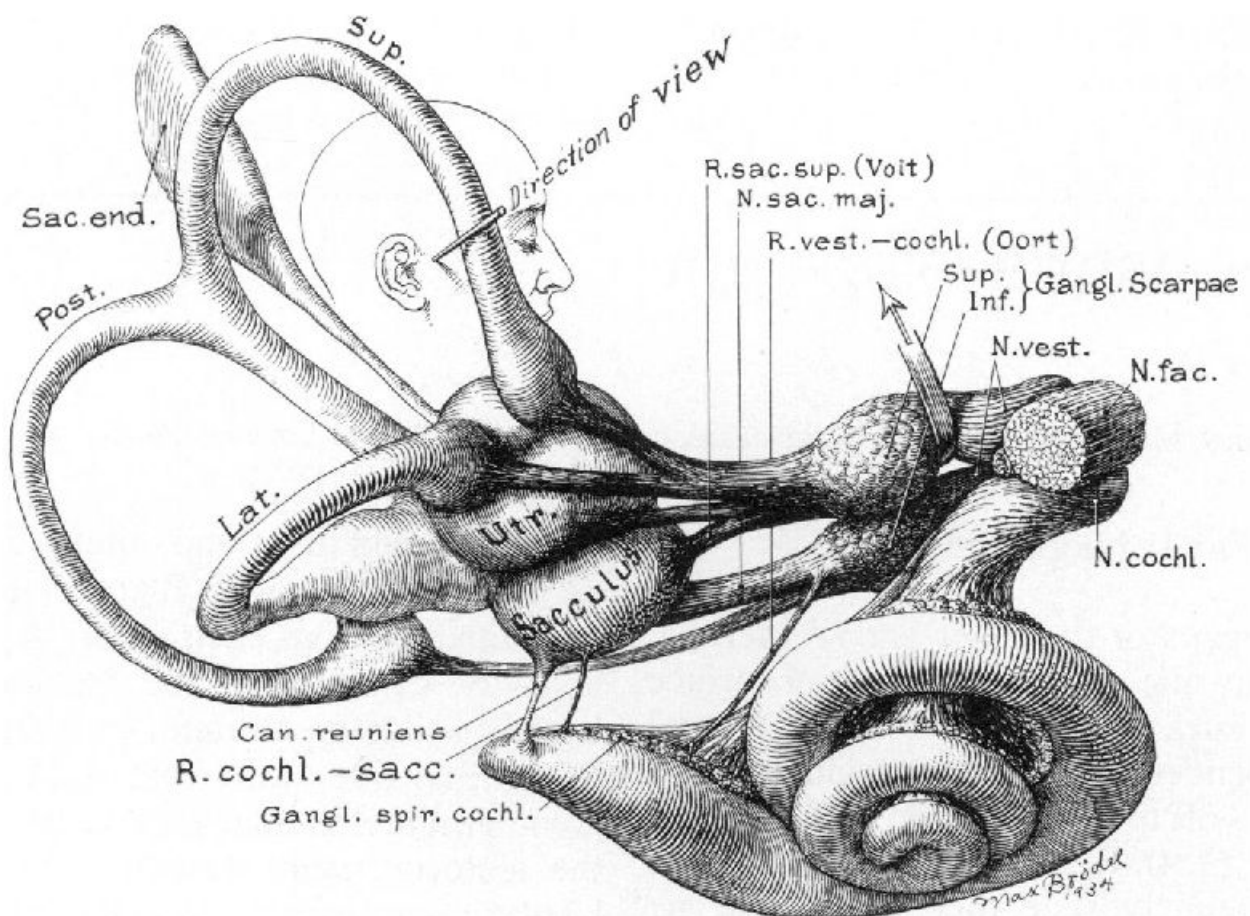
All these functions require integration with other sensory inputs and internal estimation of the postural and orientation changes. Under unnatural conditions, the estimates can be erroneous and conflicting. We describe the consequences of such conflicts that lead to perceptual illusions or motion sickness.

According to the dominant hypothesis, the same error in the estimate can lead to the neural rearrangement of the sensory processing. We describe findings related to plastic changes of vestibular processing in response to persistent changes in the vestibular or visuo-vestibular inputs. Those can be produced by laboratory experiment protocols (e.g. repetitive trials of rotation, wearing of magnifying glasses etc.), by a specific activity (e.g. gymnastics or piloting), or by deficits in the vestibular function.

Finally, we briefly introduce natural techniques that are used to stimulate the vestibular system. Some techniques would simultaneously stimulate the angular and linear acceleration sensors, some would act differentially on one receptor type. Angular acceleration is easier to induce in laboratory conditions, so the majority of the methods would be related to the stimulation of the receptors detecting linear acceleration and gravity.

## 2. Anatomy of the vestibular apparatus

Vestibular signals originate in the labyrinths of the inner ear. The organ is called the vestibular apparatus (Figure 1) and is composed of a system of bony tubes and chambers engraved in the bone of the petrous portion of the temporal bone (Figure 2), symmetrically on both sides. Lying within a bony structure, the membranous labyrinth contains the receptor organs for hearing (the cochlea) and equilibrium (five vestibular sensors) on both sides. The vestibular part includes three semicircular canals oriented orthogonally to each other and detecting angular velocity, and two chambers containing maculae: the utricle and the saccule that are usually referred to as the otolithic system.

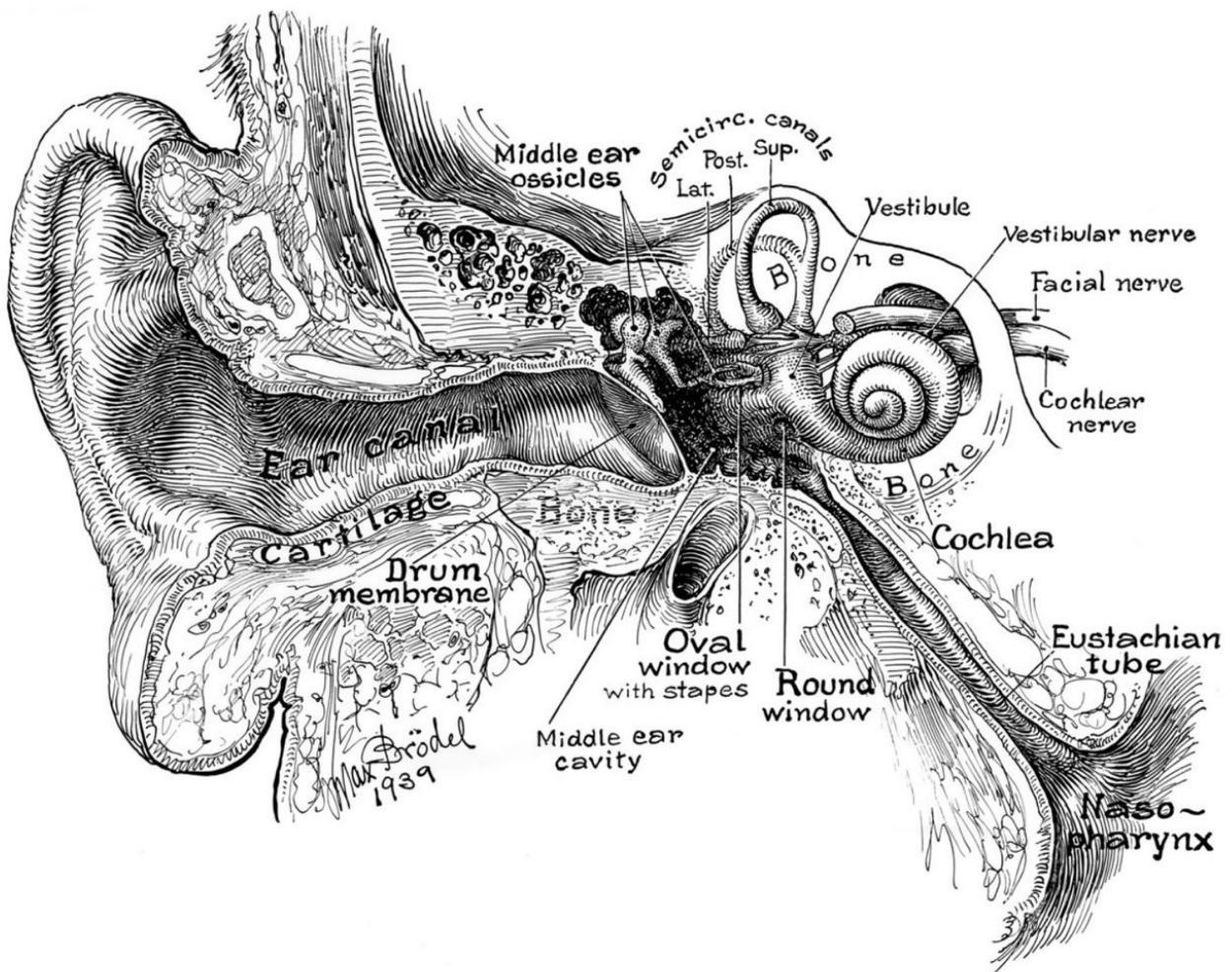


**Figure 1 – Anatomy of the vestibular apparatus, membranous labyrinth.**

Illustration by Max Brödel, 1934.



The membranous labyrinth is filled with endolymph, a sodium (Na<sup>+</sup>) -poor, potassium (K<sup>+</sup>) -rich fluid, whose composition is maintained by the action of ion pumps in specialized cells. Surrounding the membranous labyrinth, in the space between the membranous labyrinth and the wall of the bony labyrinth, another fluid – perilymph is contained. Perilymph is a high-sodium (Na<sup>+</sup>) and low-potassium (K<sup>+</sup>) fluid similar to cerebrospinal fluid, with which it communicates through the cochlear aqueduct. The endolymph and perilymph are kept separate (Herdman, 2007).



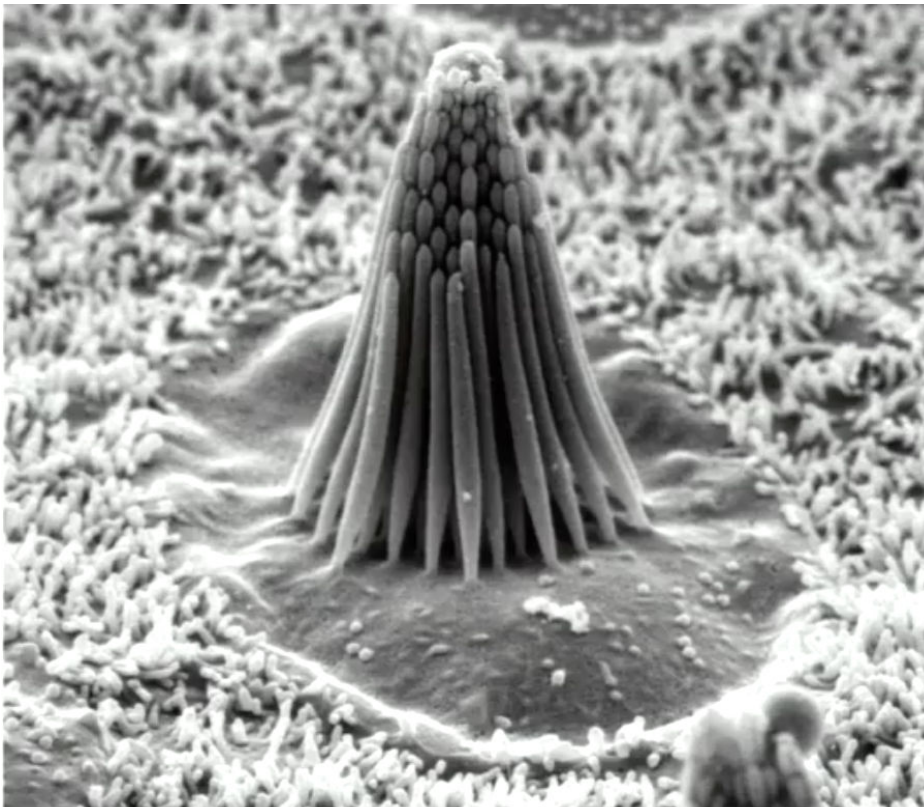
**Figure 2 – The inner ear and the location of the vestibular apparatus.**

Illustration by Max Brödel, 1939.

### 3. Hair cells and the transduction of a signal

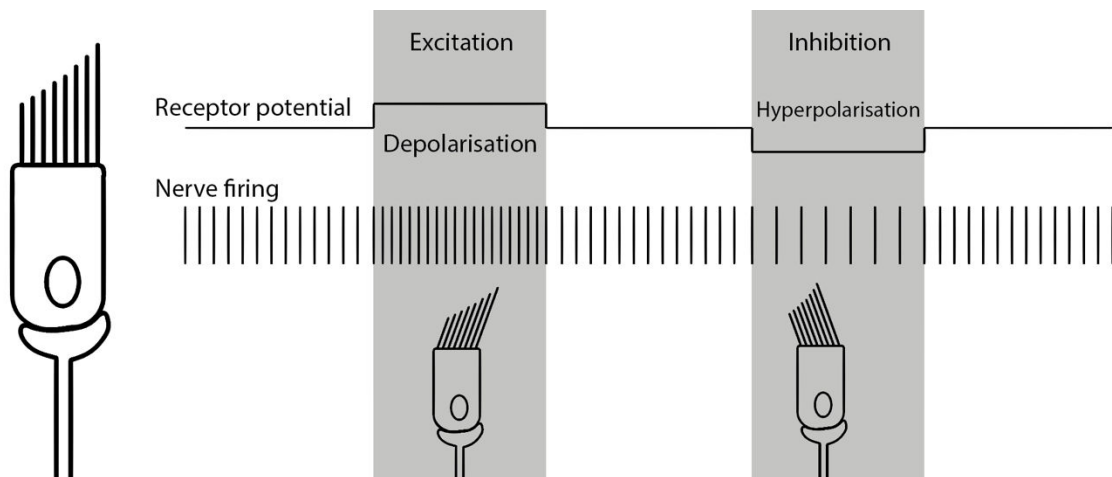
The vestibular sensory neuroepithelium forms either macula for the otolithic system or crista ampullaris for the semicircular ducts. Each of the five receptor organs has a cluster of hair cells responsible for transducing head accelerations into vestibular signals. Vestibular signals are then carried from the hair cells to the brainstem by branches of the vestibulocochlear nerve (cranial nerve VIII).

Each hair cell is embedded in a membrane of neuroepithelium and has a bundle of cilia called the stereocilia and one large cilium called the kinocilium (Figure 3). The stereocilia are grouped in a way that the lengths of the stereocilia increase gradually towards kinocilium.



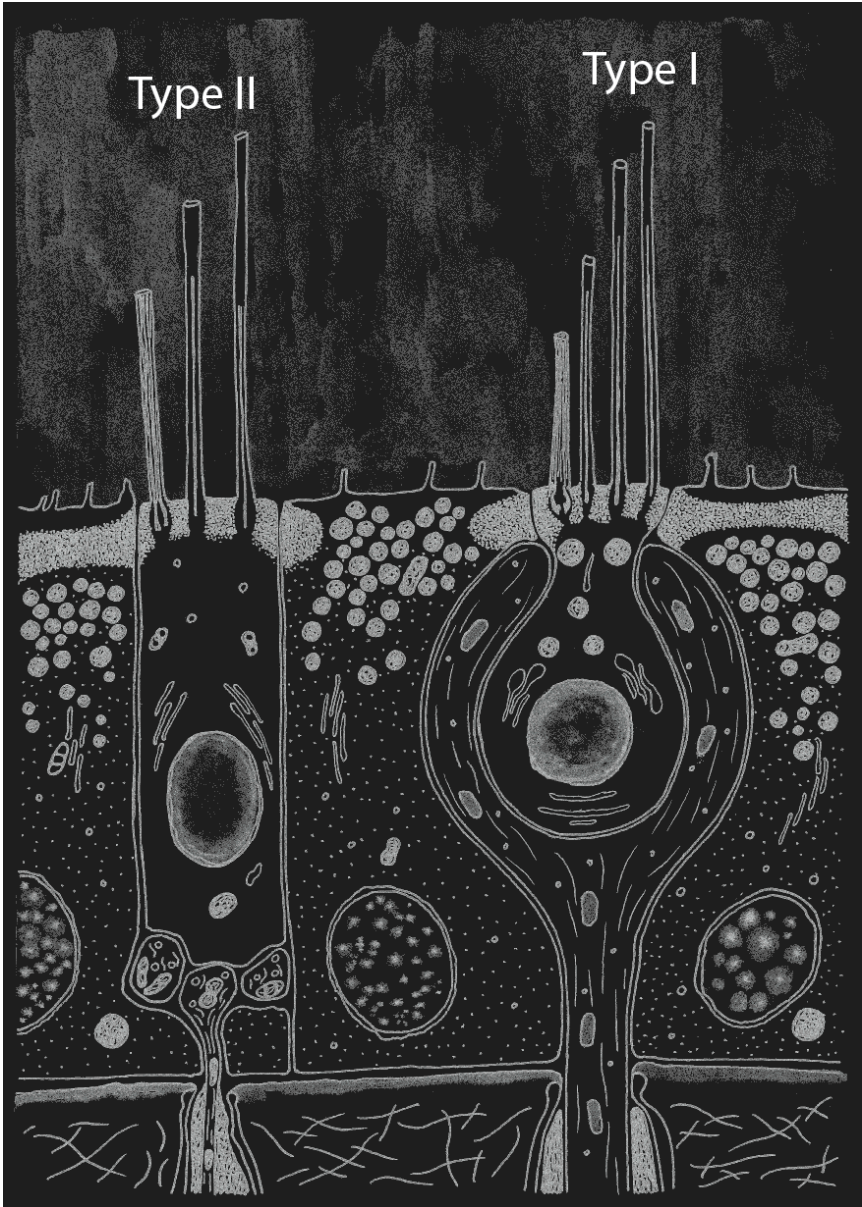
**Figure 3 – The cilia of the hair cell.** A high power scanning electron micrograph, demonstrating a bundle of cilia, gradually increasing in length. Image by the laboratory of David P. Corey, Howard Hughes Medical Institute.

Movements of the head lead to a deflection of the cilia in hair cells. The cilia are tied with each other by a protein-chain connection. When the otoconia weight or the fluid flow in the canals cause the cilia to bend, the cilia pull each other, opening or closing the ion channels leading to the hyperpolarization or depolarization of the cell. The membrane potential of a receptor cell depends on the direction in which the cilia bundle is bent. Deflection of stereocilia towards the kinocilium causes potassium channels in the apical portions of the stereocilia to open. Potassium flows into the cell from the endolymph, causing the cell membrane to depolarize and the rate of firing in the afferent fibers increases. Bending away from the kinocilium causes the cell to hyperpolarize, thus decreasing the afferent firing rate (Figure 4).



**Figure 4 – Hair cells receive mechanical stimuli and transduce it into neural signals.** Bending of the cilia towards kinocilium excites the cell, increasing the neural firing, while bending away from cilia decreases firing and inhibits the cell.

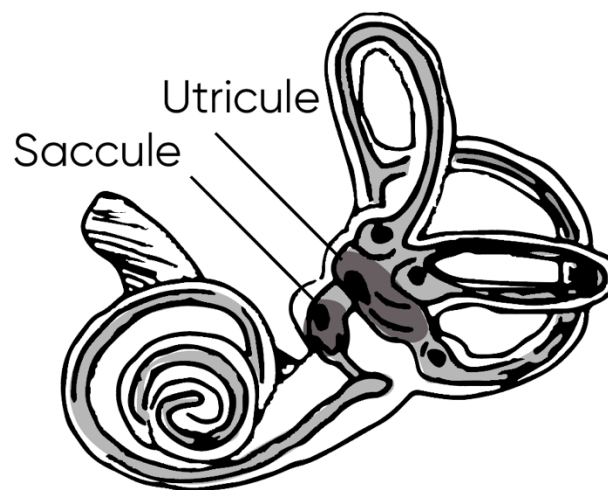
There are two structural types of hair cells in the inner ear (Figure 5). Type I cells are more round in shape and are inserted in a nerve calyx of the afferent nerve. These cells have irregular firing and produce variable interspike intervals. Type II cells represent the majority of hair cells of the inner ear. These cells have a normal synaptic connection to their afferent fibers. They create a resting discharge with rather low variability. The vestibular nuclei send efferent signals to the sensory hair cells to modulate their sensitivity (Khan & Chang, 2013).



*Figure 5 – Type I and Type II hair cells.*

## 4. Otolithic system

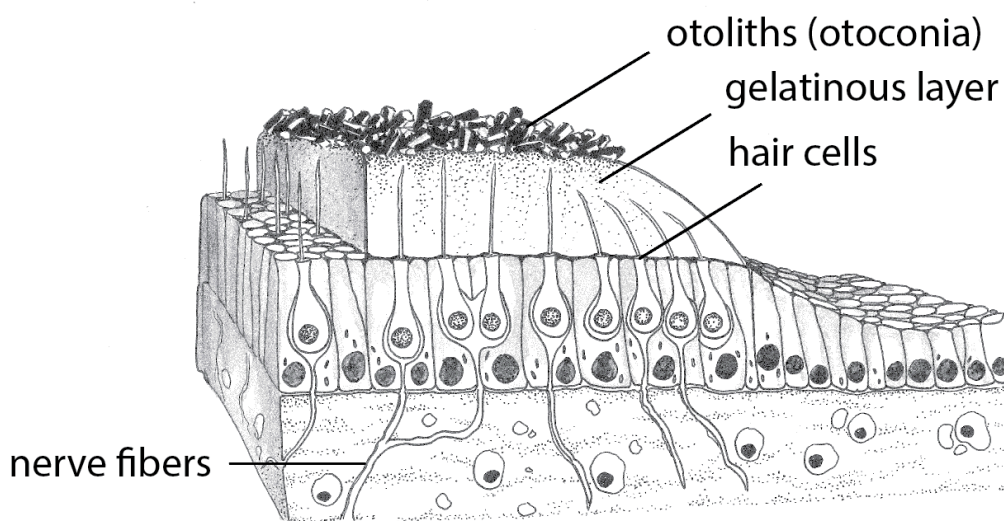
Each inner ear has two chambers called the utricle and the saccule (Figure 6). Each of these contains a sensory organ about two millimeters in diameter called macula. The macula of the utricle lies in the horizontal plane on the inferior surface of the utricle. It is oval in shape and connects to the membranous semicircular canals via five openings. It plays an important role in determining the orientation of the head with respect to the direction of linear accelerations including gravity. The macula of the saccule is located on the vertical plane on the medial wall of the saccule. The function of saccular macula is less clear, but it probably participates in the auditory function as well as in the spatial orientation detection, especially when the head is not in a vertical position.



**Figure 6 – The maculae.** The location of the saccule and utricle.

Each macula is covered by a gelatinous layer composed of acid mucopolysaccharides. Small calcium carbonate crystals called otoconia inserted on the top of the gelatinous layer (Figure 7). The otoconia range from 0.5 to 30 microns in diameter and are about 3 times heavier than the surrounding tissues. Thousands of sensory hair cells are embedded into the gelatinous layer. The bases and sides of the hair cells synapse with sensory axons of the vestibular nerve and transmit the captured signals to the nervous system. The human utricle contains approximately 30000 hair cells, whereas the saccule contains around 16000 (Goldberg, 2013).

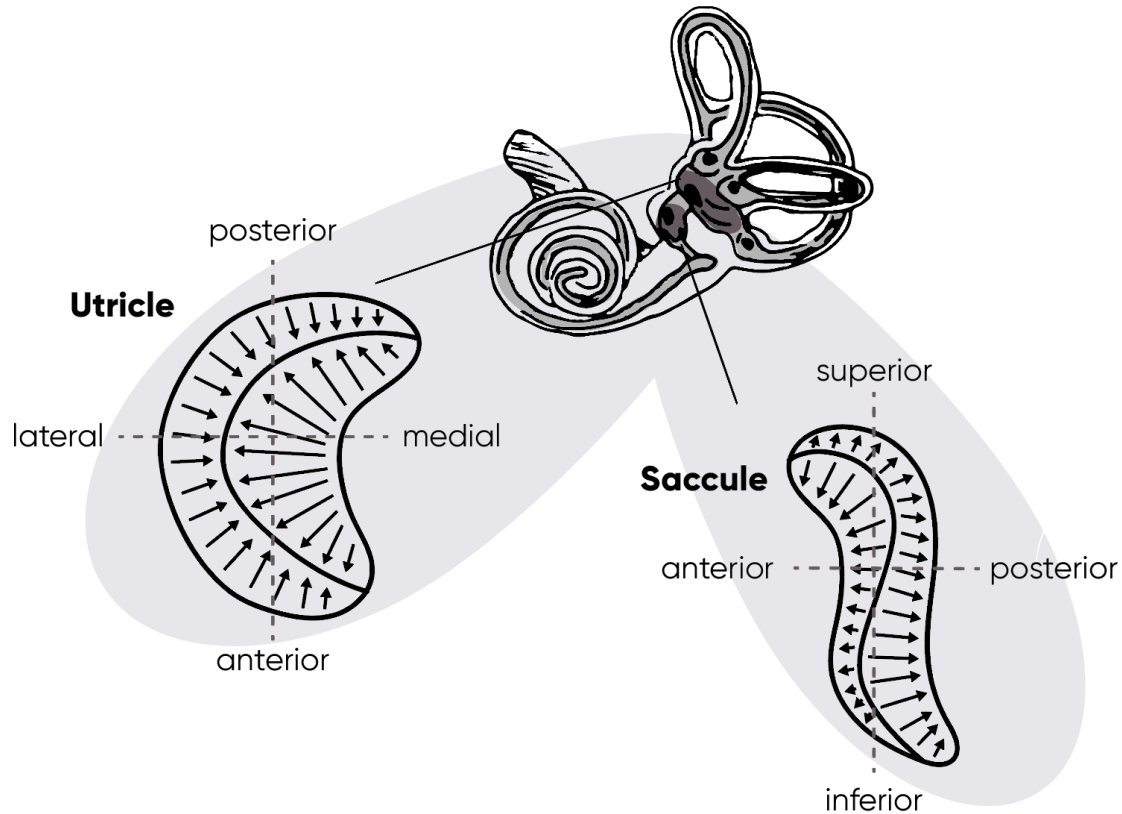
At rest, most of the nerve fibers leading from the hair cells are continuously firing with a frequency averaging at 90 impulses per second, for primates. When the head is accelerating or changing its position with respect to gravity, the weight of the otoconia bends the cilia of hair cells. This bending of the cilia towards the kinocilium increases the impulse traffic in its nerve fibers, while bending to the opposite direction inhibits the impulse traffic. Different hair cells are oriented in different directions, so the sensor has a specific signal pattern for every direction of head's orientation.



**Figure 7 – The macular structure illustration.** The otoconia are placed on the top of the gelatinous layer, into which the hair cells are embedded.

The directions of hair cells are separated by a distinctive curved zone running through the center of each macula called the striola (Tascioglu, 2005). The hair cells of a macula on each side of the striola are oriented so that their kinocilia point in opposite directions (Figure 8). In the utricle, the kinocilia face towards the striola and in the saccule they face away from it. As a consequence, displacement of macula's otolithic membrane in one direction has an opposite physiologic influence on the set of hair cells on each side of the striola. The striola is curved,

which allows hair cells to orient at different angles, detecting multiple directions of displacement.



**Figure 8 – Directional preference of the hair cells in maculae of the utricle and saccule.** The line separating the maculae in two parts with different directional preference is called the striola.

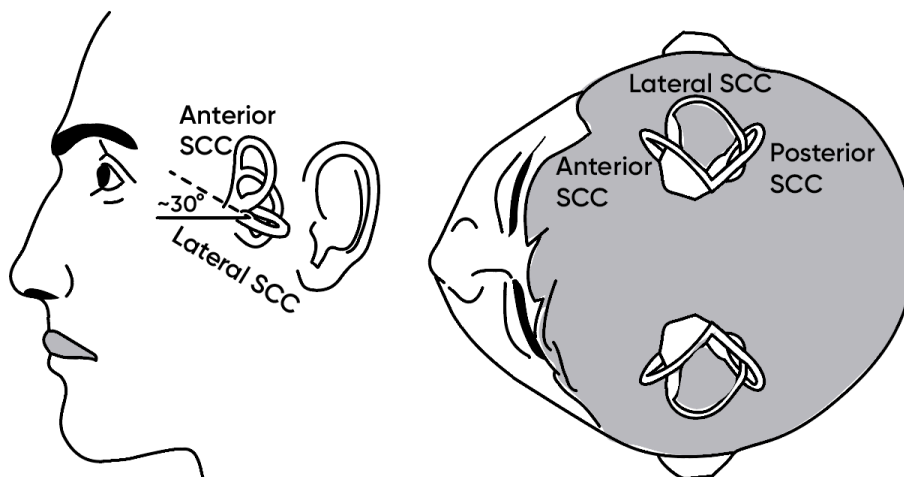
Maculae detect the tilt of the head with respect to gravity. In the near-vertical positions, the utricular macula can detect as little as half degree of tilt (Goldberg, 2013). This precision is required to maintain vertical balance and to launch the reflex responses for posture stabilization. As the head leans farther from the vertical, determination of the head orientation becomes poorer (Aubert, 1861).

On the other hand, maculae detect inertial linear acceleration. When the head accelerates forward, the otoconia fall backwards due to their inertia and bend the cilia, which send the signal to the brain. As this signal is identical for the inertial acceleration due to motion and a gravitational acceleration due to the head tilt, the

brain uses the information gathered from other sensors, and the characteristics of the signal (e.g. frequency) to discriminate the nature of the signal (Angelaki & Dickman, 2003; Merfeld, Zupan, & Peterka, 1999; Wood, 2002).

## 5. Semicircular canals

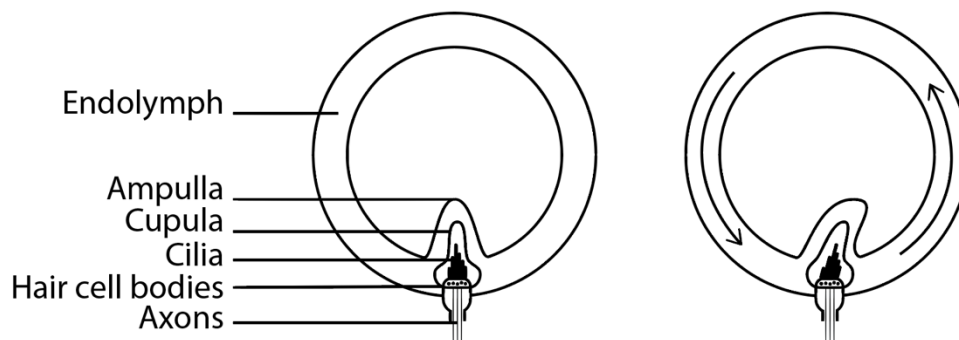
Each vestibular apparatus contains three membranous tubes with a cross-section of 0.4 millimeters, each forming about two thirds of a circle with a diameter of about 6.5 millimeters, called the semicircular canals. They are arranged strictly orthogonally to each other to represent three planes in space and are referred to as anterior, posterior and horizontal semicircular canals (Figure 9). The horizontal canals are oriented horizontally to the earth when the head is bent approximately 30 degrees forward (Khan & Chang, 2013). In this position, the anterior canals are located in vertical planes, but project forward and 45 degrees outward. The posterior canals are also then in vertical planes and project backward and 45 degrees outward.



**Figure 9 – The semicircular canals orientation.**



Semicircular canals are filled with endolymph. Each canal has an enlargement at one of its ends called the ampulla. In each ampulla there is a small crest called crista ampullaris with a gelatinous mass similar to the one of the otoliths and called the cupula. Sensory hair cells are embedded into this cupula and connect to the vestibular nerve to transmit the signals of excitation. When the head rotates, the canals with ampullas move, while the endolymph stays still due to inertia. The flow of liquid relatively to the canals bends the ampulla, and excites the sensory organ (Figure 10). As in the otoliths, bending of the cilia to one side, caused by the flow of endolymph inside the canal, stimulates hair cells while bending into the opposite direction inhibits them. However, unlike the hair cells of the otoliths, those of the cupula are all oriented in the same direction.



**Figure 10 – Deflection of the ampulla containing the cupula with sensory hair cells by the movement of endolymph.**

Six semicircular canals from both internal ears make three coplanar pairs: (1) right lateral and left lateral canals, (2) right anterior and left posterior canals and (3) right posterior and left anterior canals. Angular head acceleration causes the endolymph in anterior-posterior coplanar pairs to move in opposite directions, causing one canal to increase the neural firing and the other canal to decrease it. This is often referred to as the push-and-pull organization that helps to provide sensory redundancy. Apart from that, this push-and-pull organization prevents erroneous sensations when the two canals in pair change their firing unidirectionally, which may happen due to internal changes such as in body temperature or chemistry (Herdman, 2007).

When the head is not moving, a spontaneous tonic discharge passes through the vestibular nerves equally on both sides. The balance in firing rates of bilateral discharge indicates the stillness of the head.

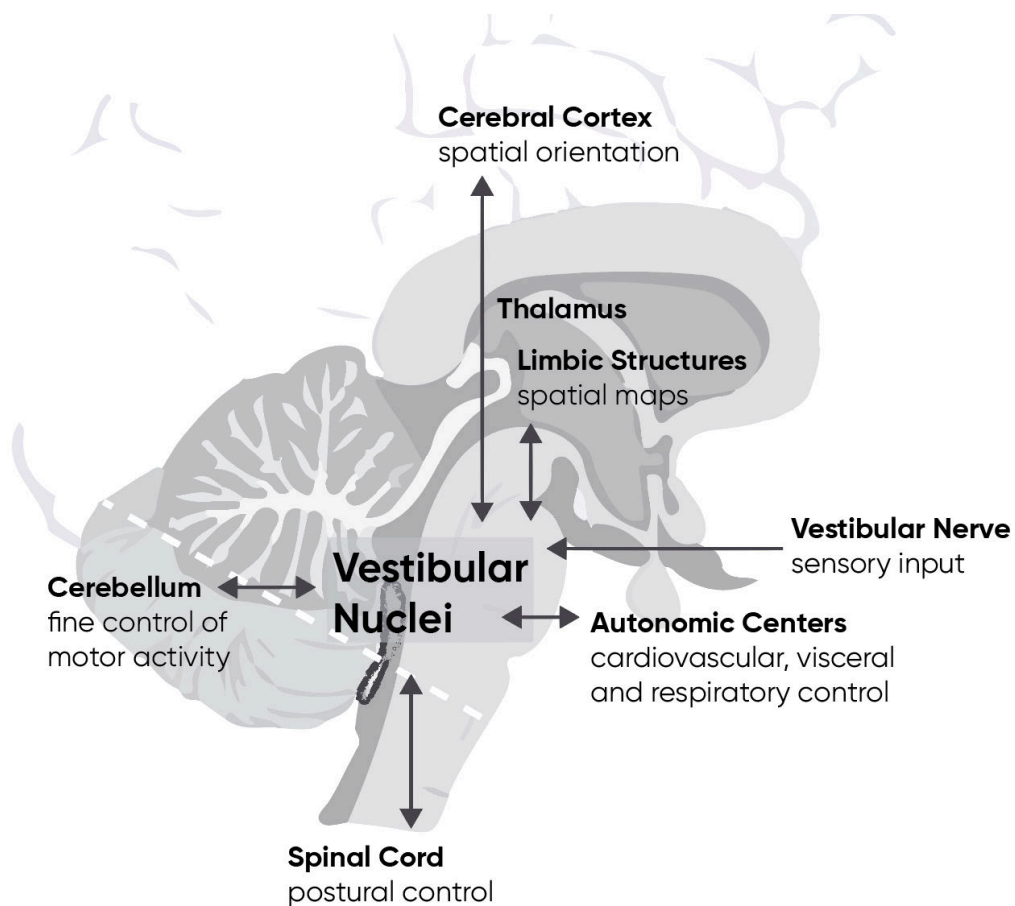
When the head rotates with a constant velocity, on the onset of rotation the inert endolymph does not move along with the head, causing the sensory cupula to bend. The inclination angle of the cupula correlates with the sensed angular velocity. After a while (~7 seconds) (Herdman, 2007), the liquid catches up with the movement of the containing structure, releasing the ampulla. At this point, no rotation is mechanically detected anymore. After the head rotation stops, the fluid continues rotating by inertia, while the head is still, causing the cupula to bend in the opposite direction. This might evoke an illusionary sensation of rotation, when no rotation is physically happening, and ocular movements called post-rotatory nystagmus.

## **6. Central vestibular system**

Vestibular signals require to be processed at different levels, as they drive motor postural and ocular reflexes, add to autonomic control and form the perception (Figure 11). Vestibular neural structure is based on bilaterally afferent and efferent pathways and at least four crossings: three in the brainstem and one in the cortex. The vestibular system can be subdivided into five main components:

- Peripheral receptors placed in the inner ear capturing and transducing head acceleration into neural signals.
- The vestibular nerve that transmits the neural signal.
- Vestibular nuclei in the brainstem that are responsible for receiving, integrating, and distributing information that controls motor activities (such as eye and head movements, postural reflexes, and gravity-dependent autonomic reflexes) and spatial orientation (Jang, Lee, Yeo, & Kwon, 2018; Yakushin, Raphan, & Cohen, 2017).

- Cerebellar projections that modulate motor control of the posture, head and eyes, as well as participate in autonomic control (Doba & Reis, 1974; Ito, 1982; Rondi-Reig, Paradis, Lefort, Babayan, & Tobin, 2014; Yates, Holmes, & Jian, 2000).
- The vestibulo-thalamo-cortical network that is responsible for the conscious perception of movement and spatial orientation (Lopez & Blanke, 2011).



**Figure 11 – The central vestibular system, its projections and functions.**

The main responses initiated by the vestibular system serve to maintain gaze and posture stability and homeostasis during postural changes. They include:

- Vestibulo-ocular reflex (stabilization of the image on the retina of the eye during movement).

- Vestibulo-spinal and vestibulo-collic reflexes (posture stabilization of body and head).
- Vestibulo-sympathetic reflex (autonomic control).

Despite they are mostly called “reflexes” in the literature, those responses often require complex processing, integration and internal models.

### **a. Vestibular nerve**

Neural impulses from otoliths and semicircular canals are carried by the afferent neural fibers that altogether form the vestibular nerve, a branch of the VIII-th cranial nerve (vestibulocochlear nerve). Cell bodies of these fibers form the vestibular ganglion (also referred to as Scarpa’s ganglion). The innervation pattern of vestibular endorgans is specific: the utricle together with horizontal and anterior semicircular canals send their signals through the superior vestibular nerve, while the saccule and the posterior canals are innervated by the inferior vestibular nerve (Kandel, 2013).

The vestibular afferents have two patterns of firing. Regular afferents have little variability of the discharge and a regular tonic rate. Irregular afferents usually do not produce firing at rest, but develop a high discharge variability when stimulated by motion.

Most of the vestibular nerve fibers end in the vestibular nuclei that are located approximately at the junction of the medulla and the pons. However, some fibers pass further to the fastigial nuclei, uvula, and flocculonodular lobes of the cerebellum. Some fibers ending in the vestibular nuclei have synapses with second order neurons projecting into the same areas of the cerebellum as well as to the cortex of other portions of the cerebellum, the vestibulospinal tract, the medial longitudinal fasciculus, and to other areas of the brainstem, particularly the reticular formation.

## **b. Vestibular nuclei**

The vestibular nuclear complex consists of four well-described major nuclei and minor nuclei that are less investigated. The whole structure is situated in the pons with extension to the medulla. The mutually inhibitory commissural paths connect the symmetric parts of the vestibular nuclear complex to provide the information exchange between the two sides and implement the push-and-pull pairing of the semicircular canals.

The vestibular nerve projects to the vestibular nuclear complex located on either side of the brainstem and subdivided into four separate anatomical and functional nuclei (Figure 12) (Goldberg et al., 2012):

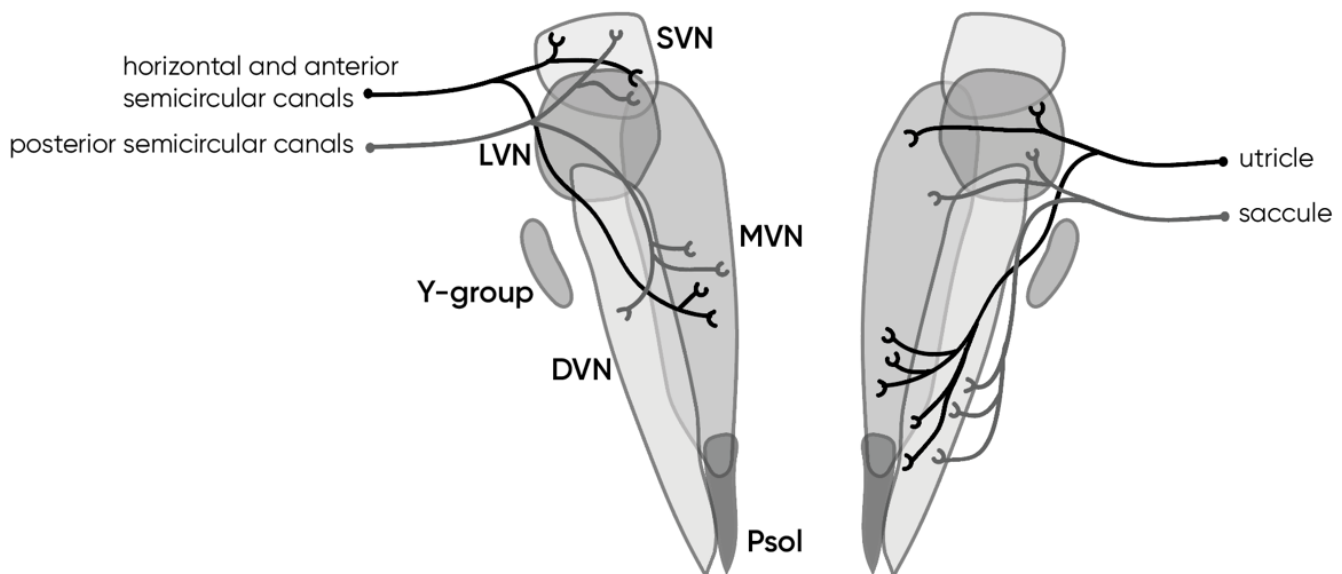
- The superior (Bechterev's; SVN) and medial (Schwalbe; MVN) vestibular nuclei receive fibers mainly from the semicircular canals (predominantly horizontal and superior SCC) and project into the medial longitudinal fasciculus (MLF) to trigger the vestibulo-ocular reflex as well as to the medial vestibulospinal tract to cause appropriate movements of the neck. Neurons in the medial vestibular nucleus are mostly excitatory and neurons in the superior vestibular nucleus are mostly inhibitory.
- The lateral vestibular nucleus (the Deiter's nucleus; LVN) gathers signals primarily from the utricle and possibly saccule and synapses with the neurons going to the spinal cord through the lateral vestibulospinal tract to control postural reflexes.
- The inferior (or descending) vestibular nucleus (IVN or DVN) receives signals predominantly from the otolithic system and from the posterior semicircular canals, and in turn sends signals into both the cerebellum and the reticular formation of the brainstem, as well as to the contralateral nuclei and the spinal cord. This nucleus is involved in integration of vestibular inputs with central motor information.

These four subdivisions are innervated directly by the vestibular nerve and are present in most species.

There are also other minor nuclei distributed in the brainstem and lying close to the four major nuclei that receive primary vestibular inputs and can participate in the processing of the vestibular information. These include parasolitary nucleus

(Psol), y-group, nucleus intercalatus (Barmack, 2003). The y-group consists of dorsal and ventral subdivisions. The dorsal part receives ipsilateral vestibular primary afferents and bilateral secondary vestibular projections. The ventral division projects to the ipsilateral flocculus, nodulus and contralateral oculomotor complex.

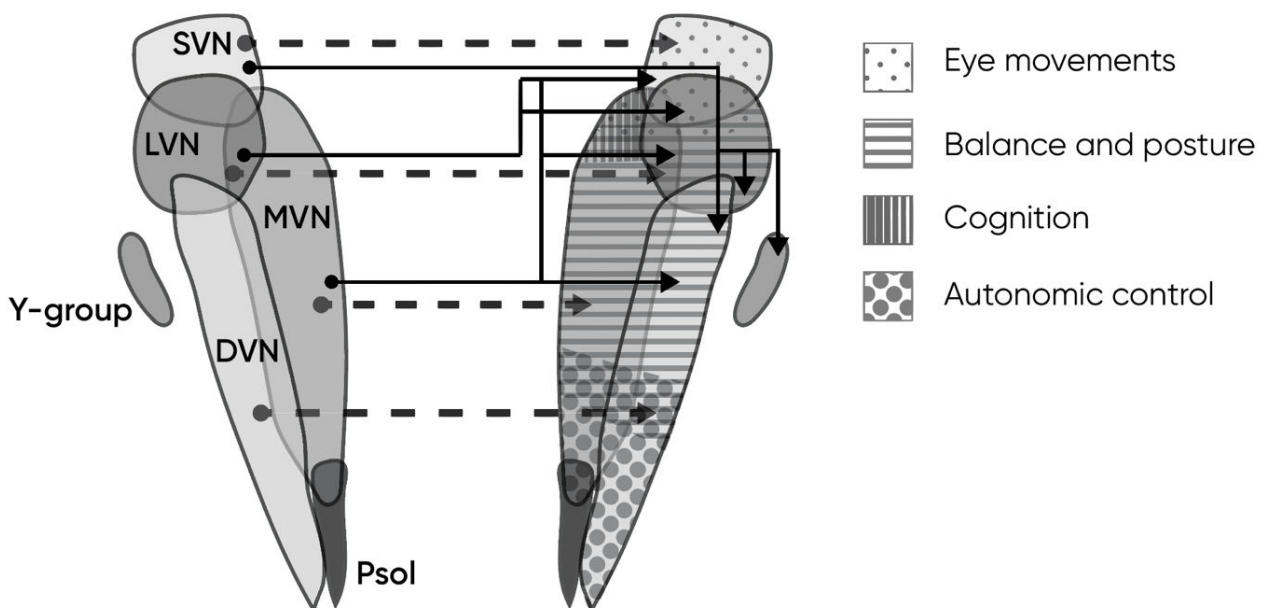
Nucleus prepositus hypoglossi (NPH) also receives scattered primary vestibular afferents as well as secondary vestibular projections and projections from the cerebellum (uvula-nodulus and the flocculus). NPH send projections bilaterally to the vestibular nuclei, flocculus and reticular formation. In addition, the neurons in NPH project to the ipsilateral oculomotor nucleus and abducens nucleus. NPH is thought to encode the vestibular and eye position information. The other small nuclei that can be related to vestibular function are the nucleus x and nucleus z.



**Figure 12 – The illustration of the bilateral vestibular nuclear complex and their primary vestibular projections from the three semicircular canals, utricle and saccule.** SVN, LVN, MVN, DVN – superior, lateral, medial and descending vestibular nuclei.

While the primary vestibular afferents transduce the information from single vestibular organs, already at the level of secondary vestibular neurons, the

convergence of signals appears. It can be the convergent signal from several semicircular canals, or this of canals and otolith organs together. However, some secondary projections relay inputs exclusively from the otolith organs, possibly to help the discrimination between the signals in an ambiguous frequency range (Barmack, 2003).

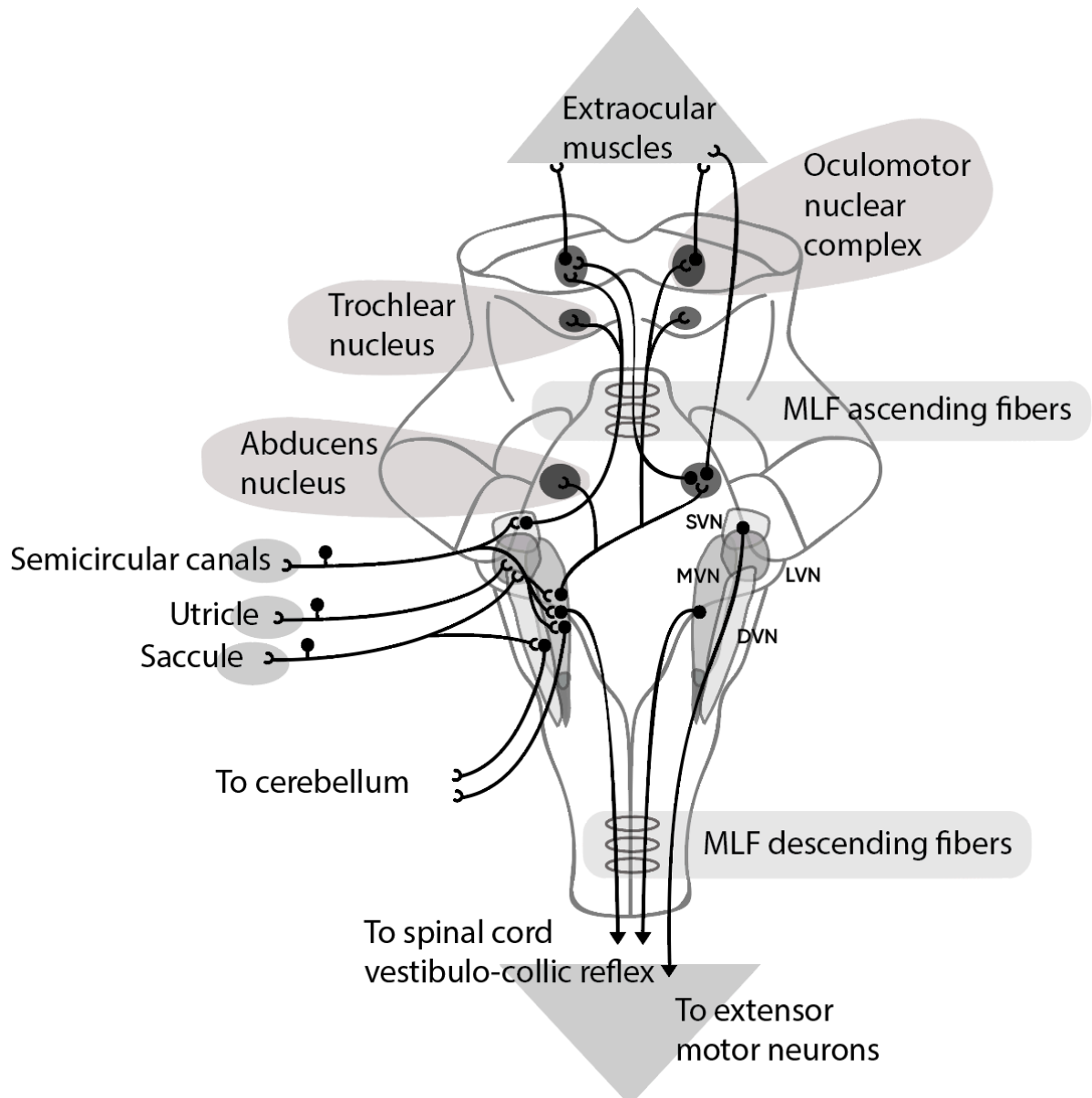


**Figure 13 – Vestibular nuclei, their commissural projections and functions.** Patterned zones localize the majority of neurons responsible for eye movements (small dots), balance and posture (horizontal stripes), cognition (vertical stripes) and autonomic control (big dots). Dashed arrows show commissural homologous connections of the vestibular nuclei. Plain arrows demonstrate non-homologous connections to contralateral nuclei.

Human vestibular nuclei pathway tracing study showed 100% connectivity of vestibular nuclei with cerebellum, thalamus, oculomotor nucleus, trochlear nucleus, abducens nucleus, and reticular formation related to the functions of the VN (equilibrium, control of eye movements, conscious perception of movement, and spatial orientation). High connectivity (over 70%) was seen with the sensory-motor cortex (primary motor cortex, primary somatosensory cortex, premotor

cortex, and posterior parietal cortex), hypothalamus, and lateral prefrontal cortex (Jang et al., 2018).

Ascending pathways from the vestibular nuclei include principally the projections to thalamus and cortex and cerebellum, in particular ventrobasal thalamus, parietal visual cortex, cerebellar vermis and flocculus.



**Figure 14 – Projections of the vestibular nuclei for the motor reflexes.** SVN, LVN, MVN, DVN – superior, lateral, medial and descending vestibular nuclei. MLF – Medial longitudinal fasciculus.



Descending pathways to the spinal cord form two principal vestibulospinal tracts: medial and lateral (Figure 14). Axons of the lateral vestibulospinal tract terminate in the ipsilateral lumbosacral region where they connect to motoneurons. The medial vestibulospinal tract terminates bilaterally in the medial part of the cervical ventral horn and drives the vestibulo-colic reflex.

Vestibular nuclei also project to the autonomic control centers. DVN, MVN and PsoI project to the Solitary Nucleus (NTS) that receives also autonomic afferents. Fastigial nucleus also receives projections from the vestibular nuclei. It responds to changes in blood pressure, heart rate and respiration, moreover, electrical stimulation of this nucleus can alter these autonomic functions (Barmack, 2003).

### **c. Multisensory integration within VN**

Primarily, neurons in vestibular nuclei integrate signals from otolithic sensors and semicircular canals to model the position and movement in space and distinguish between tilt and linear translation, which are physically indistinguishable (Angelaki & Dickman, 2003; Merfeld, Young, Oman, & Shelhamer, 1993; Merfeld, Zupan, & Gifford, 2001). Also, the integration is happening to differentiate active, voluntary movements from passive ones (Cullen & Roy, 2004).

Vestibular nuclei neurons respond to vestibular, optokinetic (Waespe & Henn, 1978), tactile, proprioceptive (Cullen & Roy, 2004; Tomlinson & Robinson, 1984) inputs.

All the sensory inputs are merged in the vestibular nuclei and the cerebellum, with weighting of every input according to their reliability, leading to the best possible estimate of motion which was demonstrated in monkeys and humans (Fetsch, Turner, DeAngelis, & Angelaki, 2009).

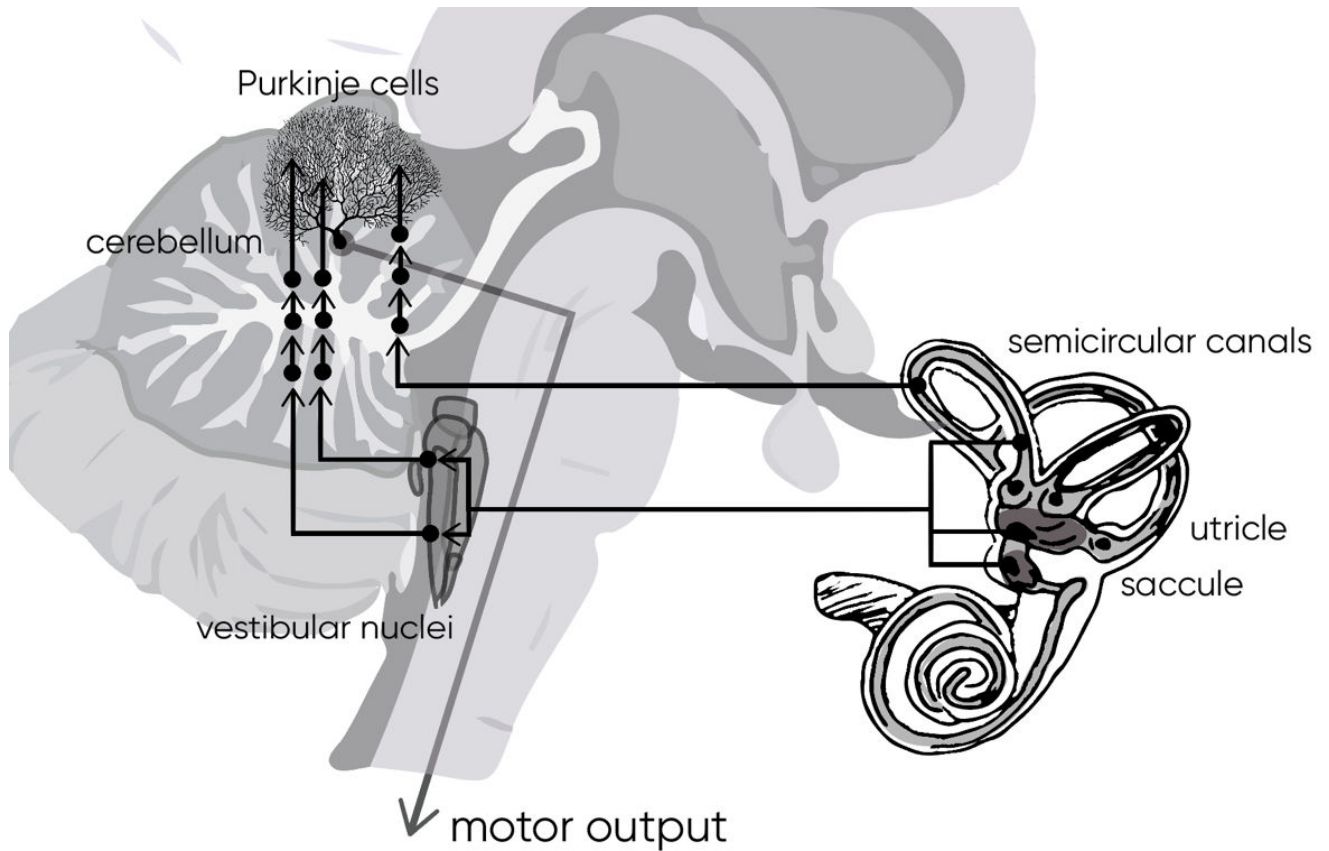
### **d. Vestibular cerebellum**

Vestibular cerebellum acts as an adaptive processor for the vestibular performance (Figure 15). The removal of cerebellar input does not abolish the vestibular reflexes, but makes them imprecise and ineffective (Herdman, 2007).

There are five main regions of the cerebellum that receive either primary (i.e. directly from afferents) or secondary (i.e. from vestibular nuclei) vestibular input, including:

- the nodulus and ventral uvula,
- the flocculus and ventral paraflocculus,
- the oculomotor vermis of posterior lobe,
- lobules I-V of the anterior lobe, and
- the deep cerebellar nuclei (e.g. fastigial nuclei).

The ipsilateral cerebellum has direct efferent connections to ipsilateral vestibular nuclei and to the contralateral vestibular nuclei indirectly through the fastigial nucleus. The latter projects to the contralateral vestibular nuclei via the juxarestiform body (Khan & Chang, 2013). These areas participate in the adjustment of posture- and orientation-related reflexes. In particular, approximately half of the neurons of the rostral fastigial nuclei (RFN) encode the motion of the body in space responding to both vestibular and proprioceptive inputs, while the other half encode the motion of the head in space in a manner similar to neurons in the vestibular nuclei (Brooks & Cullen, 2009). The caudal part of the fastigial nuclei participates in the adjustment and modulation of the saccadic eye movements (Kleine, Guan, & Büttner, 2003). The cerebellar flocculus takes part in the vestibulo-ocular reflex (VOR) and smooth pursuit function by continuously modulating the eye velocity (Ito, 1982). Modulation here is continuous correction of the gain errors and adapting the VOR to different conditions (Miles & Eighmy, 1980). It is essential, for example, for people wearing correction eyeglasses. Lenses change the focal point and so the gain of the VOR must adapt to this change. While the flocculus adapts the VOR gain, cerebellar nodulus adjusts its duration, playing role in its habituation and suppressing (Angelaki & Hess, 1994; Waespe, Cohen, & Raphan, 1985). The lesions of nodulus also affect the processing of otolithic input, causing erroneous eye nystagmus when tilting the head (Herdman, 2007). The nodulus is required for motion sickness (Bard & Woolsey, 1947). Anterior-superior vermis of the cerebellum is involved in postural regulation through the vestibulo-spinal reflex.



**Figure 15 – Primary and secondary vestibular projections to cerebellum to modulate the motor output.**

### **e. Multisensory integration within cerebellum**

The cerebellum is a center for monitoring and modulating motor function. Cerebellum receives multimodal sensory information, which it integrates together with the efference copy of the motor command. Apart from vestibular projections that originate in part directly from the vestibular organs (primary projections to the uvula-nodulus), but mostly from vestibular nuclei (secondary projections to multiple cerebellar lobules), cerebellum receives multiple other sensory projections. Primarily two areas of posterior cerebellar cortex, lobule VII and the dorsal paraflocculus receive visual projections (Kralj-Hans, Baizer, Swales, & Glickstein, 2007; Rondi-Reig et al., 2014). Cerebellum receives also proprioceptive projections (Brooks & Cullen, 2009) from limbs, neck and shoulders, which are

integrated with visuo-vestibular signals for navigation (Brooks & Cullen, 2009; Gdowski & McCrea, 2000). There is evidence that cerebellum participates in processing of tactile information from whiskers in animals (Rondi-Reig et al., 2014). The multiple sensory inputs are converged by cerebellum in the superior colliculus (Rondi-Reig et al., 2014).

#### **f. Vestibular thalamus and cortex**

Vestibular signals play a role in many cognitive functions such as navigation in space (Berthoz, Israel, Georges-Francois, Grasso, & Tsuzuku, 1995; Mittelstaedt, 1999), distinguishing self-motion and object motion (McIntyre, Zago, Berthoz, & Lacquaniti, 2001; Straube, Brandt, & Probst, 1987; Werkhoven, Snippe, & Toet, 1992), perceiving the vertical (Mittelstaedt, 1983), bodily self-consciousness (Lopez, Halje, & Blanke, 2008), and even circadian rhythms (Fuller & Fuller, 2006; Martin et al., 2016) and emotions (Lopez, 2016).

Unlike visual or auditory systems, that have a specific cortical region for processing the sensory information, the vestibular system does not seem to have an assigned cortical zone. Vestibular information is redistributed to multiple cortical areas through the thalamus. Cortical zones receiving the projections from thalamus differ significantly among species that makes it impossible to definitively match primate cortical zones with human ones. Moreover, the methods currently available to study the vestibulothalamocortical connection in human do not permit the profound investigation of this widespread network, including often a small number of neurons per connection.

#### **g. Thalamus**

As for every other sensory signal processing, the thalamus relays vestibular signals to the cortex (Figure 16). Nevertheless, the vestibular traffic organization differs fundamentally from other sensory systems. Most sensors send projections to a modality-specific thalamic nucleus and after to a respective cortical or subcortical area, creating a sensory map. The vestibular sensory information is converged in the vestibular nuclei, which makes the signals more complex and indirect. The vestibular nuclei send signals to the thalamus, however there is no specifically

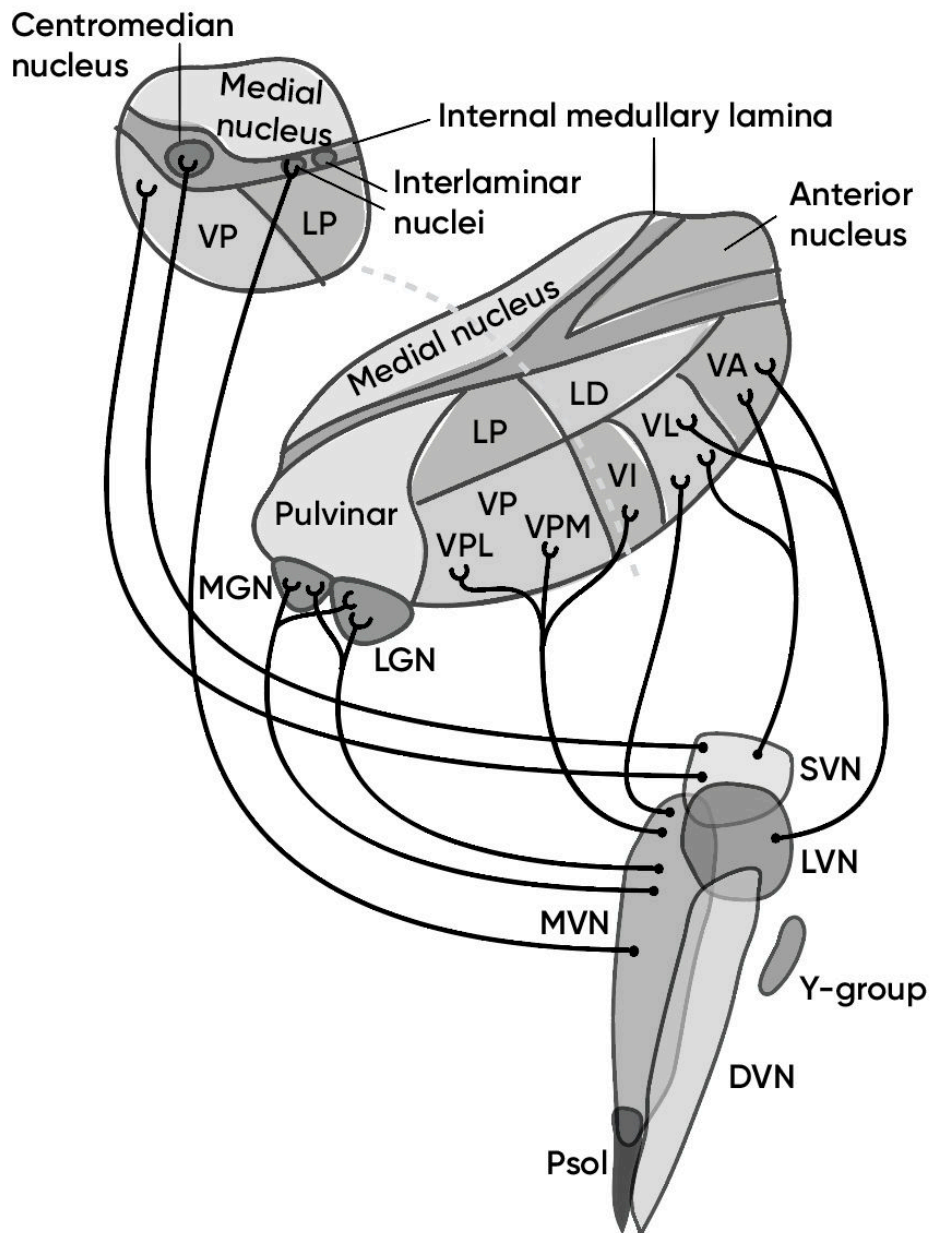
assigned nucleus relaying vestibular signals. Various thalamic nuclei receive second order neurons projected from the vestibular nuclei to process and redistribute the vestibular signals to various cortical zones. Most of the thalamic nuclei receiving vestibular projections are not specific to the vestibular system, receiving multiple inputs from other sensory systems and cortical zones. This fact accentuates the multisensory and integrative character of the vestibular information.

**In animals**, multiple thalamic zones have been reported to receive vestibular projections. Ventral posterior lateral nucleus (VPL) and the nucleus ventralis intermedius (Vim) in the ventroposterior complex in rat receive projections primarily from the medial and superior vestibular nuclei (MVN, SVN) (Nagata, 1986) and from descending vestibular nuclei (DVN) (Shiroyama, Kayahara, Yasui, Nomura, & Nakano, 1999). The VPL-Vim complex is considered a major relay of proprioceptive and cutaneous inputs to primary and secondary somatosensory cortex in primates including human (Behrens et al., 2003; Lopez & Blanke, 2011). This thalamic nuclear complex also projects to other multiple cortical zones, such as anterior suprasylvian cortex and posterior cruciate region, superior parietal lobule and intraparietal sulcus (Lopez & Blanke, 2011). The VPL receives efferents from the somatosensory cortex. The ventral posterior thalamus is thought to be the origin of the main thalamocortical pathway to the parieto-insular vestibular cortex (PIVC), which is known to be the principal vestibular cortical zone in non-human primates (Akbarian, Grüsser, & Guldin, 1992). The ventral posterior inferior nucleus (VPI) neurons respond to rotatory vestibular stimulation and are connected with the primary somatosensory cortex (Akbarian et al., 1992). Ventral posterior medial (VPM) nucleus neurons receive inputs primarily from the MVN and SVN and respond to both rotational and translational stimulus, as well as electrical stimulation of the vestibular nerve (Deecke, Schwarz, & Fredrickson, 1977; Matsuo, Hosogai, & Nakao, 1994; Meng et al., 2001). The ventroanterior thalamic nucleus (VA) and ventrolateral thalamic nucleus (VL) receive inputs from the MVN and SVN via the medial longitudinal fasciculus and, in Rhesus monkey, also from the cerebellar nuclei. The VA-VL thalamic nuclear complex relays the major vestibulomotor pathway, connecting vestibular nuclei with the primary motor and premotor cortex. The intralaminar nuclear complex (IL) serve as a major relay of the vestibulo-thalamo-striatal pathway, likely involved in the control of body and limb movements. The medial geniculate nucleus (MGN) neurons

receive projections from MVN, SVN and DVN and respond to electrical stimulation of the vestibular nerve. This nucleus is involved in auditory, vestibular and somatosensory integration. The lateral geniculate nucleus (LGN) is known to be the main visual pathway from the retina to the primary visual cortex, however it contains vestibular projections that respond to the horizontal or vertical angular stimulations (Magnin & Putkonen, 1978). Neurons in the pulvinar also respond to vestibular activation.

**In human**, the methods for tracing vestibular higher pathways are limited. Neuroimaging and clinical neurological data help to describe vestibular processing in the human thalamus. While the thalamic connections for other sensory systems have been successfully traced with neuroimaging, description of the vestibular connections meets strong limitations. Small sizes of the thalamic nuclei, their deep location and moreover, the fact that the vestibular information is redistributed by small patches of neurons to multiple nuclei over thalamus, make the signal harder to detect (Lopez & Blanke, 2011).

Neuroimaging during galvanic vestibular stimulation demonstrated the activation of the paramedian and dorsolateral thalamus (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001). Caloric stimulation activated the posterolateral and posteromedial thalamus (Dieterich, 2003). Nucleus medialis, nucleus habenularis and pulvinar have been reported to participate in vestibular processing in human (Bucher et al., 1998). Neurological data support the participation of posterolateral thalamus in relaying vestibular signals to the cortex (Ceballos-Baumann et al., 2001; Dieterich et al., 2005). The MGN is also suggested to be involved in vestibulothalamic connection in human (Hawrylyshyn, Rubin, Tasker, Organ, & Fredrickson, 1978).



**Figure 16 – Projections of the vestibular nuclei to the thalamus.** Thalamic nuclei abbreviations: LP – lateral posterior, LD – lateral dorsal, VP – ventral posterior, VPL – ventral posteromedial, VPM – ventral posteromedial, VI – ventral intermediate, VL – ventral lateral, VA – ventral anterior nuclei. SVN, LVN, MVN, DVN – superior, lateral, medial and descending vestibular nuclei.

## h. Multisensory integration within thalamus

The neurons in the vestibular thalamus have responses that are very similar to those of vestibular nuclei, they respond to vestibular, proprioceptive, visual and tactile stimuli (Lopez & Blanke, 2011). As has already been described, all thalamic nuclei that use vestibular information, also receive inputs from other sensory systems. Basing on the clinical studies where thalamic lesions or strokes led to the perturbances of visual vertical and postural vertical (Johannsen, Broetz, Naegele, & Karnath, 2006; Karnath, Ferber, & Dichgans, 2000; Masdeu et al., 2005), it has been suggested that the thalamus acts not only as a signal relay, but that thalamic nuclei participate in the complex processing of vestibular information (Wijesinghe, Protti, & Camp, 2015). It was demonstrated that thalamic neurons respond to a combination of visual and vestibular information (Magnin & Putkonen, 1978; Meng, May, Dickman, & Angelaki, 2007). Vestibular neurons in ventral posterior medial, lateral and inferior thalamic nuclei respond to proprioceptive inputs from joints, muscles and skin from limbs, trunk, neck and head (Blum & Gilman, 1979; Deecke et al., 1977). Vestibular nuclei in thalamus were also shown to be responsive to touch in paws in cats (Sans, Raymond, & Marty, 1970). It is possible that thalamus acts as one of the centers of multisensory integration for signals from the labyrinth and other sensory signals (Tyll, Budinger, & Noesselt, 2011).

## i. Vestibular cortex

Walzl and Mountcastle realized the first description of vestibular projections to the cortex in cats in 1949. Later, a number of studies have been devoted to describe “vestibular cortex” in various species including human (Figure 17).

**In animals**, the parietal cortex, the area 2v of the primary somatosensory cortex was first shown to receive vestibular inputs (Fredrickson, Figge, Scheid, & Kornhuber, 1966). In cat and monkey the 2v area responded to both otolith and semicircular canals inputs (Büttner & Buettner, 1978; Jijiwa, Kawaguchi, Watanabe, & Miyata, 1991). Also the area 3aHv situated in the somatosensory cortex area representing the hand and arm in squirrel monkey and the forelimb in cat and guinea pig (Odkvist, Liedgren, Larsby, & Jerlvall, 1975; Odkvist, Rubin, Schwarz, & Fredrickson, 1973; Odkvist, Schwarz, Fredrickson, & Hassler, 1974), and the 3aNv zone in the area encoding the neck and trunk representations and



stretching till the primary motor cortex (Akbarian, Grüsser, & Guldin, 1994; Guldin & Grüsser, 1998) are responsive to vestibular inputs. The ventral intraparietal area (VIP) and medial intraparietal area (MIP) of the parietal sulcus have also been revealed to receive vestibular neurons (Bremmer, Klam, Duhamel, Ben Hamed, & Graf, 2002; Schlack, 2005; Schlack, Hoffmann, & Bremmer, 2002). The VIP area participates in three-dimensional spatial coding and in visuo-vestibular integration and is reciprocally connected with motor cortex (Schlack, 2005; Schlack et al., 2002). Area 7 has shown vestibular activation in monkeys (Faugier-Grimaud & Ventre, 1989; Ventre & Faugier-Grimaud, 1986), however some researchers tend not to consider the area 7 as a part of the vestibular cortex due to a low percentage of neurons responsive to vestibular inputs (Guldin & Grüsser, 1998). Grüsser and Guldin first described the area called “parieto-insular vestibular cortex” (PIVC) that is considered now the principal vestibular cortical area in non-human primates (Grüsser, Pause, & Schreiter, 1990a, 1990b; Guldin & Grüsser, 1998). However, the PIVC location is variable between species (for example, it is located on the parietal lateral sulcus in macaque and on the temporal lateral sulcus in squirrel monkey). Visual posterior sylvian area (VPS) posterior to PIVC was also found to be responsive to vestibular signals in about 30% of its neurons together with visual information (Guldin & Grüsser, 1998). Some PIVC neurons converge vestibular, somatosensory and visual signals and also respond to muscle pressure, vibrations and rotation of the neck (Grüsser et al., 1990b). In the experiment of Grüsser and colleagues (Grüsser et al., 1990b), trunk rotation with the stable head activated the PIVC neurons, which were sensitive to the direction of rotation as well as velocity and acceleration. The vestibular and neck proprioceptive signals interact in the PIVC possibly to differentiate between passive and active movement. Also the PIVC neurons in macaque are reported to respond to both rotational and translational vestibular stimulation (Chen, DeAngelis, & Angelaki, 2010). Areas in primary motor cortex (area 4) and premotor cortex (area 6) that are associated with motor and oculo-motor control also receive vestibular inputs (Ebata, Sugiuchi, Izawa, Shinomiya, & Shinoda, 2004; Fukushima, Akao, Kurkin, Kaneko, & Fukushima, 2006; Fukushima et al., 2010). There is evidence that these areas participate in generation of eye saccades and smooth pursuit eye movements (Fukushima et al., 2006). Cingulate sulcus also has neurons that participate in vestibular processing in monkey, even though they do not receive direct vestibular input (Guldin & Grüsser, 1998). This region

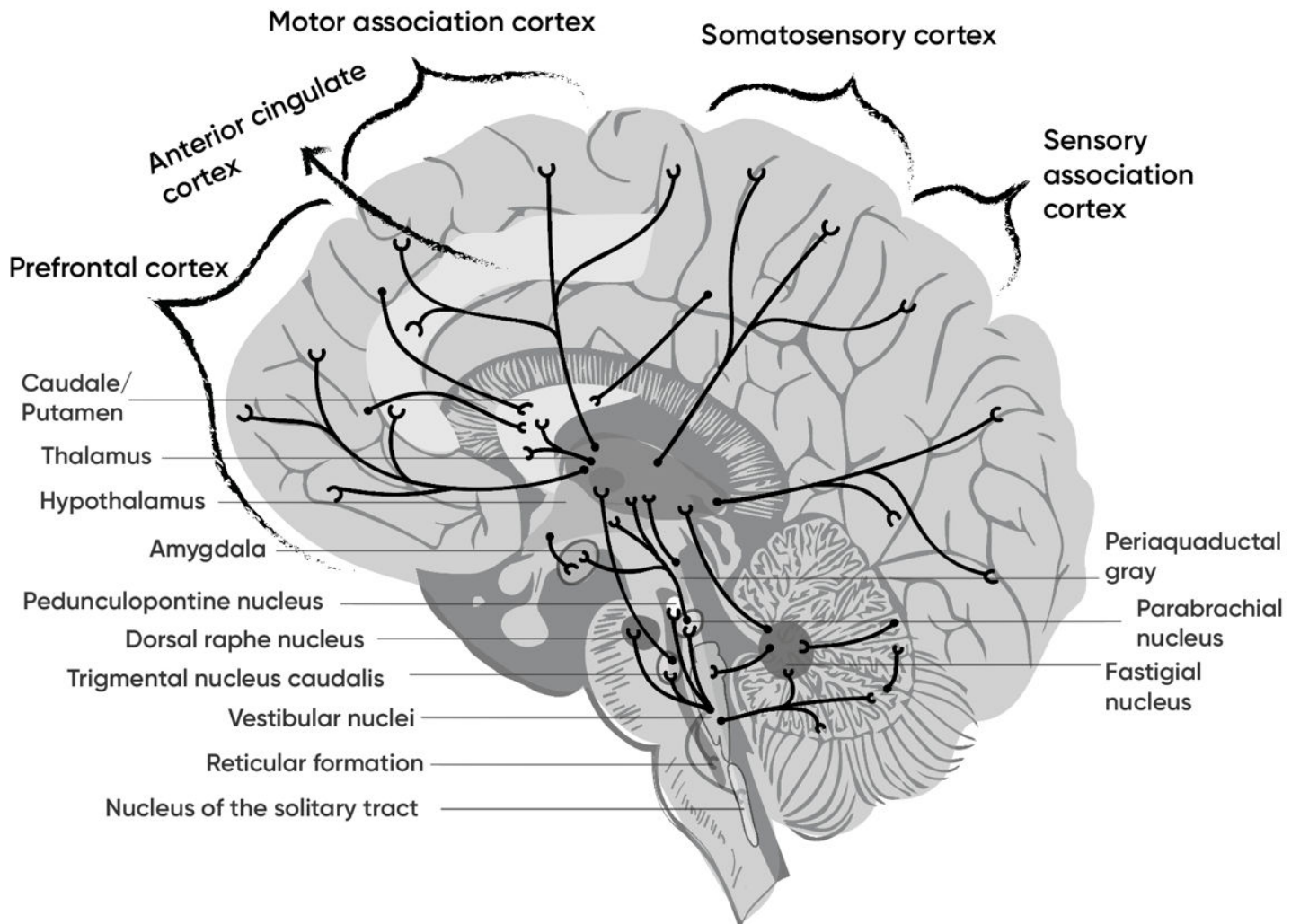
probably participates in integration of visual and self-motion cues for spatial coding and navigation (Cooper, Manka, & Mizumori, 2001). Vestibular projections have been found in primary and secondary visual cortex in cats (areas 17, 18, 21 and 19) (Grüsser & Grüsser-Cornehls, 1972; Vanni-Mercier & Magnin, 1982). Vestibular inputs are found also in medial superior temporal area (MST) in monkey, which represents a major area for visual motion perception, including self-motion derived from visual cues (Bremmer et al., 2002; Bremmer, Kubischik, Pekel, Lappe, & Hoffmann, 1999; Page & Duffy, 2003). Finally, the hippocampus is modulated by vestibular stimulation (Horii, Russell, Smith, Darlington, & Bilkey, 2004). Even though direct vestibular projections have not been found, the firing of “place cells” encoding the location in space and “head direction” cells encoding the face direction, was found to be adjusted by vestibular inputs.

**In humans**, functional neuroimaging studies revealed the anterior part of the intraparietal sulcus region to respond to vestibular stimulation (Fasold et al., 2002; Lobel, Kleine, Bihan, Leroy-Willig, & Berthoz, 1998), which might be a human analogue of cat’s and monkey’s area 2v (Lopez & Blanke, 2011). Other neuroimaging studies have described the primary somatosensory cortex to be activated following vestibular stimulation, this area could be homologue to the areas 3aHv and 3aNv in monkeys (Emri et al., 2003; Fasold et al., 2002). A human homologue to area 7 in monkey can be the inferior parietal lobule or lateral superior parietal lobule which is activated by head movements and change of gaze direction (Fasold et al., 2002; Lobel et al., 1998; Vitte et al., 1996). Intraparietal sulcus has also demonstrated the vestibular activation both by otolithic and canal inputs (Miyamoto, Fukushima, Takada, de Waele, & Vidal, 2007; Suzuki et al., 2001). Human cortical zone analogous to PIVC could be in the posterior insula and temporo-parietal junction (Emri et al., 2003; Fasold et al., 2002; Lobel et al., 1998; Miyamoto et al., 2007; Vitte et al., 1996). However, the exact location of the PIVC-homologue area is not yet clear as the difference in its location varies between studies. Anterior insula being an important center of bodily awareness is also involved in the vestibular processing (Bense et al., 2001; Dieterich et al., 2005; Fasold et al., 2002; Trousselard, Barraud, Nougier, Raphel, & Cian, 2004). Several frontal zones are also involved in vestibular processing in human, such as regions in primary motor cortex (precentral gyrus), the premotor cortex, superior, middle and inferior frontal gyri (Bense et al., 2001; Emri et al., 2003; Fasold et al., 2002; Lobel et al., 1998). The frontal gyri neurons are involved in the control of saccadic

eye movements, smooth pursuit and nystagmus (Blanke et al., 2000). Anterior and posterior cingulate cortex in human might be homologue to the monkey vestibular cingulate region (Bense et al., 2001; Fasold et al., 2002; Miyamoto et al., 2007; Suzuki et al., 2001). The analogue to the optic-related MST in monkey could be the middle temporal gyrus (area 37) that are activated during galvanic vestibular stimulation (Bense et al., 2001). It was also found that several visual cortex zones are deactivated during vestibular stimulation, while visual fixation was found to be related to a deactivation of the vestibular cortex (Bense et al., 2001; Lobel et al., 1998), which might suggest the existence of reciprocal inhibitory visuo-vestibular interactions (Brandt, 1998). In addition, vestibulo-hippocampal interaction on human is suggested.

#### **j. Multisensory integration in cortex**

As it has been described above, there is no vestibular-specific cortical area. Instead, the vestibular signals are redistributed to multiple cortical zones, which are highly multimodal and integrative. The PIVC area in monkeys is connected to all the other vestibular-sensitive regions and thus is considered to be the primary vestibular region, the vestibulo-visuo-somatosensory convergence is happening in this area (Grüsser et al., 1990a, 1990b; Guldin & Grüsser, 1998). Visual-vestibular convergence was also demonstrated in the MST area (Bremmer et al., 1999), and vestibulo-somatosensory convergence was found in the intraparietal sulcus and areas 2v and 3aHv and 3aNv in monkeys and the secondary somatosensory cortex in humans (Bremmer et al., 2002; Fasold et al., 2002; Guldin & Grüsser, 1998).



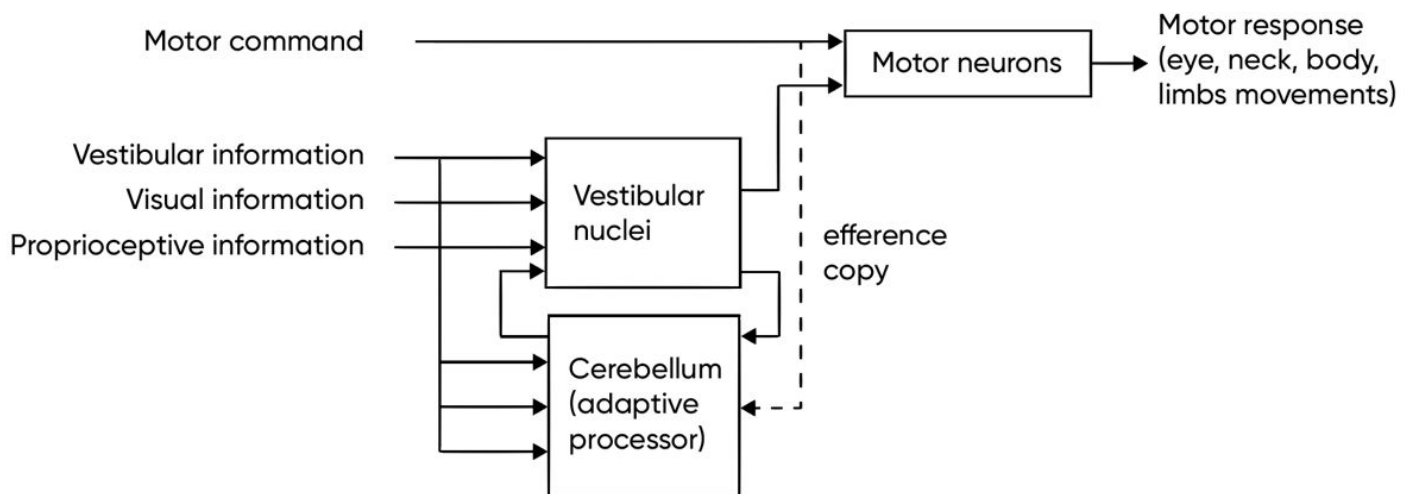
**Figure 17 – The scheme of central vestibular projections that form a network throughout the brain. Illustration based on the figure in (Black & Rogers, 2018).**

Vestibular system

Central vestibular system

## Vestibular reflexes and higher vestibular functions

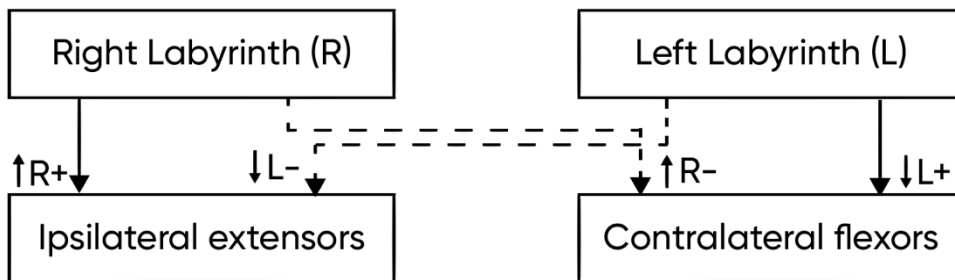
As it was pointed out in the previous part, the peripheral vestibular system does not act in isolation. An orientation system mainly localized in the brainstem, integrates the vestibular information with that of other senses (e.g. vision, somatosensation), motor efference, and expected head and body orientation. The composite signal is used to stabilize gaze and posture, as well as to adjust blood circulation to the change of position in space (Figure 18).



**Figure 18 – Illustration of the basic organization of vestibular motor reflexes.**

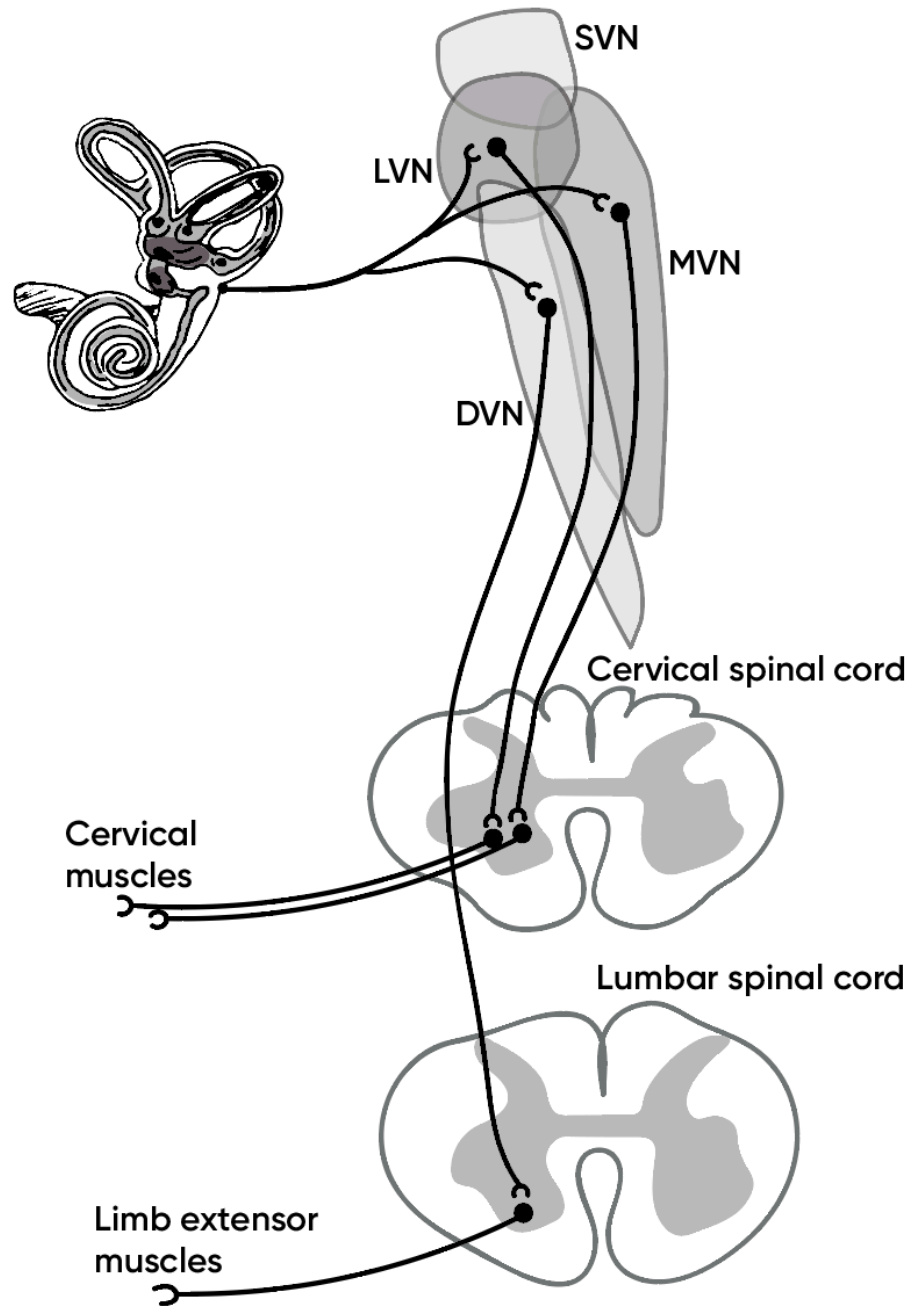
### 1. Vestibulo-spinal and vestibulo-collic reflexes

The vestibulospinal reflexes (VSR) contribute to maintaining of postural stability. The effectors of this reflex are the “antigravity” muscles – extensors of neck, trunk and extremities. The reflex is organized in a push-and-pull manner, to counterbalance the activity of extensor and flexor skeletal muscles (Figure 19).



**Figure 19 – Illustration of a push-and-pull organization of vestibulospinal reflexes.**

There are three major pathways that provide vestibulo-spinal reflexes (Figure 20). They are: (1) the lateral vestibulo-spinal tract, (2) the medial vestibulo-spinal tract, and (3) the reticulospinal tract. The lateral and medial vestibulo-spinal tracts arise directly from the neurons of the vestibular nuclei, while the reticulospinal tract arises from the neurons in the reticular formation that receive vestibular inputs (as well as other types of inputs). All of these pathways are closely interconnected with the cerebellum that adjusts and modulates reflexes.



**Figure 20 – Illustration of the organization of vestibulo-spinal reflexes.**

The purpose of the VSR is to stabilize the body. The VSR can be divided into two functional categories, one acting on the limb muscles for stabilizing the posture and the other acting on the neck muscles for stabilizing the head position. The



latter is usually referred to as vestibulo-colic reflex (VCR). Vestibulo-spinal reflexes are also tightly connected to the cervico-spinal reflexes, changes of skeletal muscle tonus due to the change of head position relative to the trunk. The vestibular signals alone give the position of the head in space, but not the position of a trunk. The combination of the sensors from the labyrinth and neck can give the representation of the trunk position and thus accurately stabilize the posture.

While the VSR is elicited by the activation otoliths or the semicircular canals, the VCR is activated by stimulation of neck spindle afferents, particularly those located in the deep perivertebral muscles, which show tonic or tonic-phasic responses to neck displacement (Manzoni, 2009)

The general VSR mechanism due to the body inclination can be described as following:

1. When the head is tilted to one side, both the canals and otoliths are stimulated. Endolymphatic flow deflects the cupula and shear force deflects hair cells within the otoliths.
2. The vestibular nerve and vestibular nucleus are activated.
3. Impulses are transmitted via the lateral and medial vestibulospinal tracts to the spinal cord.
4. Flexor muscles activity is induced on the side opposite to the side to which the head is inclined. For the limbs, together with the flexors, the extensor muscles are activated on the side to which the head is inclined. The head movement opposes the movement registered by the vestibular system. (Hain, 2011)

VS reflexes are also involved in the landing reactions evoked by the linear acceleration associated with a fall, which include the increase of activity of the plantar flexors of the feet, increasing the stiffness of the muscles and serving to amortize the impact (Lacour, Xerri, & Hugon, 1978).

The VC reflexes are elicited by the whole body rotations and induce a contraction of neck muscles on the side opposite to the inclination to stabilize the head position in space (Baker, Goldberg, & Peterson, 1985). While the aim of the VCR is stabilization of the head in space, the reflex referred to as cervico-colic acts to

stabilize the head on trunk. To achieve better stabilization, these two reflexes act synergistically.

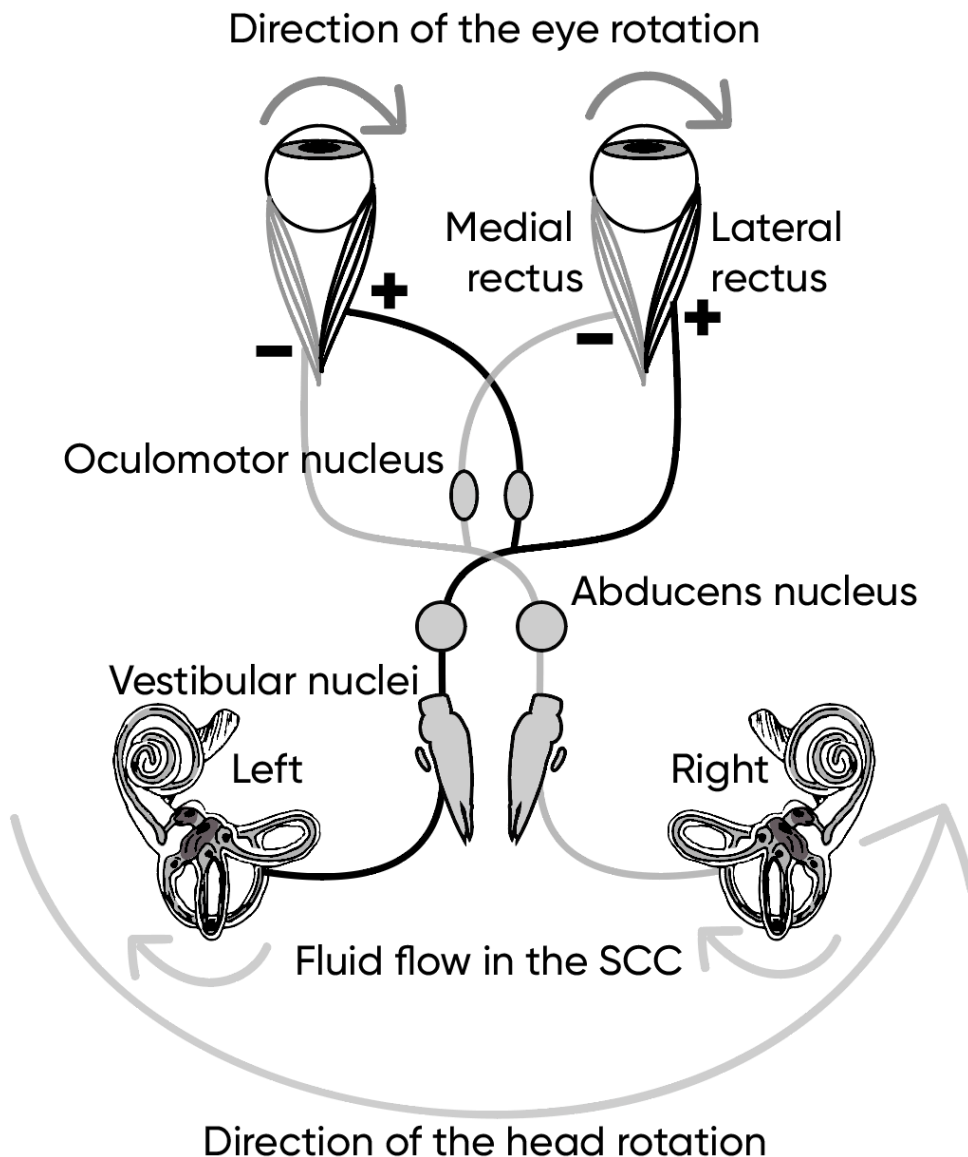
## **2. Vestibulo-ocular reflexes**

While the VSR and VCR act for stabilization of the body and head in space, the movement still might induce the image slipping on the eye retina, causing disturbances in vision. To counteract this slipping and to stabilize the gaze, a short-latency VOR takes place. This reflex generates the rotation of the eye around three spatial axes to compensate for the rotational or translational movement of the head.

The VOR can be subdivided into canal-ocular reflex (COR) that compensates for the angular velocity of the head and is induced by activation of the semicircular canals, and the otolith-ocular reflex (OOR) that compensates for the linear accelerations, including gravity, and is mediated by the otolith system.

### **a. Canal-Ocular Reflex**

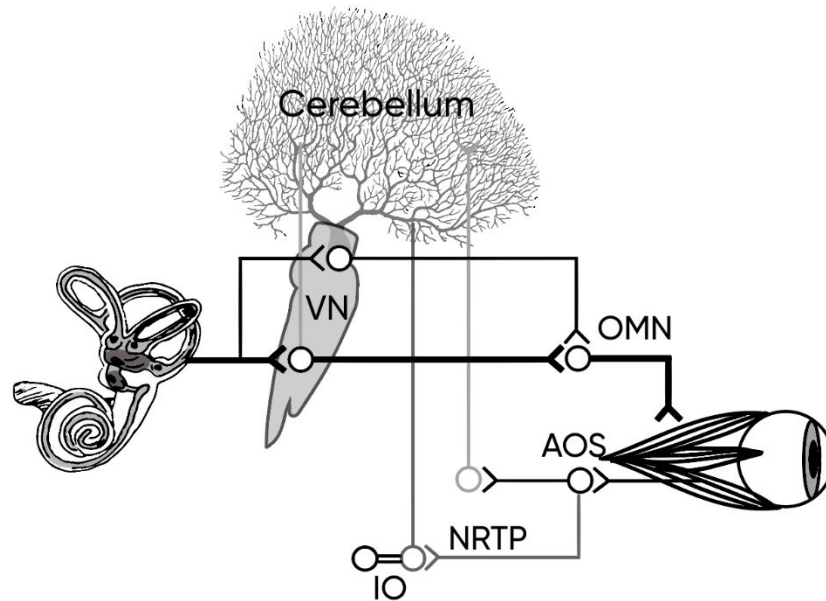
The core neurophysiologic organization of the canal-ocular reflex (COR) is a simple three-neuron reflex (Figure 21). This simplicity helps for the rapid response that the oculomotor system can provide to stabilize the gaze during rotation of the head.



**Figure 21 – Illustration of a push-and-pull organization of the canal-ocular reflex.** The head turns to the left, the ocular compensation is to the right. The left semicircular canal (SCC) is excited, while the right one is inhibited. Signals from the left SCC excite the ipsilateral Medial rectus and the contralateral Lateral rectus.

Head rotation activates semicircular canals that send the signal via the vestibular nerve to the vestibular nuclei (VN) and then to oculomotor nuclei (OMN). The OMN send the command for the ocular muscles to contract.

The cerebellum modulates the reflex. The simple three-neuron arc receives inhibitory input from the cerebellum at the level of the VN (Figure 22). The involvement of the cerebellum is determined by the estimation of the retinal slip, coming from the accessory optic system (AOS) via the nucleus tegmenti pontis (NRTP) and inferior olive (IO).

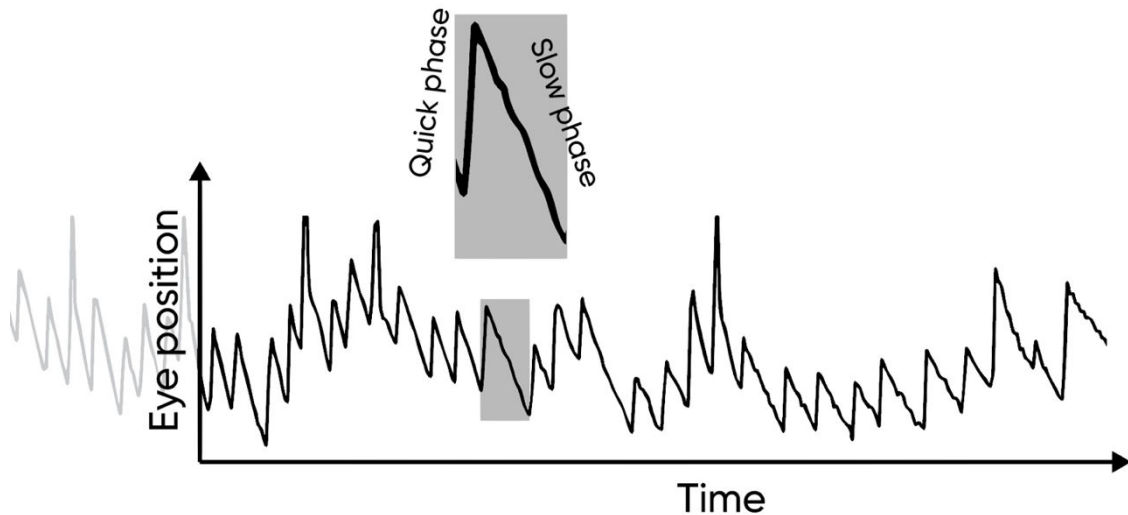


**Figure 22 – Illustration of a neural organization of the vestibulo-ocular reflex.**

VN – vestibular nuclei, OMN – oculomotor nuclei, AOS – accessory optic system, NRTP – nucleus tegmenti pontis, IO – inferior olive.

During the rotation of the head, the eyes rotate in the opposite direction. Ideally, to minimize the retinal image motion, the eye velocity should correspond to the velocity of the head rotation. When the rotation is sufficiently prolonged, so that the single motion of the eye in the orbit cannot compensate it, the smooth compensatory eye movement is interrupted with a rapid resetting movement in the opposite direction. This alteration of slow and rapid phases is called nystagmus (Figure 23). The slow phases are the eye movements in the direction opposite to the direction of rotation serving to fix the visual image on the retina. They are aimed to stabilize the vision. The rapid phases are the fast movements in the

direction of the head rotation. They are aimed to reset the eye position to make it possible for the eye to continue the slow phase compensation.



**Figure 23 – Illustration of the nystagmic eye movements, containing quick and slow phases.**

The COR basic process is the following:

1. When the head turns to the right, endolymphatic flow deflects the cupulae to the left.
2. The receptor potential from hair cells in the right crista increases in proportion to the velocity of the head motion, while the receptor potential from hair cells in the left lateral crista decreases.
3. These changes in receptor potential induce changes in firing rate of the vestibular nerve and influence the discharge of the neurons of the medial and superior vestibular nuclei and cerebellum.
4. Excitatory impulses are transmitted via white matter tracts in the brainstem to the oculomotor nuclei which activate the right (ipsilateral) medial rectus and the left (contralateral) lateral rectus. Inhibitory impulses are also transmitted to their antagonists.

5. Simultaneous contraction of the left lateral rectus and right medial rectus muscles, and relaxation of the left medial rectus and right lateral rectus occurs, resulting in lateral compensatory eye movements toward the left.

6. If the eye velocity is not adequate for the given head velocity and retina image motion is  $>2^\circ$  per second, the cerebellar projection to the vestibular nuclei will modify the firing rate of the neurons within the vestibular nuclei to reduce the error. (Hain, 2011)

When the rotation remains at the constant velocity for a sufficiently long time, the nystagmus decay due to the inertia of the endolymph, that keeps up with the head velocity. Physically, it takes about 7 seconds for the endolymph to release the cupula, and the semicircular canals afferents stop firing, although the head is still rotating. However, the time constant of nystagmus is considerably greater, making approximately 15-28 seconds (Raphan, Matsuo, & Cohen, 1979). This prolongation is due to the neural mechanism called the *velocity storage*. This mechanism was first proposed in 1979 by Cohen and colleagues (Raphan et al., 1979), and recently the velocity storage neurons were found in the medial and lateral vestibular nuclei in monkey (Yakushin et al., 2017). The velocity storage keeps the information of the velocity of movement and signals it to the oculomotor system, even though the vestibular nerve no longer signals the head movement.

When the rotation stops, the endolymph keeps rotating by inertia in the same direction the head had been rotating. This creates the stimulation of the semicircular canals in the direction opposite to the direction of the preceding rotation. Even if actually the head is not moving, this stimulation creates the nystagmus and the feeling of rotation, if no visual input is present.

Within the range of natural head movements (0.1–5 Hz) the semicircular canals act as sensitive speedometers, sending angular velocity information to the vestibular nuclei. In the limits of this frequency range, the compensation is close to perfect: the COR has roughly  $180^\circ$  phase shift comparing to the head movement, and the gain is close to unity. Phase shift of  $180^\circ$  refers to the slow phase movements in the direction opposite to the one of the head. The unity gain means that the absolute velocity of the slow phase eye movement is equal to the velocity of the head. Outside this frequency band specific gain and phase changes occur,

such that there is a phase lead and decrease in gain at very low frequencies, whereas there is a phase lag at very high frequencies.

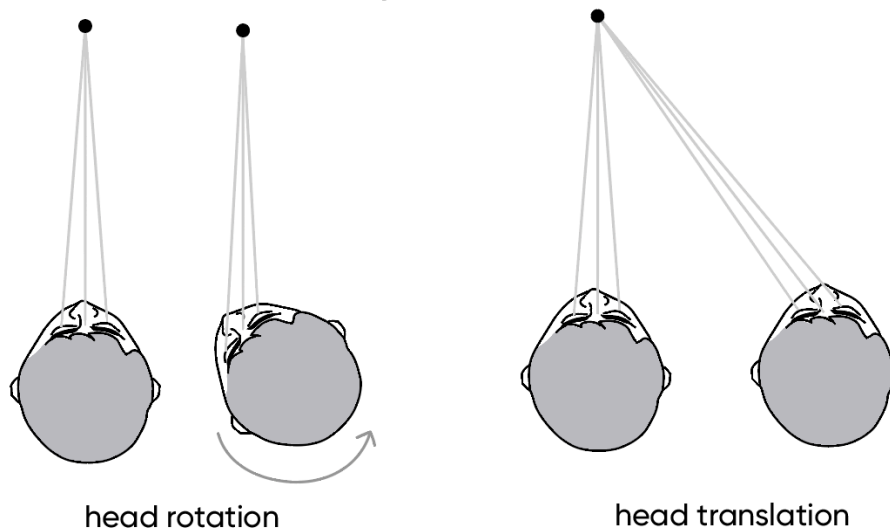
The time constant and gain of the slow phase nystagmus are used as the major parameters to assess the COR. The time constant is classically the time the reflex decays to 33% of the initial value. The gain is the ratio of eye movement to the head movement velocity. These parameters define the efficiency of the COR in stabilizing the visual image on the retina during head rotations.

### **b. Otolith-Ocular Reflex**

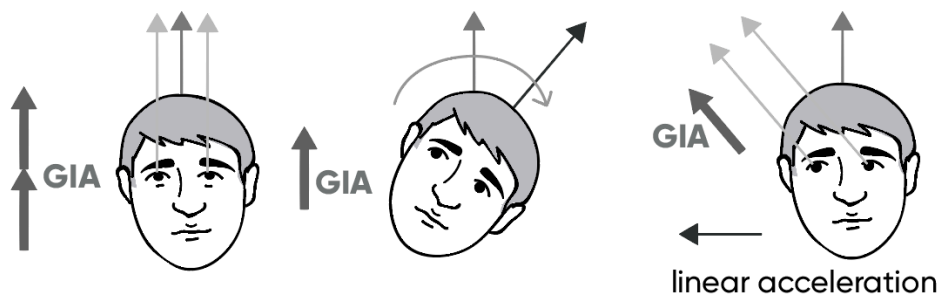
The otolith-ocular reflex (OOR) compensates for linear motion or head inclination with respect to gravity. The pathways for the OOR are less well defined than the ones for COR. The multidirectional organization of macular hair cells creates a complex firing pattern in the afferent nerves. However, the latency of eye muscle response indicates that a disynaptic pathway for the OOR exists as well as for the COR (Baloh, Honrubia, & Kerber, 2011). To simplify the model, the utricular and saccular sensors are often regarded as one single sensor placed in the center of the head and sensing the gravito-inertial acceleration (GIA), which is a resultant vector sum of linear motion accelerations and gravitational acceleration.

The OOR produces two modes (Figure 24) of response to otolith input: orienting and compensatory (Raphan & Cohen, 2002). The orienting OOR compensates for the tilt of the head with respect to the gravitational vertical. In fish, amphibians and rodents OOR is able to compensate the tilt of the head with the gain of about 0.6 (which makes 60% of the angle of the tilt of the head). In humans, the orienting OOR is less efficient, having the gain of only about 0.1. However, for the compensatory OOR, while lateral eyed species have a limited response to linear accelerations, in humans and primates this response is performant.

## Compensatory gaze mechanisms



## Orienting gaze mechanisms



**Figure 24 – Compensatory and orienting otolith-ocular reflexes.**

The orienting OOR consists of either torsional or vertical eye movements during the head tilt in roll and pitch, respectively. These ocular counterrollings last as long as the head tilt persists. The orienting OOR is driven primarily by the otoliths.

The compensatory OOR, also named translational VOR (tVOR) or linear VOR (IVOR) (Paige & Tomko, 1991), helps to maintain the binocular fixation during linear translations of the head. Therefore, this reflex is closely related to smooth pursuit optokinetic reflexes. When the gaze is orthogonal to the direction of motion, horizontal or vertical responses occur. This reflex is highly dependent on the gaze fixation distance. The compensatory OOR is a result of activation not only of otolith organs, but of the convergent signal from both otolith and canalar



structures. This implies that the OOR involves internal computations to distinguish the translational component of the GIA.

During a complex prolonged stimulation such as constant velocity rotation on a rotatory chair with an inclined axis, the OOR is characterized by two components. One component, the bias, compensates for the inclination and represents a steady-state horizontal slow phase eye velocity (Kushiro et al., 2002). For small angles of tilt, the magnitude of the bias at a given velocity of rotation is proportional to the angle of tilt (Young & Henn, 1975). The other component, modulation, is the amplitude of harmonic eye oscillations related to the position of the head with respect to gravity (Kushiro et al., 2002).

### **c. VOR interactions**

If the rotation is performed in light, in presence of the visual input, the VOR is supported by optic reflexes. Optokinetic nystagmus appears as a response to whole-field visual motion. Pursuit is smooth following a visual target. However, these reflexes work better at low frequencies due to the delays in visual processing.

Neck proprioceptors contribute to the generation of nystagmus. Under normal conditions the cervico-ocular reflex gain is very low, however it can be facilitated following the loss of vestibular sensors. Cervico-ocular reflex is considered to function in coupling with the VOR.

Somatosensation is also capable of inducing nystagmus. It was demonstrated that subjects with bilateral vestibular loss (BVL) can develop more pronounced somatosensory nystagmus than normal subjects, which can indicate that BVL subjects use somatosensory information to a greater extent than normal subjects (Bles, Jong, & de Wit, 1984).

## **3. Vestibular effect on autonomic functions**

Changes in posture challenge the cardio-vascular regulation and blood circulation in an organism. The vestibular system is not the only, but the primary organ to

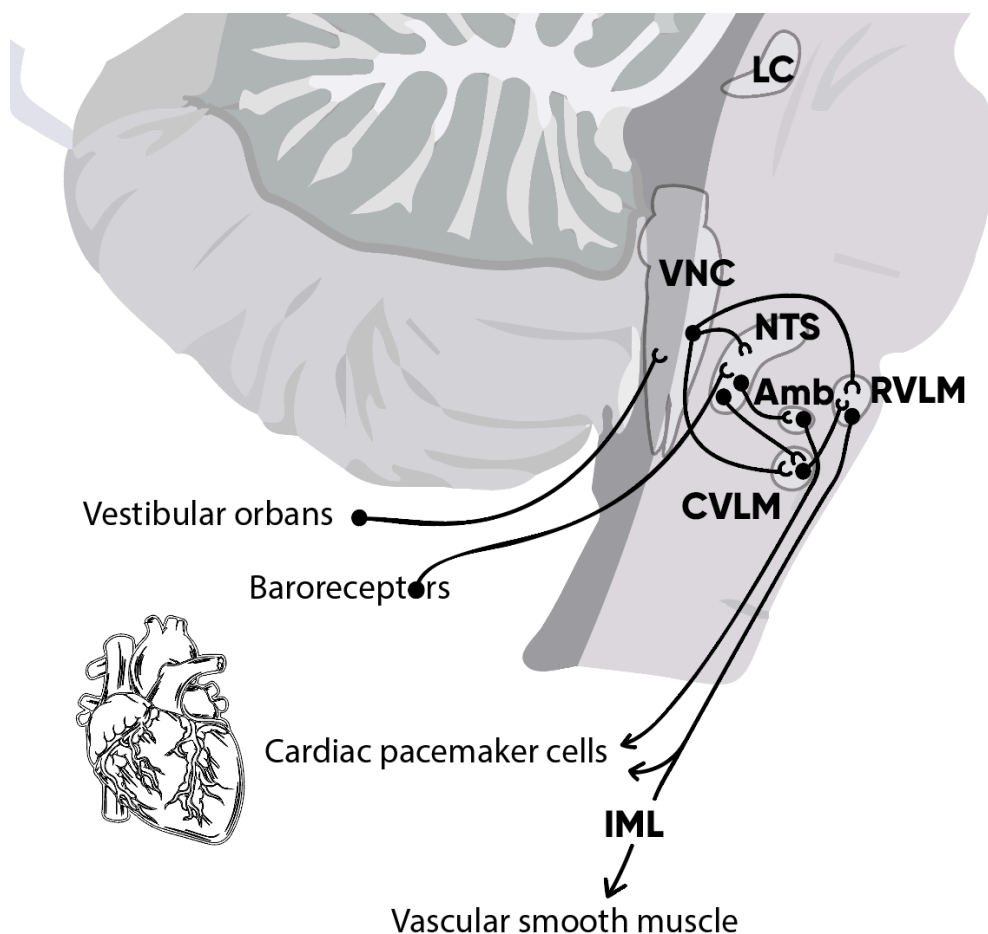
detect the reorientation in space and with respect to gravity. It rises the hypothesis of possible vestibulo-autonomic interactions and questions the role of the vestibular system in modulating cardio-vascular function.

Autonomic functions of the body include processes that do not require the cognitive involvement, such as vascular contractility and cardiac activity. Such processes are regulated by two nervous system subdivisions: the sympathetic (SNS) and parasympathetic (PNS) nervous systems. Both systems have their preganglionic cells located in the central nervous system that connect to postganglionic cells situating in the peripheral ganglia. The postganglionic neurons innervate smooth muscles or cardiac muscles and pacemaker cells in the heart. Often the systems are described to work in a push-and-pull manner, where sympathetic system is responsible for stress responses (increase in heart rate, inhibition of digestion, dilatation of pupils etc.), while parasympathetic is responsible for relaxation and recuperation. Indeed, it is the case for many functions, however, there are many exceptions. For example, the pacemaker of the heart is influenced by the two systems, while the vascular resistance is controlled almost exclusively by the sympathetic subdivision, with parasympathetic innervation of vascular smooth muscles only in a few specific zones. Rostral ventrolateral medulla (RVLM) is a critical brain region for basal and reflex control of sympathetic activity (Figure 25).

### **a. Pathways**

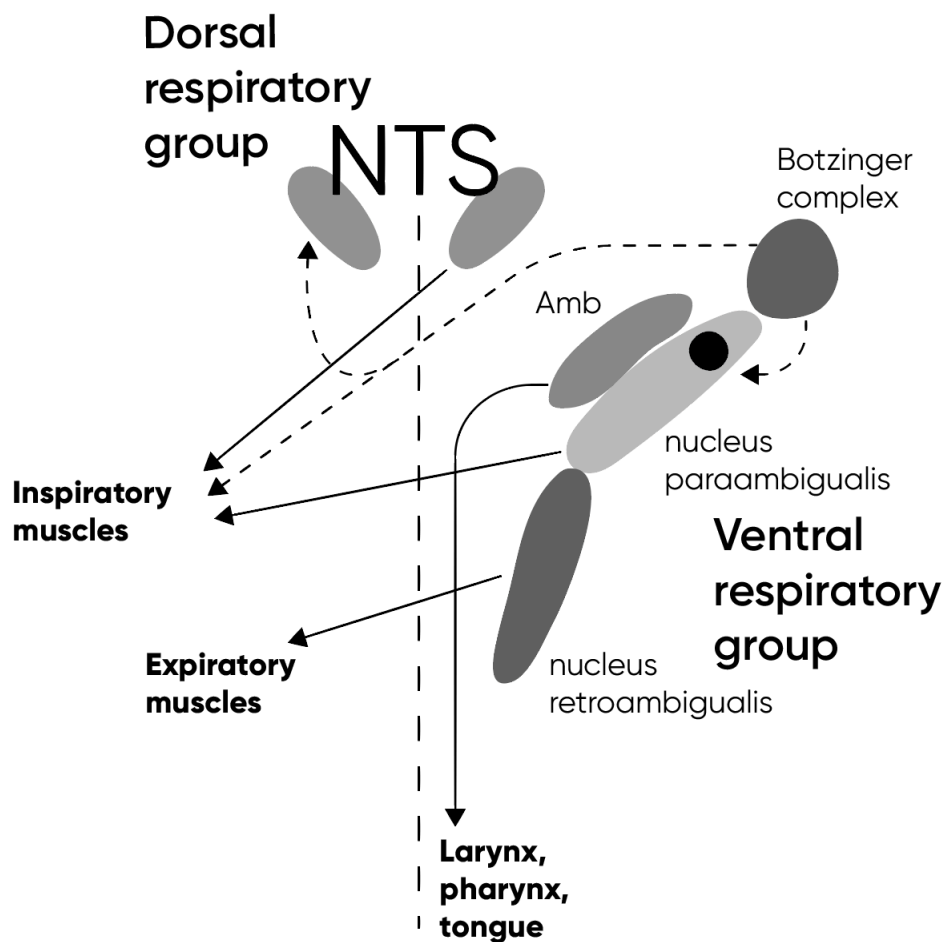
The current knowledge of the pathways that can mediate the vestibular effect on cardio-vascular and respiratory regulation is not exhaustive, though it reveals the real implication of the vestibular signals in autonomic regulation. There is a number of pathways that allow the vestibular system to influence the regulation of circulation. Lesions of the portions of the medial and inferior vestibular nuclei located immediately caudal to the lateral vestibular nucleus, abolish the changes in sympathetic activity, caused by electrical or natural vestibular stimulations (Uchino, Kudo, Tsuda, & Iwamura, 1970; Yates, Jakus, & Miller, 1993). Reticulospinal neurons in the rostral ventrolateral medulla (RVLM), which is considered to be the major region providing excitatory input to the SNS, is also influenced by the vestibular system. More than two thirds of neurons in this area

respond to electrical stimulation of the vestibular nerve (Yates, Siniiaia, & Miller, 1995), while lesions of this region abolish the vestibular effect on the sympathetic regulation (Yates, Yamagata, & Bolton, 1991). The inflow of the vestibular signals to the RVLM is mediated primarily by the reticular formation of the caudal ventrolateral medulla (CVLM), lesions of which also abolish vestibulo-sympathetic responses (Steinbacher & Yates, 1996). In sum, CVLM mediates the projections from medial and inferior vestibular nuclei to the RVLM that excites the sympathetic nervous system. The pathway through CVLM is the major, however other pathways are hypothesized.



**Figure 25 – Illustration of major pathways for the vestibulo-sympathetic reflex and baroreflex.** The RVLM is the major zone for the control of sympathetic activity. VNC – Vestibular Nuclear Complex, RVLM – Rostral Ventrolateral Medulla, CVLM – Caudal Ventrolateral Medulla, Amb – Nucleus Ambiguus, NTS – Nucleus Tractus Solitarius, LC – Locus Coeruleus. The indirect pathway from VNC to RVLM through LC is also possible (not indicated in the figure).

The same portions of medial and inferior vestibular nuclei seem to participate in respiratory control. Lesions of these areas abolish respiratory responses elicited by natural and electrical stimulations (Rossiter, Hayden, Stocker, & Yates, 1996; Yates et al., 1993). Respiratory center is located in the brainstem and consists of medullary and pontine respiratory groups (Figure 26). Dorsal respiratory group (DRG) is located in the ventrolateral portion of the nucleus of the solitary tract (NTS) in medulla and contains mostly inspiratory neurons. It receives signals from a variety of receptors.



**Figure 26 – Illustration of major pathways for vestibulo-respiratory interaction.** Ventral respiratory group (VRG) and dorsal respiratory group (DRG; in NTS) can both receive vestibular inputs. NTS – Nucleus Tractus Solitarius or nucleus of the solitary tract; Amb – Nucleus Ambiguus.

The Ventral respiratory group (VRG) is located in the ventrolateral medulla and contains both inspiratory and expiratory neurons, as well as “pacemaker” respiratory cells. VRG is shown to be affected by the electrical stimulation of the vestibular nerve (Miller, Yamaguchi, Siniaia, & Yates, 1995; Shiba, Siniaia, & Miller, 1996). However, other pathways mediating vestibular signals to respiratory motoneurons might exist, because lesions in VRG does not abolish vestibulo-respiratory responses in respiratory muscles (Shiba et al., 1996).

Electrical stimulation of the vestibular nerve has shown a broad range of responses recorded from the sympathetic nerve (Ishikawa & Miyazawa, 1980; Kerman & Yates, 1998; Steinbacher & Yates, 1996; Tang & Gernandt, 1969; Uchino et al., 1970; Yates et al., 1993; Yates et al., 1995). The responses were both inhibitory and excitatory, and were found to be patterned differently in the upper and lower body (Kerman, Yates, & McAllen, 2000). Blood pressure was affected by electrical stimulation of the vestibular nerve (Ishikawa & Miyazawa, 1980; Kerman et al., 2000; Uchino et al., 1970).

While electrical studies revealed the influence of vestibular activation on sympathetic activity, natural stimulation studies provided insights into the physiological significance of the reflex.

### **b. Vestibular effect on the cardiovascular control**

Yates and colleagues examined the splanchnic nerve activity during rotation of the head in decerebrate and broadly denervated cats. Splanchnic nerve activity was modulated mostly by pitch rotations, increasing in head-up position and decreasing in head-down position (Yates & Miller, 1994). The maximal amplitude of rotations was 20°. Another study used the similar protocol with the amplitude of rotation of 50° to assess the effect of head rotations on blood pressure (Woodring, Rossiter, & Yates, 1997). As in the previous study, the head-up pitch tilts elicited a significant increase in blood pressure that was not supported by an increase in heart rate, which suggests the changes to be due to the increase in peripheral vasoconstriction. The increases in blood pressure were abolished by transection of the VIIIth cranial nerve, that confirms the labyrinthine origin of the reflex. Interestingly, a later study showed that the vestibular effect of head-up rotation on a stationary body was present only following an upper cervical

rhisotomy to eliminate neck inputs (Bolton, Kerman, Woodring, & Yates, 1998). When the neck receptors were intact, the neck and vestibular inputs to the vestibular nuclei were cancelled and thus produced no changes in blood pressure. This finding highlights that the vascular responses for the head-only and the head-and-body reorientations are differentiated. Bilateral VIIIth nerve transection impaired the blood pressure adjustment during passive whole-body pitch tilts in anesthetized (Doba & Reis, 1974) and awake (Jian, Cotter, Emanuel, Cass, & Yates, 1999) cats. Lesions in the caudal aspect of the vestibular nucleus complex also resulted in decrease of blood pressure during nose-up tilts in conscious cats (Mori, Cotter, Arendt, Olsheski, & Yates, 2005). In another study, whole body head-up tilt in conscious cats elicited a decrease in both hindlimb and forelimb blood flow (Wilson et al., 2006). However, a bilateral vestibular neurectomy abolished the changes in blood flow of the hindlimbs, but not of the forelimbs, which supports the finding of electrical studies about an anatomically patterned character of vestibulo-sympathetic responses (Kerman et al., 2000).

In human, the vestibular involvement in the cardiovascular regulation has been more difficult to ascertain. However, it is not surprising, as far as the methodologies to study the human vestibulo-sympathetic interaction are more challenging and indirect than those used in animal studies.

Studies using galvanic vestibular stimulation (GVS) have shown that dynamic sinusoidal GVS could induce a short-lasting increase in muscle sympathetic nerve activity (MSNA) (Bent, Bolton, & Macefield, 2006; Bolton, Wardman, & Macefield, 2004). Interestingly, the galvanic effect on MSNA seems to be differentially bilaterally driven – at low frequencies, the GVS induces two peaks of MSNA per cycle, supposedly one for depolarization of ipsilateral vestibular nerve and the other for depolarization of contralateral (Hammam, James, Dawood, & Macefield, 2011). Skin sympathetic nerve activity (SSNA) demonstrated the same lateralized expression as MSNA in response to sinusoidal GVS (Hammam, Dawood, & Macefield, 2012). It is worth mentioning that the modulation of SSNA response positively correlated with the intensity of nausea reported by subjects (Hammam et al., 2012). Studies using GVS have demonstrated that the vestibular stimulation affects the sympathetic activity in human.

Natural stimulation studies have given insights into the characteristics and more precise nature of the response. First, it was demonstrated that the activation of the

horizontal semicircular canals during yaw rotations does not increase sympathetic outflow to muscles and skin (MSNA and SSNA) (Ray & Hume, 1998). At the same time, linear acceleration on a chair was demonstrated to evoke an increase in blood pressure and heart rate in healthy volunteers (Yates, Aoki, Burchill, Bronstein, & Gresty, 1999). Moreover, in the same study three patients with profound bilateral reduction in vestibular function presented a much smaller response (Yates et al., 1999). These results strongly suggest the otolithic origin of the vestibulo-sympathetic interaction.

The study of Essandoh et al. showed that the head-down neck flexion (HDNF, see figure 39) in ventrally lying subjects, which is considered a primarily otolithic stimulation, decreased blood flow in the forearm and calf with the blood pressure unchanged (Essandoh, Duprez, & Shepherd, 1988), while the same manoeuvre induced an increase in blood pressure and heart rate in another study (Shortt & Ray, 1997). Normand and colleagues repeated the experiment with addition of the HDNF in a lateral decubitus position, and concluded that the cardiovascular adjustment during the HDNF did not originate from the neck receptors (Normand, Etard, & Denise, 1997). Prolonged HDNF increased the frequency of MSNA bursts, the heart rate and diastolic blood pressure, as well as the calf vascular resistance in another study by Ray and colleagues (Ray, Hume, & Shortt, 1997; Shortt & Ray, 1997). Cardiovascular responses to HDNF were modulated by the amplitude of neck flexion (Hume & Ray, 1999). Even though the HDNF is shown to induce increases in MSNA firing frequency, SSNA seems to be unaffected by the manoeuvre (Ray et al., 1997). Unlike in animals, in human the MSNA activity was found to be affected equally in the arm and leg, however the vasoconstriction was 61% greater in the calf than in the arm (Monahan & Ray, 2002). Interestingly, it did not affect much the arterial blood pressure, which might suggest that vasodilation in other vascular beds counterbalanced the vasoconstriction.

While the HDNF studies find an increase in sympathetic response during head down position, the study using OVAR stimulation conversely demonstrates the increase in MSNA in lower limbs in humans in nose-up position (Kaufmann et al., 2002). The effect of respiration or baroreceptors on the change in MSNA was ruled out in the study. The studies using sinusoidal sled linear acceleration also demonstrated conflicting results. One team found that MSNA burst rate decreased during sled oscillations along both naso-occipital and interaural axes (Cui, Iwase,

Mano, Katayama, & Mori, 1998, 2001). Respiration was controlled, and the arterial blood pressure remained unchanged that indicates that the change in MSNA was not due to respiration or activation of the baroreceptors. Another research team used the same type of stimulation, but at very low frequencies (Grewal, Dawood, Hammam, Kwok, & Macefield, 2012; Hammam et al., 2012). The response also occurred for translations along both naso-occipital and interaural axes, but the lower limb MSNA and SSNA increased. The discrepancies in the results of different studies are tremendous. Even if almost all studies conform to the idea that the otolithic stimulation induces changes in sympathetic activity, the direction of head movement eliciting the responses varies with stimulation technique and the modulation of the response seems to inverse with differing frequencies of stimulation. Different vestibular stimulation techniques used in studies with human subjects activate a variety of different non-vestibular receptors along with the vestibular ones. Moreover, different characteristics of the stimulation might be interpreted differently, if they pass by a central estimator, like they do for the generation of the VOR (Merfeld et al., 1999). Thus, we could suggest that sympathetic responses to vestibular stimulation in humans might be integrative, and be modulated by a variety of different signals.

The effect of the vestibular stimulation on cardiac output was demonstrated by Radtke et al., (Radtke, Popov, Bronstein, & Gresty, 2000, 2003). The small amplitude head drops, actively stimulating vestibular system, evoked a shortening of the time between the beat preceding the head drop, and the following one, in healthy subjects. In the subjects with bilateral vestibular loss, the cardiac response was significantly delayed. The authors suggested that this cardiac output was more probably due to the parasympathetic, rather than sympathetic action due to the short latency of the response. At the same time, more delayed blood pressure changes were attributed to the sympathetic activation. The authors have attributed the cardiac effect to the activation of the semicircular canals during the head drop. However, similar findings were reported in the study of Yates (Yates et al., 1999). Linear sled translation, that activates the otolith system, but not the semicircular canals, also evoked rapid decrease in the RR interval within the first one or two heartbeats (Yates et al., 1999). Another study also reported the increase in the heart rate within the first or second heartbeat following the linear translation stimulus in healthy subjects, but not the vestibular patients. The effect was present regardless if the stimulus was expected or unexpected (Jáuregui-Renaud,



Reynolds, Bronstein, & Gresty, 2006). HDNF in prone subjects was reported to significantly affect heart rate variability (Lee, Wood, & Welsch, 2001), in particular the increase in the low-frequency components, that is thought to reflect the sympathetic activity, and a decrease in the high-frequency component, attributed to the parasympathetic activity on the heart. HDNF in lateral decubitus position did not cause such effect on heart rate variability (Lee et al., 2001).

### **c. Vestibular effect on respiration**

Respiratory effect of vestibular stimulation has been investigated using electrical and natural stimulations.

In animals, electrical stimulation of the vestibular nerve in decerebrate cats produced reflex activations in a variety of respiratory muscles (Siniaia & Miller, 1996; Yates, Jakus, et al., 1993). In a study using natural stimulations, the activation of phrenic, abdominal and hypoglossal nerves was maximal in denervated cats during the nose-up pitch (Rossiter et al., 1996; Rossiter & Yates, 1996). The responses were abolished with the elimination of the vestibular input.

In human, natural and caloric stimulations were used to reveal the vestibular effect on respiration. Pitch rotations increased the respiratory rate in healthy subjects, while no conclusive effect was observed in vestibular-deficient patients (Jauregui-Renaud, Gresty, Reynolds, & Bronstein, 2001). Caloric stimulation of semicircular canals also increased the rate of respiration in healthy subjects, but not in a labyrinthine defective patient (Jauregui-Renaud, Yarrow, Oliver, Gresty, & Bronstein, 2000). However, only one patient was investigated in this study. Another study examined vestibulo-respiratory reflex through a range of natural stimulations (Monahan, Sharpe, Drury, Ertl, & Ray, 2002). Dynamic head-on-body rotations activating both semicircular canals and otoliths (pitch and roll) and only semicircular canals (yaw and pitch in lateral decubitus position), as well as head-and-body rotations in yaw on the rotatory chair, increased the respiratory rate. Static head down neck flexion did not affect the respiratory rate. The authors concluded that only semicircular canals, but not the otoliths, affect respiration. However, this study used only static otolithic stimulation by changing the head position with respect to gravity, moreover, other sensors except otoliths are involved during HDNF. Hence, the absence of ventilatory alteration during HDNF

does not provide definitive proof of the lack of involvement of the otolithic system in respiratory control. Indeed, another study by Omlin and colleagues shows that dynamic otolith stimulation by rocking movements along the longitudinal axis of a body affect human respiration frequency (Omlin et al., 2016). A study by Kaufmann et al. (Kaufmann et al., 2002) used the stimulation on the rotatory chair with an inclined axis (OVAR) to verify the effect of otolithic stimulation on respiration. During OVAR, in head-fixed coordinates, the component of the gravity vector perpendicular to the axis of rotation revolves around this axis and periodically stimulates the graviceptors (both otolithic and visceral). When the angular velocity is constant, only the graviceptors are stimulated but not the semicircular canals. The study demonstrated that ventilation synchronizes with chair rotation (Kaufmann et al., 2002). However, we cannot attribute the effect solely to the otoliths, as far as OVAR can stimulate other sensors such as graviceptors and proprioceptors.

It is known that aging can induce significant morphological changes to the vestibular endorgans and nuclei (Smith, 2016), reducing the redundancy of the vestibular information. Consistently, aging was shown to attenuate the vestibulo-sympathetic reflex (Ray & Monahan, 2002), as well as vestibulo-respiratory reflex (Kuipers, Sauder, & Ray, 2003)

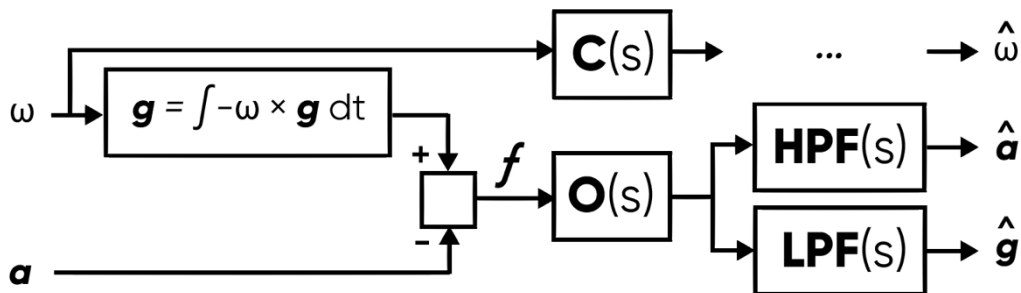
#### **4. Estimation of gravity: tilt-translation ambiguity**

The estimation of vertical is closely related to the perception of the direction of gravity. However, the task is not trivial as the otolithic input is intrinsically ambiguous, because the activation pattern for the tilt with respect to gravity, or for the linear translation is actually the same. As stated by Einstein's Equivalence Principle, the inertial linear acceleration is physically indistinguishable from gravity. In spite of that, perceptive and ocular responses evidence that the CNS can distinguish the gravity and inertial acceleration.

The otolith input itself is a resultant acceleration (**GIA**), containing a vector sum of the linear translation component (**a**) and gravity (**g**),  $\mathbf{GIA} = \mathbf{a} + \mathbf{g}$ . Thus, according to the GIA resolution hypothesis, the translation component could be

found by the operation of a vector subtraction  $\mathbf{a} = \mathbf{GIA} - \mathbf{g}$ . When the internal estimate of gravity is derived erroneously, due to a misleading stimulation, the model may result in an illusory perceptions or erroneous responses (Clément, Moore, Raphan, & Cohen, 2001; Merfeld et al., 1999).

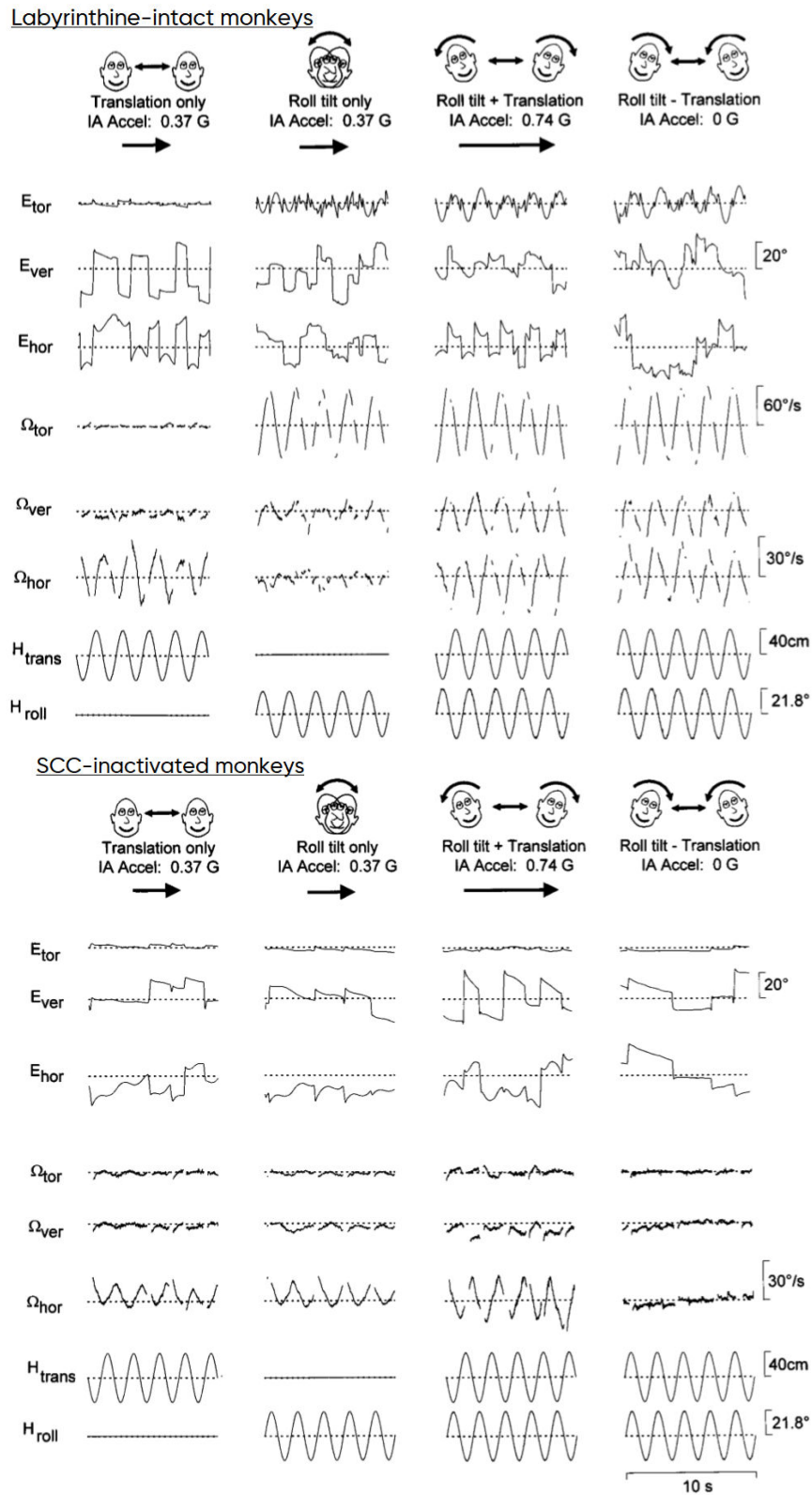
Two different approaches are used to explain how the nervous system manages the processing of the resultant gravito-inertial acceleration (GIA) to distinguish the gravity component from the translation. The first and simpler approach is frequency segregation of the GIA signal (Figure 27). It is based on the assumption that the gravity inputs are less dynamic than the translational ones. If so, the gravity component of the GIA stimulus would have low-frequency characteristics, while the translational component would be characterized by high frequencies. Therefore, simple low-pass filtration of otolith signals would help to distinguish the gravity component (Mayne, 1974; Paige & Tomko, 1991).



**Figure 27 – The frequency segregation model using low-pass filtering of otolithic inputs.**  $\mathbf{a}$ ,  $\mathbf{g}$ ,  $\omega$  are the estimates of the linear, angular and gravitational acceleration respectively,  $\mathbf{f}$  is the gravito-inertial acceleration. The same with circumflex stand for the neural estimates of these values.  $\mathbf{C}(s)$  and  $\mathbf{O}(s)$  are the functions of semicircular canals and otolithic organs. HPF – high-pass filter; LPF – low-pass filter. From (Merfeld, Park, Gianna-Poulin, Black, & Wood, 2005).

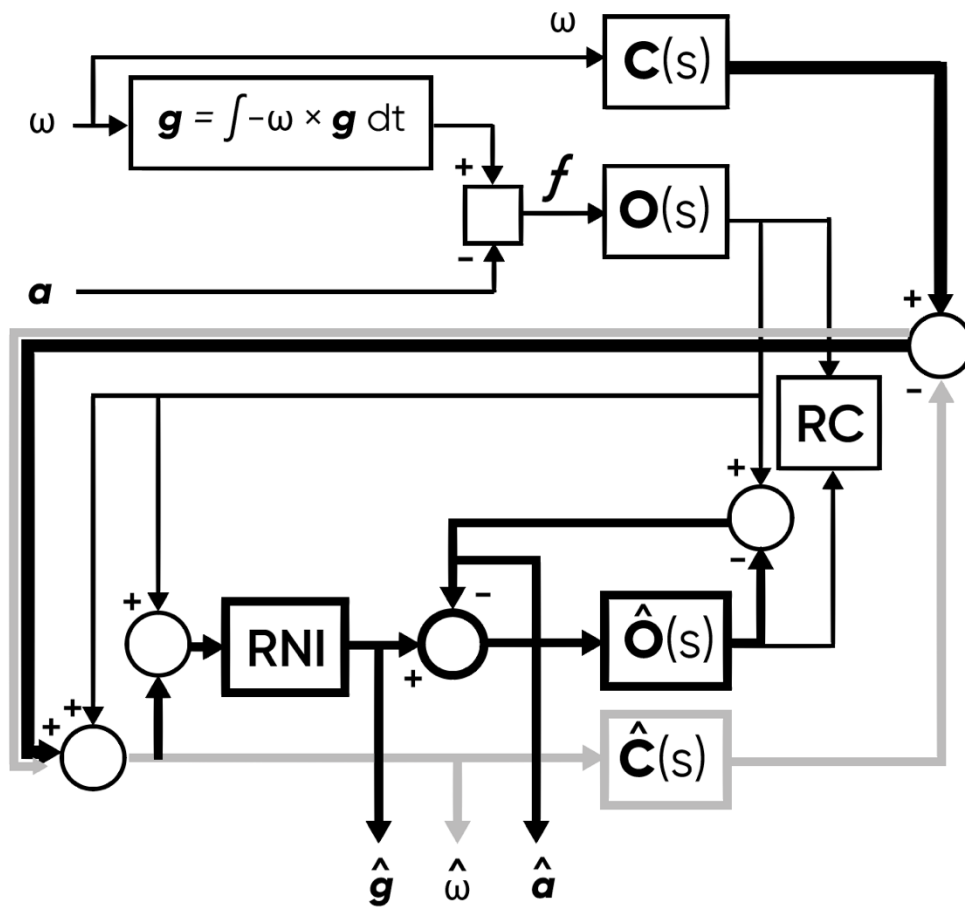
Another approach is the “multisensory integration” that refers to the integration of signals from otoliths and semicircular canals, and probably other sensors, to recreate the internal estimates of parameters of spatial orientation such as gravity direction, linear acceleration, angular velocity (Angelaki, Shaikh, Green, & Dickman, 2004; Angelaki, McHenry, Dickman, Newlands, & Hess, 1999; Merfeld & Zupan, 2002; Merfeld et al., 1999; Oman, 1982, 1990).

The study of Angelaki et al. (Angelaki et al., 1999) on labyrinthine-intact monkeys and monkeys with plugged canals has demonstrated that the cues from semicircular canals are necessary for discrimination between tilt and translation (Figure 28). The motion protocols for vestibular stimulation included lateral translation, roll tilt and combinations of both. While the horizontal ocular responses of labyrinthine intact monkeys reflected the translational component of the otolith input, those of monkeys with plugged canals reflected the primary unseparated otolith input. In the figure 28 we can see, for example, that the ocular response for the tilt and translation protocol that cancelled the otolithic input ( $GIA = 0$ ), compensates well to the actual motion with horizontal, vertical and torsional components, while it is absent in the monkeys with plugged canals. This study demonstrates that the semicircular canals input is required for the CNS to distinguish tilt from translation.



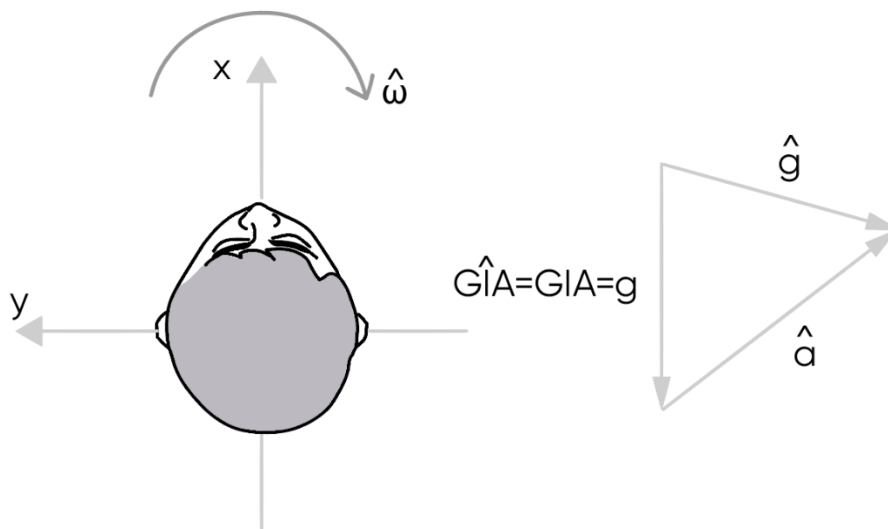
**Figure 28 – Ocular responses to tilt/translation protocols in monkeys with intact and plugged semicircular canals.** E – eye position,  $\Omega$  – eye slow phase velocity, H – motion stimulus. From (Angelaki et al., 1999).

The internal model has been developed by many researchers (Angelaki et al., 2004; Barra et al., 2010; Clark, Newman, Karmali, Oman, & Merfeld, 2019; Clark, Newman, Oman, Merfeld, & Young, 2015; Merfeld et al., 1999; Merfeld et al., 2005; Oman, 1982). The internal model (Figure 29) refers to the neural representation of physical values, assuming also that the CNS models the dynamics of sensory organs (Oman, 1982).



**Figure 29 – The internal model representation.**  $a$ ,  $g$ ,  $\omega$  are the estimates of the linear, angular and gravitational acceleration respectively,  $f$  is the gravito-inertial acceleration. The same with circumflex stand for the neural estimates of these values.  $C(s)$  and  $O(s)$  are the functions of semicircular canals and otolithic organs. The same with circumflex are the internal models of the sensory dynamics of these organs.  $RNI$  – rotational neural integrator;  $RC$  – rotational comparator. Gray pathways relate to the velocity storage mechanism. From (Merfeld et al., 2005).

Internal model predictions were confirmed in natural stimulations experiments (Clark et al., 2015; Merfeld et al., 1999). For example, Merfeld and colleagues (Merfeld et al., 1999) demonstrated that due to the internal model the ocular compensation for horizontal translation can occur even without actual movement. Human subjects were tilted immediately after the rapid deceleration to a stop after rotation around the vertical axis. The tilt was performed in one of the eight directions: nose-up, nose-down, right-down, left-down or the directions in between these orientations. The static tilt in presence of post-rotatory residual stimulation of semicircular canals evoked the erroneous ocular compensation for translation, even if no translation is actually happening. The internal model can predict this erroneous response (Figure 30).



**Figure 30 – Post-rotatory semicircular canals activation in non-vertical position.** Without real motion, post-rotatory stimulation of semicircular canals turns the estimated direction of gravity from the real direction of gravity. This causes also the non-zero estimation of translational component.

Many vestibular responses such as perception of the vertical or the VOR require the estimates of gravity and translation. It is possible that both the frequency segregation and internal model approaches could be employed by the central

processing (Merfeld et al., 2005). VOR and perception of movement were found to employ different neural strategies to resolve the tilt/translation task. According to Merfeld et al. (Merfeld et al., 2005), the low-pass filtering, which is simpler and faster, is used to control the VOR responses, while the perception operates the internal models to get the estimates of tilt and translation components of graviceptor signal. This assumption seems logical in regard that the VOR demands rapid processing, while more complex circuitries of perception can be integrative to get the best, though not as reactive, estimate of spatial parameters.

Apart from the gravity direction estimation, many processes require internal models. The most elaborate models were created in attempt to simulate motion sickness and understand the mechanism of its origin (Oman, 1982).

## **5. Subjective vertical**

The vestibular system is reliable in a specific frequency range. To make the process of estimation of the gravitational vertical more robust, it is possible that the CNS implies the integration of other sensory and central systems in a weighted manner. Vestibular inputs are thus combined with proprioceptive signals from muscle and tendon receptors, visceral signals (from the kidneys, vena cava, etc.), and visual signals. Zupan et al. (Zupan, Merfeld, & Darlot, 2002) proposed the “multi-cue weighted averaging” hypothesis, suggesting that the “central estimate” of a physical variable is computed as a weighted sum of all available intermediate estimates of this physical variable derived from central processing of every sensory system concerned. The combination of multisensory inputs makes the estimates of the vertical quite accurate and precise. Indeed, in an upright position without visual cues a person can estimate the vertical with an error of less than 2° of bias from the real vertical by aligning an initially tilted luminous bar with their subjective vertical (Vingerhoets, De Vrijer, Van Gisbergen, & Medendorp, 2009).

However, when the position of the head is not upright, the error rises significantly, moreover it tends to tilt towards the body longitudinal axis, which is known as Aubert effect (Aubert, 1861). The amount of the error is dependent on the angle of the head and body tilt. At the same time, the subjects are able to report the angle



of the head and body tilt rather accurately. This led Mittelstaedt to introduce a hypothesis of an idiotropic vector (Mittelstaedt, 1983). According to Mittelstaedt, the estimate of the vertical tends to be aligned with one's body longitudinal axis, "idiotropic vector". Mittelstaedt predicted that the tilt is overestimated in hypergravity, which was later demonstrated experimentally (Clark et al., 2015). This bias might be induced by the somatosensation. Indeed, the somatosensation was shown to contribute to the estimation of the subjective vertical. The loss of somatosensory cues decreases the *precision* of perceived vertical, though not the *accuracy* (Barra et al., 2010). This means, that the distribution of error of visual vertical estimate around the real vertical becomes larger, however, no constant bias occurs. In addition, the patients with somatosensory loss do not present the Aubert effect (Anastasopoulos & Bronstein, 1999; Anastasopoulos, Bronstein, Haslwanter, Fetter, & Dichgans, 1999; Yardley, 1990).

At the same time, unilateral vestibular loss affects the *accuracy*, inducing a shift of the perceived vertical towards the direction of lesion (Anastasopoulos, Haslwanter, Bronstein, Fetter, & Dichgans, 1997).

The visual cues are particularly strong and can significantly influence the perceived vertical. A Rod-and-Frame Test (RFT) was developed to reveal the individual dependence on the visual field (Asch & Witkin, 1948; Witkin & Asch, 1948). The task is similar to the assessment of the subjective vertical, except that the rod, that is supposed to be reset vertical, is presented inside a rectangular frame, tilted by an experimenter. The test reveals an individual strategy to perform a multisensory integration with weighting of the cues. The visual field dependence is characterized by a shift in the visual vertical towards the shift of the visual frame.

## Limitations of the vestibular system

As any other system, the vestibular system efficiency is limited to a certain range of typical or physiologically “possible” stimuli. Within the natural range of self-movements, the vestibular system usually copes with all the challenges. However, with the development of transport, the passive movement with characteristics out of the range that is natural for human, the system reveals some limitations. It can become problematic, if awareness and control are required. On the perceptual level, perceptive illusions and confusion might occur leading to imbalance or the loss of control. Motion sickness can be an autonomic expression of the vestibular limitations. These consequences do not result from the vestibular dysfunction, but from the normal function of the vestibular system, though, under unusual or unnatural conditions.

### 1. Sensory Ambiguity

Due to the intrinsic ambiguity of the otolith input, the CNS can only make estimates of the gravity and translation, basing on the previous experience and the characteristics of the input. These estimates work well in the range of natural motion, but under certain conditions the mechanism fails, causing perceptive illusions and erroneous responses.

Under certain conditions, these illusions can be dangerous. For example, many aviators experience the somatogravic illusion. During takeoff, under conditions of low visibility, a pilot may feel an erroneously high value of upward pitch, that may lead to an attempt to correct the aircraft attitude by pitching downward, which may result in an airplane crash. In this case, the GIA as a vector sum of gravity and backward inertial acceleration is misperceived as the actual orientation relative to the vertical, which is an erroneous estimate. Interestingly, this illusion can be explained with the frequency segregation approach described earlier, which suggests that low frequency inputs to the otoliths are interpreted as tilt rather than translation.

In the laboratory conditions, the time constant of the somatogravic illusion was shown to differ with varying frequency (Correia Grácio, de Winkel, Groen, Wentink, & Bos, 2013). In the study of Glasauer (Glasauer, 1995), the hilltop illusion (a sensation of climbing a small hill when being translated sinusoidally) was also found to be frequency-dependent. The study of Clément and Wood (Clément & Wood, 2014) also shows that the lateral sinusoidal translation evokes the perception not only of translation, but also of tilt. They showed that the perception of tilt is high at low frequencies (0.15 Hz in the study) and low for higher frequencies (0.6 Hz), while the perception of translation is on the contrary high at high frequencies and low at low frequencies. Therefore, the perceived tilt angle caused by the otolith stimulation tends to align with GIA at low frequencies and diminishes with the higher frequencies. The cross-over frequency, which is roughly about 0.3 Hz, is found to be the most ambiguous (Clément & Wood, 2014; Wood, 2002). This frequency dependency characteristics with the cross-over frequency of about 0.3 Hz were reported as the most ambiguous or provocative in numerous other studies on vestibular perception and responses, as well as motion sickness (Bos & Bles, 2002; Clément & Wood, 2014; Denise, Etard, Zupan, & Darlot, 1996; Green & Galiana, 1998; Merfeld et al., 2005; Paige & Tomko, 1991; Wood, 2002).

## **2. Motion sickness**

The motion sickness syndrome is characterized by drowsiness, dizziness, nausea that can terminate by vomiting. The motion sickness symptoms are caused by specific motion, most often in an unnatural environment (in a boat, car, bus, plane, space station etc.).

It seems that the intact vestibular system is essential for production of motion sickness since patients with bilateral vestibular deficit do not become motion sick (Denise, 1987; Graybiel, 1967; Johnson, Sunahara, & Landolt, 1999).

Motion sickness occurs in the presence of a functional vestibular system, under a specific provoking motion stimulus. Considering the characteristics of the stimulus, it was found that it is rather the low-frequency repetitive movement that causes motion sickness. Bos and Bles based their model on findings that the peak

of motion sickness occurrence was about the frequency of 0.16 Hz (Bos & Bles, 1998). Others reported the frequency of 0.3 Hz to be the most nauseogenic (Denise et al., 1996). This frequency has also been reported by multiple studies as the most ambiguous in the sense of tilt-translation segregation processing, according to perceptual responses and ocular movements (Bos & Bles, 2002; Clément & Wood, 2014; Denise et al., 1996; Green & Galiana, 1998; Merfeld et al., 2005; Paige & Tomko, 1991; Wood, 2002).

However, just the characteristics of the stimulus like frequency and magnitude are not enough to be able to predict the motion sickness occurrence.

Sometimes the sickness occurs even without movement which is the case of the simulator sickness (Barrett & Thornton, 1968). Wearing spectacles that distort vision might also evoke the same motion sickness symptoms. Therefore, vestibular stimulation characteristics are not sufficient to explain the phenomena. Moreover, active involvement in the movement decreases the susceptibility. These facts suggest that there is a complex processing that stands behind the motion sickness generation.

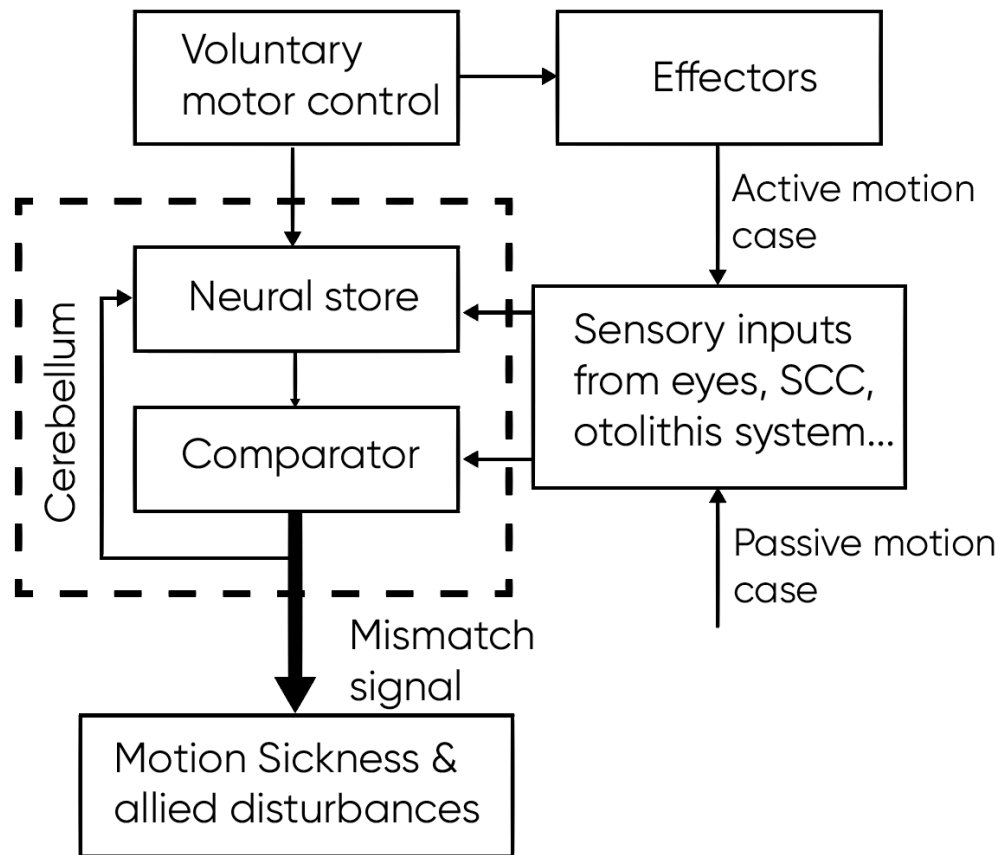
One of the most largely accepted and scientifically based hypotheses is the “sensory conflict” theory. The most basic of the sensory conflict interpretations is the conflict occurring between different sensory modalities (Claremont, 1931; Reason & Brand, 1975). Later approaches proposed different internal estimates to be the source of the conflict.

After proposing and then rejecting the inter-sensory cues conflict classification (Reason & Brand, 1975), Reason and Brand proposed another version of the sensory conflict theory (Reason, 1978). It was based on concepts introduced by Von Holst (von Holst, 1954) and Held (Held, 1961). Von Holst addressed the question of how the CNS can distinguish the passive and active movement from the sensory inputs. He suggested that the brain creates a copy of a motor command, “efference copy” and compares it to the sensory “reafference” input, caused by the movement. The difference between the two would leave the passive component of the sensory input, “exafference”. Held addressed the perceptual adaptation modeling. In addition to the efference and afference comparison principle, he hypothesized that the efference copy signal is generated based on the previous experience. The

mismatch between the expected and the real sensory return triggered the adaptive sensory rearrangement.

Reason applied these ideas to the motion sickness modeling. He postulated that motion sickness originates from a sensory mismatch between actual versus expected invariant patterns of vestibular and visual inputs (Reason, 1978).

The approach to the “sensory conflict” hypothesis that he called a “neural mismatch” hypothesis is based on the principle of reaffirmation: motion sickness occurs when vestibular, visual and proprioceptive sensors, stimulated by an ongoing movement, provide inputs mismatching with what is expected as a function of an internal model of sensory organs and of body dynamics (Figure 31). The afferent signals of the movement coming from the different sensory systems (visual, vestibular, proprioceptive) and the motor system (efferent copy) can therefore be inconsistent with other signals or with an internal representation of expected motion variables. The "sensory conflict" is a result of a continuous comparison (at the level of a structure called "comparator") between the real sensory signals and the prediction of these sensory signals. The internal model would be elaborated on the basis of past experience and it will be constantly updated. Thus, typically, motion sickness would appear during the unusual movements of the body, which would induce a discordance between the sensory-motor signals, because these messages concerning the displacements in the environment would not reflect the physical reality.



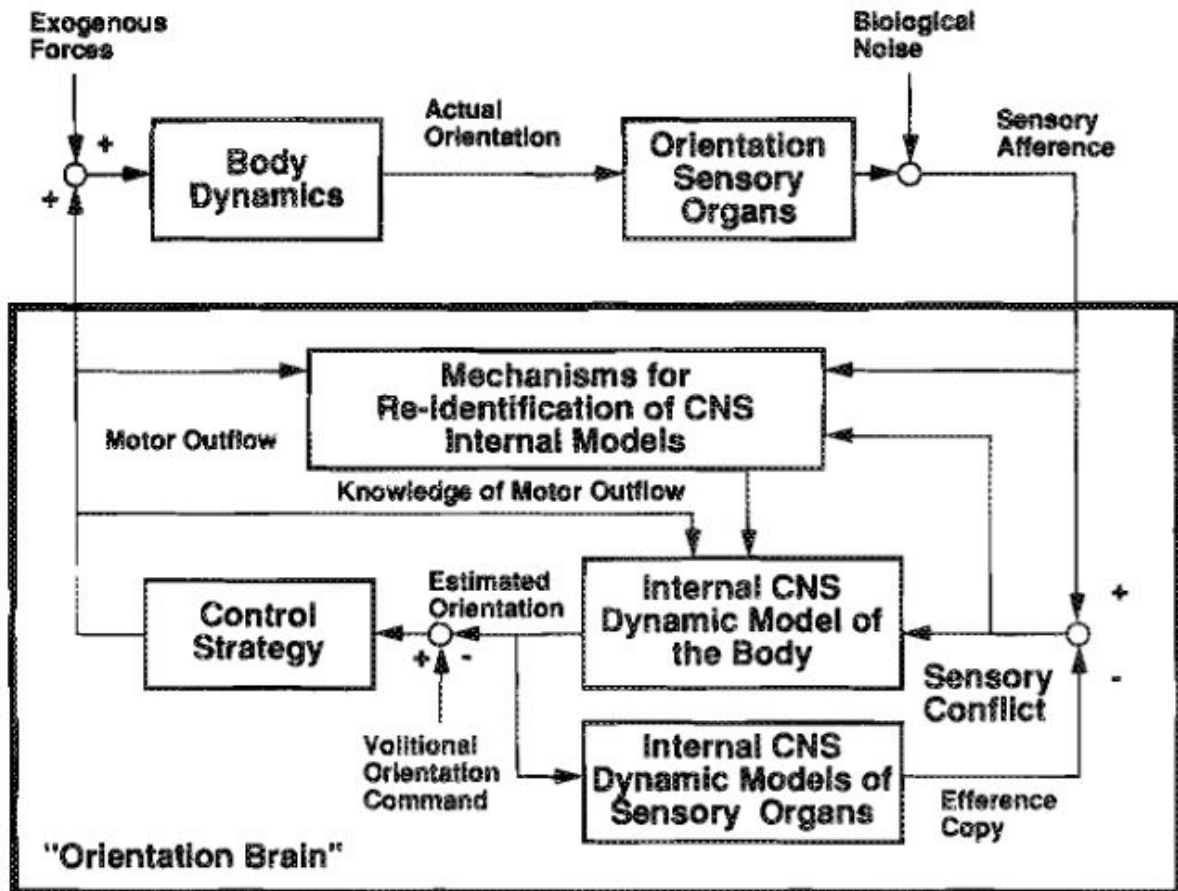
**Figure 31 – The basic “neural mismatch” model representation.** From (Oman, 1982). Model proposed by Reason (Reason, 1978).

Another model basing on this conflict theory is proposed by Bos and Bles (Bos & Bles, 1998). They calculated this conflict vector as a difference between a vertical sensed by receptors and the subjective vertical as determined on the basis of previous experience. This creates sensory ambiguity, which results in appearance of motion sickness symptoms. This approach centered on the subjective vertical seems to be equivalent to the sensory conflict hypothesis, however it offers a slightly different spectrum of stimuli that can be considered as nauseogenic (Bertolini & Straumann, 2016).

Another approach is based on the dynamic properties of the angular VOR and its dependence on the orientation of the gravito-inertial vector, GIA. Cohen and colleagues (Cohen, Dai, & Raphan, 2003) postulated that the motion sickness is caused by the difference between the GIA and the axis of the eye rotation.

Basically, both subjective vertical and VOR-GIA alignment models link the motion sickness triggering to the velocity storage mechanism (Cohen et al., 2003; Mingjia Dai, Kunin, Raphan, & Cohen, 2003). Habituation protocols have demonstrated that motion sickness symptoms diminish along with habituation of the time constant of the velocity storage (Dai et al., 2003). Indeed, the correlation of the motion sickness severity with the VOR parameters has been largely reported. For example, Shupak and colleagues (Shupak et al., 1990) proposed the VOR gain as a physiologic correlate helping to predict the susceptibility to motion sickness after a study of student sailors before and after 6 months of regular sailing, the time constant was not evaluated in the study. It should be mentioned, that habituation often involves the diminution of both the time constant and the gain of the VOR, however sometimes the gain is not altered. In line with that, another study reported that general MS susceptibility positively correlated with the time constant, but not the gain of the COR, and negatively correlated with the magnitude of the OOR (Quarck, Etard, Darlot, & Denise, 1998).

The model of Oman (Oman, 1982, 1990), which is called the Observer model due to the engineering principle employed, reviews the neural mismatch model of Reason and provides mathematical basis to it. It incorporates the continuous comparison of the efference copy, calculated basing on the previous experience and the actual multisensory input. This comparison continuously redefines the conflict vector that is used to maintain a correct spatial orientation estimate, when the efference copy vector does not match the multisensory afference. Naturally, the passive movement is quite rare and is usually temporary, so the conflict is minimal or not persistent. However, when one is subjected to passive motion, like being a passenger on a moving vehicle, or when the dynamic characteristics of any sensory organ involved have suddenly and significantly changed, like being exposed to weightlessness, or wearing vision distorting spectacles, the conflict would be sustained. Hypothetically, the CNS monitors the conflict level, and when the conflict is significant and prolonged, the dynamic models are adapted in order to reduce the conflict (Figure 32). The approach incorporates the questions of multisensory integration, motion sickness triggering, and sensory-motor adaptation.



**Figure 32 – The model for sensory conflict and movement control based on Observer principle.** From (Oman, 1990).

The Observer model has been used and adapted to interpret a variety of vestibular experimental data, like the perception of whole-body orientation (Merfeld et al., 1993; Merfeld & Zupan, 2002; Zupan et al., 2002).

The sensory conflict theory has opponents, for example, Stoffregen and Riccio (Stoffregen & Riccio, 1991) argued that the theory lacks reification and cannot provide a theoretical explanation to the motion sickness occurrence. Indeed, when proposed, the sensory conflict theory was not supported by neural basis, being a “black-box” model of the possible sensory processing. However, to date, a number of neuronal studies have brought the evidence in support of the internal model and the conflict-based origin of the motion sickness (Angelaki et al., 2004; Green &



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Motion sickness

Angelaki, 2010; Lacquaniti et al., 2014; Oman & Cullen, 2014). It was shown that brainstem contains the so-called vestibular-only neurons that respond differentially to the passive and active movements, that confirms the initial hypotheses built on the basis of engineering principles (Cullen & Roy, 2004; Cullen, 2012; Oman & Cullen, 2014).

# Vestibular plasticity

Maintaining proper responses to vestibular inputs is essential for normal living and performance. However, changes in the environmental conditions, activities and tasks as well as challenges imposed by growing, aging, disease and traumas can make the previous strategies ineffective. A capacity to detect errors in performance and adapt it to new circumstances is required to restore adequate motor behavior and homeostasis.

## 1. Habituation, adaptation and compensation

Basically, vestibular plasticity can be categorized in three major mechanisms: habituation, adaptation and compensation. Habituation usually follows repetitive prolonged stimulus, when the generation of a proper response is not crucial. It is characterized by diminishing in the response. Adaptation takes place as a change in the response characteristics, following a prolonged change in the environment or a novel activity. Compensation (can be considered as a variant of adaptation) usually follows the loss or impairment in some sensory inputs, when the response is still important. For example, the loss of vestibular inputs might be compensated by integration and reorganization in processing of other sensory inputs in order to restore the essential response.

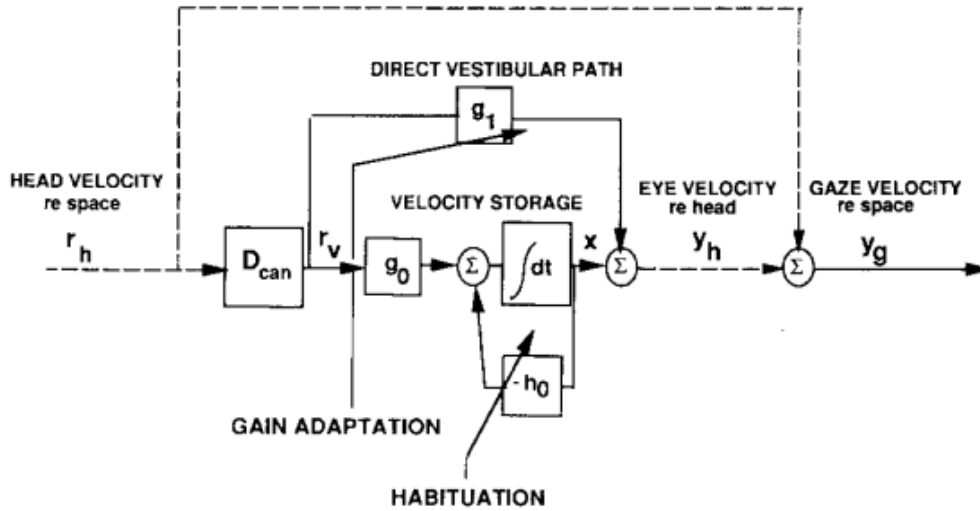
### a. Habituation

Habituation can be observed in sportsmen, who need to suppress their reflex responses in order to improve performance. It was shown, that ballet dancers (Osterhammel, Terkildsen, & Zilstorff, 1968; Tschiasny, 1957), who perform high-velocity rotations during their everyday training with the use of the so-called spotting technique aimed to fix the gaze and diminish the retinal slip, present a smaller vestibulo-ocular reflex during rotations than normal people. Similarly, the diminution of the vestibulo-ocular response, in particular canal-ocular response, was demonstrated for figure skaters (Collins, 1966; McCabe, 1960; Tanguy, Quarck, Etard, Gauthier, & Denise, 2008) and aviators (Ahn, 2003; Aschan, 1954; Lee, Kim, & Park, 2004; Schwarz & Henn, 1989). Interestingly, when the stimulation is usually delivered in one preferable direction, as it often is the case

for the figure skaters, the VOR habituates unilaterally (Clément, Courjon, Jeannerod, & Schmid, 1981; Tanguy et al., 2008). The habituation protocols were employed in the laboratory conditions as well, both on animal and human subjects (Clément et al., 1981; Clément, Tilikete, & Courjon, 2008; Cohen, Cohen, Raphan, & Waespe, 1992; Courjon, Clément, & Schmid, 1985; Jäger & Henn, 1981). The VOR habituation, which is represented in the studies almost solely by the horizontal COR, is characterized by the diminution of the time constant of the per-rotatory and post-rotatory nystagmus, and diminution of the gain of the ocular compensatory response and an increase in the advance in phase between the ocular compensation and the actual predictable movement.

Recordings of activity of the vestibular nerve fibers in anesthetized squirrel monkeys (Fernandez & Goldberg, 1971) and in alert rhesus monkeys (Buttner & Waespe, 1981) demonstrated that the time constant of the activity is about 6 seconds and it remained the same in naïve and habituated monkeys (Buttner & Waespe, 1981). At the same time, the nystagmus time constants were longer, and shortened with habituation. The neuronal activity in the vestibular nuclei corresponded tightly to the nystagmus velocity and time constant and reflects the habituation process (Buettner, Buttner, & Henn, 1978). This led to a conclusion that the habituation process takes place beyond the first-order neuron. Interestingly, the habituation was achieved only within the low stimulus frequencies (0.005 Hz – 0.1 Hz), where the phase advance was observed even before the habituation. These observations suggested that there is a neuronal mechanism, capable of predicting the movement and being able to reorganize, in order to minimize the response and increase the phase advance.

Raphan and colleagues (Raphan & Cohen, 2002; Raphan et al., 1979) investigated the characteristics of nystagmus (Figure 33) to build a model of an underlying central mechanism, which they termed a velocity storage. They have postulated, that the velocity storage mechanism is shared for generating vestibular nystagmus, optokinetic nystagmus and optokinetic afternystagmus.



$$r_h = r_0 u(t) \quad u(t) = \begin{cases} 1 & t > 0 \\ 0 & t < 0 \end{cases} \quad (1)$$

$$r_v = -r_0 e^{-h_c t} \quad (2)$$

$$y_h = \underbrace{-g_1 r_0 e^{-h_c t}}_{\text{DIRECT PATH RESPONSE}} + \underbrace{\frac{-g_0 r_0}{h_0 - h_c} [e^{-h_c t} - e^{-h_0 t}]}_{\text{INTEGRATOR STATE RESPONSE}} \quad (3)$$

**DIRECT PATH RESPONSE    INTEGRATOR STATE RESPONSE**

$r_0$  = MAGNITUDE OF HEAD VELOCITY STEP

$h_c$  = 1/TIME CONSTANT OF CUPULA

$h_0$  = 1/TIME CONSTANT OF VELOCITY STORAGE INTEGRATOR

$g_0$  = COUPLING TO VELOCITY STORAGE INTEGRATOR

$g_1$  = DIRECT PATH GAIN

**Figure 33 – Simplified model of VOR.** From (H. Cohen et al., 1992).

It was noticed, that the habituation of the vestibular nystagmus is usually coupled with the diminution of motion sickness. Cohen and colleagues also investigated this link, performing habituation protocols with a nauseogenic stimulus (Dai, Sofroniou, Kunin, Raphan, & Cohen, 2010). They postulated that the

spatiotemporal properties of velocity storage are likely to represent the source of the conflict responsible for producing motion sickness (Cohen et al., 2003; Dai et al., 2003). Experimental habituation of the VOR with protocols using repetitive passive movement are known to habituate the motion sickness (Clément et al., 1981; Dai et al., 2003; Jäger & Henn, 1981). More interestingly, a recent study on mice provided evidence that habituating the VOR with a visuo-vestibular protocol without inducing passive movements, can diminish the motion sickness during nauseogenic motion stimulus (Idoux, Tagliabue, & Beraneck, 2018).

### **b. Adaptation**

Vestibular adaptation has also been investigated mostly in relation to the VOR. One of the most impressive examples of adaptation was presented by Gonshor and Melvill Jones (Gonshor & Jones, 1976; Jones, 1983). Subjects of the study wore left-right reversing glasses, which led to the reversal in the direction of the VOR. Similar, but less striking adaptations are experienced by many people in everyday life – vision correction lenses require and produce adaptive increases or decreases in the VOR gain (H. Cohen et al., 1992; Istl-Lenz, Hydén, & Schwarz, 1985). Psychological factors such as the level of alertness and attention, effort and motivation can play a role in the VOR generation and in the adaptation process. It was shown that mental arithmetic tasks are capable of enhancing VOR gain (W. E. Collins & Guedry, 1962; William E. Collins, 1962), as can sleep deprivation (Quarck, Ventre, Etard, & Denise, 2006). Simply imagining a visual target moving in a way as if it created an image slip on the retina can cause adaptive changes in the VOR (Jones, Berthoz, & Segal, 1984).

Finally, a stimulus like a prolonged exposure to microgravity can induce long-term plastic changes to the vestibular system. Rotational VOR (Clarke, Grigull, Mueller, & Scherer, 2000), linear VOR (Hallgren et al., 2016), vestibulo-spinal reflex (Reschke, Anderson, & Homick, 1986) were shown to be significantly attenuated during space flight missions. Vestibulo-sympathetic reflex has also been shown to be adaptable. A study on astronauts was performed before and after the space flight of 4-6 months of duration (Morita, Abe, & Tanaka, 2016). The blood pressure response to a constant head up tilt was dramatically attenuated in astronauts after the flight. However, it was restored completely after about 2 months after return on Earth.

### c. Compensation

Adaptive mechanisms also take place in attempt to restore normal functioning, following the unilateral or bilateral loss of vestibular afferents.

Unilateral vestibular loss (UVL) offers two types of challenges to compensate. The first is a static imbalance, which is related to the differences in the tonic discharge in the vestibular nuclei, when the afferents from one side are absent. This imbalance might lead to the increase in the sensitivity to the remaining sensory inputs, as well as by increasing the weight of extralabyrinthine afferents. Rebalancing the vestibular nuclei restores the vestibulo-spinal balance and eliminates spontaneous nystagmus by restoring the proper the vestibulo-ocular control. The static imbalance does not depend on the exposure to the visual cues, as was demonstrated by a study on monkeys (Fetter & Zee, 1988b, 1988a). It suggestively relies more on proprioceptive and somatosensory cues as sources of sensory afference and error signal. Together with the static imbalance, the dynamic disturbances also challenge the vestibulo-motor control after unilateral vestibular loss. Contrary to the static imbalance, the recovery of the dynamic VOR necessitates visual cues. No increase in gain of the VOR after the UVL was observed until exposure to light (Fetter & Zee, 1988b). The same was seen in monkeys with unilateral plugging of a lateral semicircular canal (Paige, 1983). Similar dependence on vision was observed in cats recovering after vestibular neurectomy (Zennou-Azogui, Xerri, & Harlay, 1994). Dependence of the recovery of dynamic VOR on vision can be explained by recalling the major purpose of the VOR. The ocular compensation serves primarily to stabilize visual images on the retina. The image slip, appearing when the VOR is not adequate might serve as an error signal to drive adaptive changes.

Another evidence for participation of vision in adapting the VOR is that bilateral occipital lobectomy can cancel the adaptative changes acquired after the UVL, as was shown by Zee and colleagues (Fetter & Zee, 1988b, 1988a). However, occipital lobectomy performed in animals with intact labyrinths did not cause the same decrease in VOR, indicating that the occipital cortex alone is not the source of adaptation. Nucleus of optic tract (NOT) in the midbrain is also known to participate in VOR adaptation process (Yakushin, Reisine, Büttner-Ennever, Raphan, & Cohen, 2000). The NOT receives visual information from the cerebral cortex and directly from retina and projects to the inferior olive and other

brainstem nuclei that project to the cerebellum. Lesions of the NOT impair VOR adaptation and change the baseline VOR gain (Stewart, Mustari, & Perachio, 2005).

Bilateral vestibular loss (BVL) is even more challenging to compensate for, as no information from the peripheral vestibular organs is accessible. Multiple strategies for compensation are observed, such as sensory substitution, motor substitution, predictive and anticipatory mechanisms (Herdman, 2007).

In the absence of peripheral vestibular inputs, the ocular motor compensation for movement requires visual information. Animals with BVL could still generate slow phases of eye movements during head rotations in light, which are driven mostly by visual inputs, however the rapid phases were lost (Baarsma & Collewijn, 1974; Waespe & Wolfensberger, 1985). Optokinetic afternystagmus were also lost (Cohen, Uemura, & Takemori, 1973; Waespe & Wolfensberger, 1985). In the dark, the ocular response to head rotation was found to be abolished in animals after bilateral labyrinthectomy (Baarsma & Collewijn, 1974; Waespe, Schwarz, & Wolfensberger, 1992; Waespe & Wolfensberger, 1985). In human, the effect of the bilateral vestibular loss is similar. VOR, as well as optokinetic afternystagmus are abolished without the functioning vestibular organs (McCall & Yates, 2011). The VOR does not seem to be recovered over time (Baloh, Enrietto, Jacobson, & Lin, 2006). However, it can be partly replaced by cervico-ocular reflex, which is normally very low in humans, but can be facilitated with the loss of vestibular inputs, at least for the low-frequency movements (Bronstein & Derrick Hood, 1986). The ocular compensation can also be facilitated by the central preprogramming (when subject is aware of the location of the next visual target), or the efference copy of the voluntary movement (Herdman, Schubert, & Tusa, 2001; Maurer, Mergner, Becker, & Jurgens, 1998). Finally, in light, optokinetic responses can also partly substitute the absent VOR at low frequencies (Leigh, Sawyer, Grant, & Seidman, 1992).

Postural control in BVL subjects is also challenged and needs to compensate for the loss of vestibular signals. As for the VOR, the data on animals suggest that vision plays a role in maintaining the balance and walking (Marchand & Amblard, 1990). Some abilities like a straight course in darkness or limb extension reflex during falling are completely lost with the loss of the vestibular organs, impairing stability (Marchand & Amblard, 1990; Thomson, Inglis, Schor, & Macpherson,

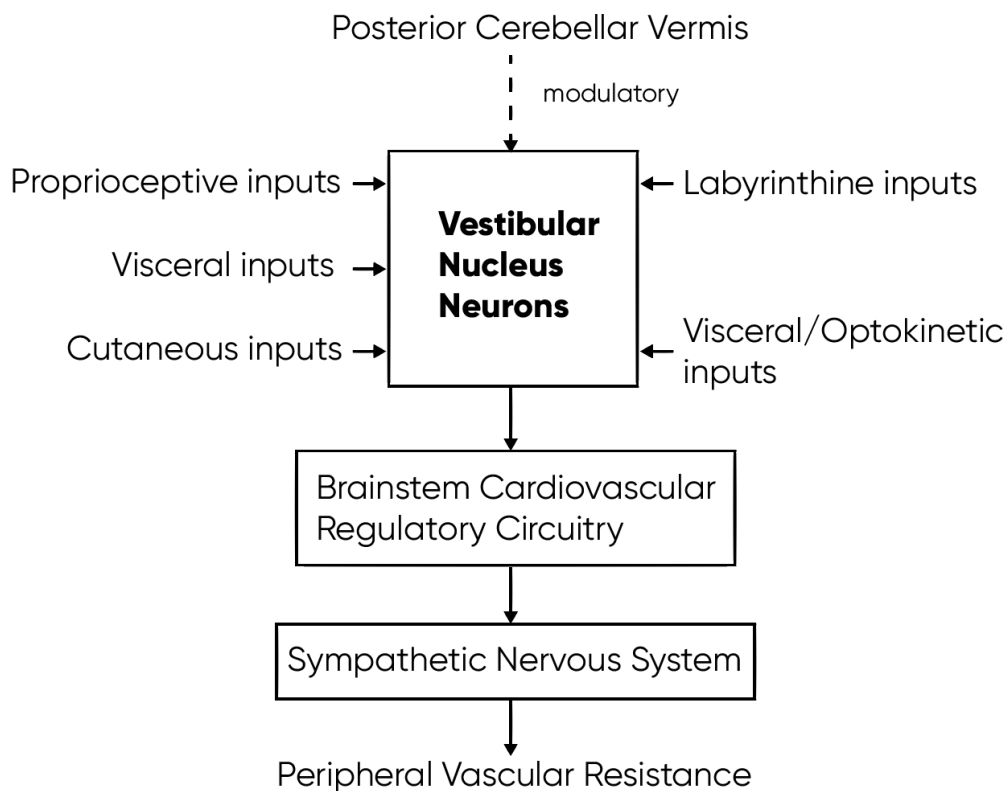
1991). However, animals with BVL are shown to be able to recover the maintenance of normal posture and movement within approximately 10 days (Thomson et al., 1991). It suggests that the compensatory strategies exist to restore the postural control.

Postural control in human subjects with BVL is also impaired (Mergner, Schweigart, Fennell, & Maurer, 2009). However, postural stability is controlled not only with the afferents from vestibular organs but also with the visual information and proprioception. The relative weight of every sensory input can be adjusted, for example when a normal subject stands on a piece of foam rubber in a tilted visual surrounding, the impact of the somatosensory cues decrease, while it increases for vision (Bles, Kapteyn, Brandt, & Arnold, 1980). A tilting room and a moving platform were used by Bles and colleagues to estimate the roles of proprioception and vision in normal and vestibular deficient subjects with different duration since the diagnosis (Bles, Vianney de Jong, & de Wit, 1983). They concluded that the rehabilitation from bilateral vestibular loss begins with increased reliance on vision, and then the relative weight of somatosensory information increases over time. Some data suggest that the proprioceptive influence is enhanced in BVL subjects, as the paraspinal muscular activity is increased in response to toes up pitch rotation in BVL subjects, which is the opposite to the response observed in patients with proprioceptive loss (Allum, Bloem, Carpenter, & Honegger, 2001). Indeed, BVL can detect the small angles of roll and pitch with almost the same threshold (Bringoux, 2002).

Finally, studies on animals have shown that cardiovascular responses to postural changes impair significantly immediately after the loss of vestibular afferents. The reduction of blood flow in hindlimbs that ordinarily occurs in response to 60° nose-up tilt to maintain stable blood pressure, is attenuated in animals following bilateral labyrinthectomy (Wilson et al., 2006; Yavorcik et al., 2009). Blood pressure was also unstable at the onset of the movement (Jian et al., 1999). However, it was demonstrated that these deficits are able to recover within a month after the loss of vestibular inputs. The same study demonstrated that visual inputs decrease the deficits in adjusting the blood pressure stability following in vestibular-lesioned animals, suggesting that the visual input can participate in the vestibulo-autonomic control, as is the case for other vestibularly driven responses (Jian et al., 1999).



Basing on physiological and anatomical studies, Yates et al (Yates et al., 2000) proposed a model of neural interactions for the vestibulo-vascular control that integrates the signals from multiple sensors (Figure 34). Vestibular nuclear complex receives inputs from the labyrinth, and viscera, cutaneous and proprioceptive inputs as well as optokinetic information. Posterior cerebellar vermis serves to modulate the integrative response of the vestibular nuclei. It should be mentioned that this modulation becomes particularly important in cases of deficiency of information, such as BVL, or the contradiction of signals from different sensors. Brainstem circuitry provides cardiovascular regulatory functions via sympathetic activity that increases peripheral vascular resistance.



**Figure 34 – The model of circuitry that mediates vestibulo-sympathetic reflexes.** From (Yates et al., 2000).

The data on cardiovascular control in human subjects with BVL are less clear. Rattke (Rattke et al., 2000, 2003) and colleagues report that the blood pressure response to the head drop stimulation in BVL patients is comparable to the normal response, and the acceleration of cardiac rhythm is also present, though delayed. Otolithic stimulation on a linear sled also evoked cardiovascular responses in BVL subjects, however they were less pronounced than in normal subjects (Yates et al., 1999). The authors suggested that the response might originate from the possible residual activity of the vestibular organs in BVL subjects, though it remains hypothetical. In both studies, subjects had the eyes closed during the experimental trials, which eliminates the involvement of vision in generating the response.

The role of cerebellum has been underlined for the recovery of all orientation-related reflexes with the absence or lesions of the vestibular organs or nerves (McCall & Yates, 2011).

Vestibular plasticity

Habituation, adaptation and compensation

## **Natural methods used to stimulate the vestibular system in human**

Several methods of natural stimulation of the vestibular system will be briefly presented. In this context, natural stimulation means that real accelerations are acting on the vestibular system, due to movement. It is contrary to electric stimulation, delivered directly to the vestibular nerve or the Galvanic Vestibular Stimulation (GVS) delivered to the vestibular nerve in a non-invasive manner, with the help of a galvanic current applied at the level of the mastoid bone. Natural stimulations are non-invasive and help to observe the vestibular responses to movements and spatial orientation changes, and also to act distinctively on otolithic system or pairs of semicircular canals.

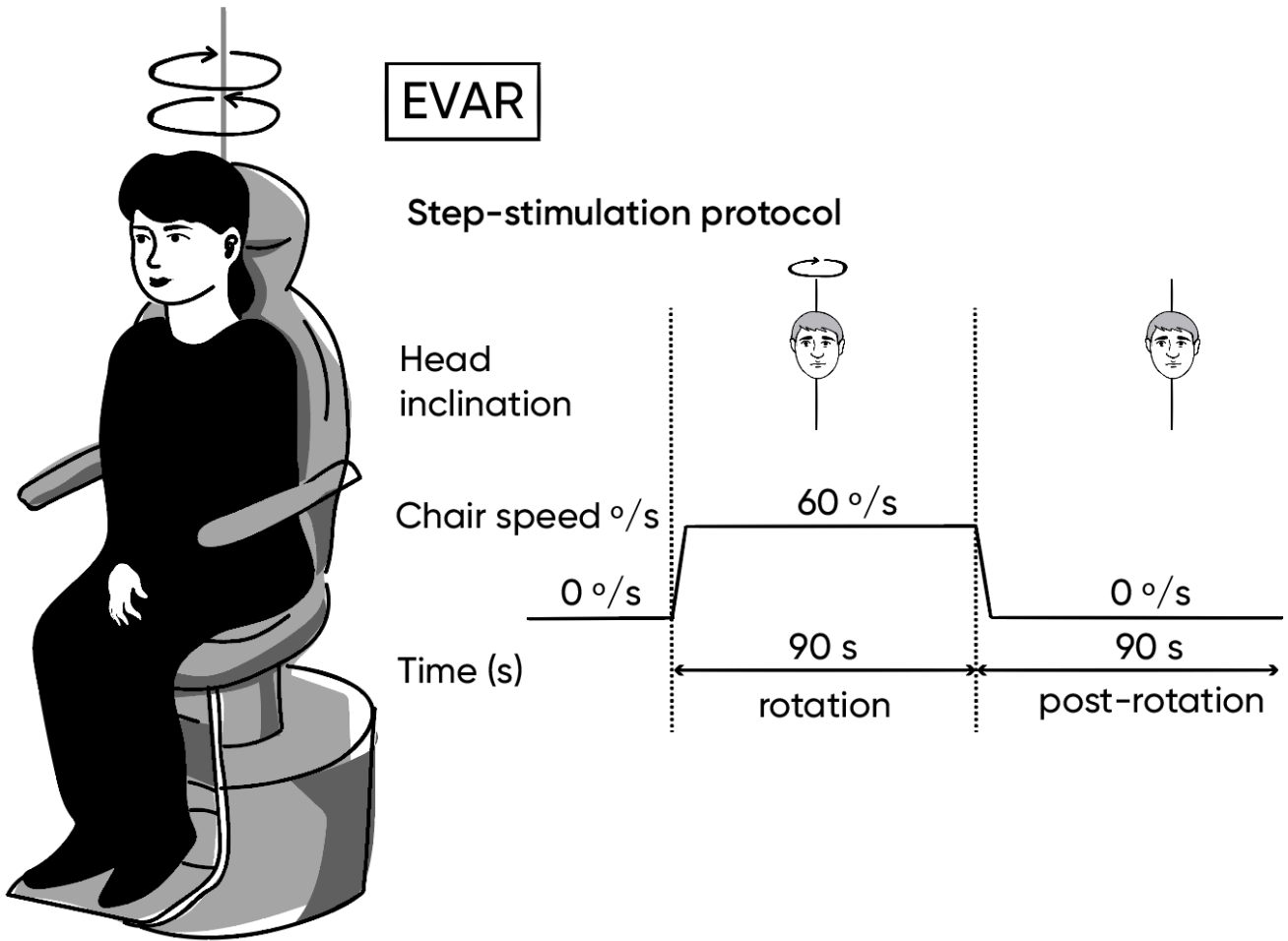
Semicircular canals are stimulated by rotations of the head, whether it is the head-on-body or head-and-body movement. It is a dynamic sensor, capturing the rotatory acceleration and deceleration. Only one method will be presented here.

Otolithic system captures the linear accelerations induced by inertial movement and the gravitational acceleration as a type of linear acceleration. Therefore, multiple types of stimulation are possible, both static and dynamic. Static stimulation by the head tilt changes the orientation of the gravity vector relative to the head, the tilt is constantly detected by the otolithic system. Dynamic methods can use linear translation with no change of orientation with respect to gravity, or dynamic change in orientation. This makes the stimulation of otolithic system more variable.

## **1. EVAR**

The abbreviation stands for the Earth-Vertical Axis Rotation and represents passive rotation of a subject around the longitudinal axis of the body set vertically (Figure 35). The rotations are performed on the automatically driven rotatory chair, capable of inducing the required acceleration and velocity of rotation in the required direction (i.e. Clockwise or Counterclockwise). The test is used for assessment of the horizontal semicircular canals. The evaluation of the canalar function is usually performed by recording the compensatory eye movements.

The most typical protocol for canalar assessment is Velocity-Step stimulation. The acceleration/deceleration phases are the ones that induce activation of the semicircular canals. When the head rotates with the constant speed, on the onset of rotation the endolymph does not move along with the head, which causes the ampulla to bend, but after a while (~7 seconds) (Herdman, 2007), the liquid catches up with the containing structure, releasing the ampulla. Although physical stimulation is rather short, on the neural level it is prolonged to 30-60 seconds by the velocity storage mechanism (Raphan et al., 1979). At this point, no rotation is sensed anymore. After rotation has stopped, the fluid continues rotating, while the head is still, causing the ampulla to bend in the opposite direction.



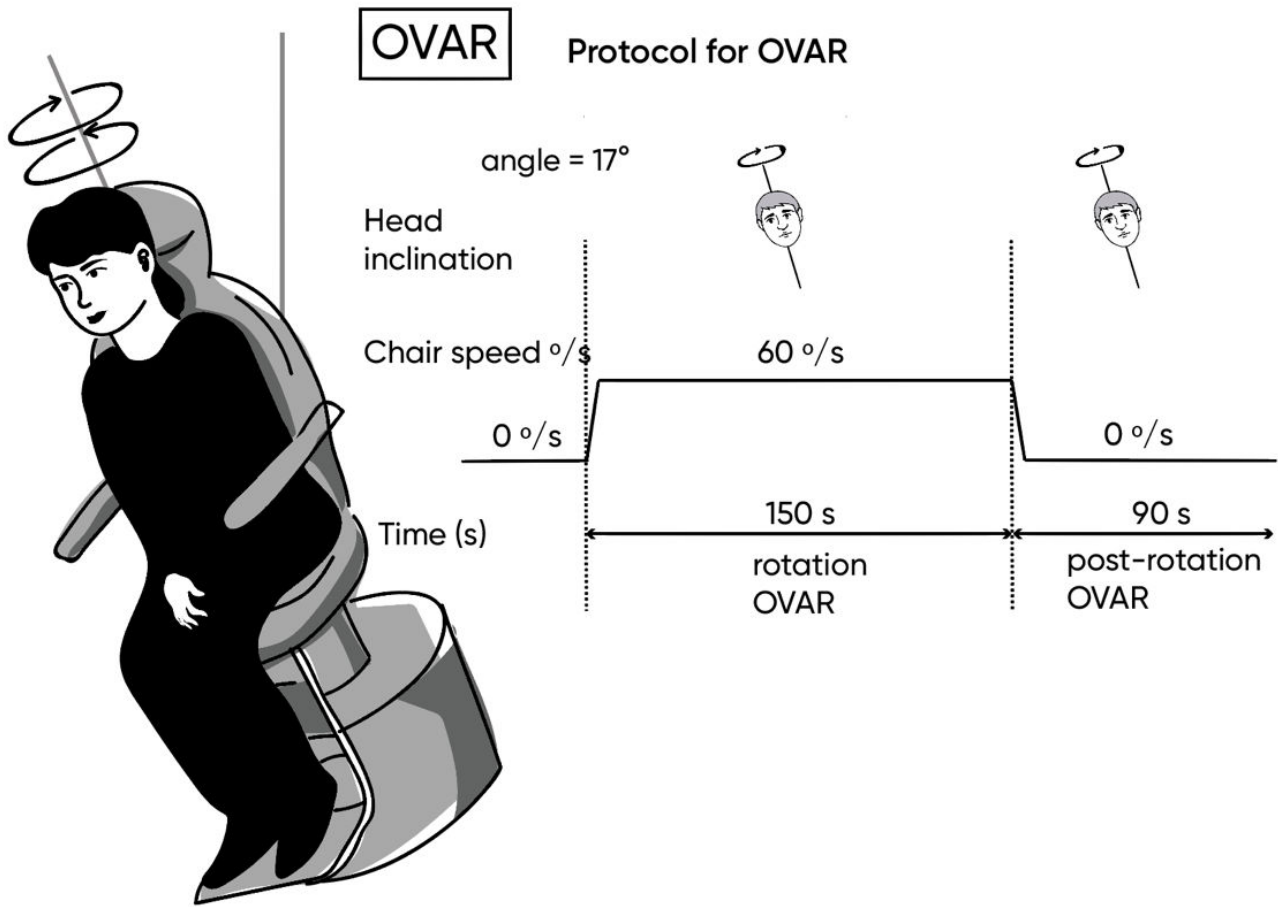
**Figure 35 – Illustration of the rotatory chair, positioned straight for EVAR and the step-stimulation protocol for EVAR.**

## **2. OVAR**

The abbreviation stands for the Off-Vertical Axis Rotation and represents passive rotation of a subject around the longitudinal axis of the body, inclined with respect to vertical (Figure 36). It is a dynamic method of stimulation of the vestibular system.

The inclination angle can vary regarding the protocol. The rotations are performed on the automatically driven rotatory chair, capable of inducing the required acceleration and velocity of rotation in the required direction (i.e. Clockwise or Counterclockwise), as well as the angle of inclination of the rotation axis. The test is used for assessment of the otolithic system. The evaluation of the otolithic function is often performed by recording the compensatory eye movements.

After about a minute after acceleration to a constant velocity rotation, the semicircular canals are deactivated and no longer sense the rotation, so, only the otolithic stimulation remains. The otoliths are stimulated by the gravity; the inclined rotation periodically changes the respective direction of the vector of gravity, which evokes compensatory otolith-driven eye responses.



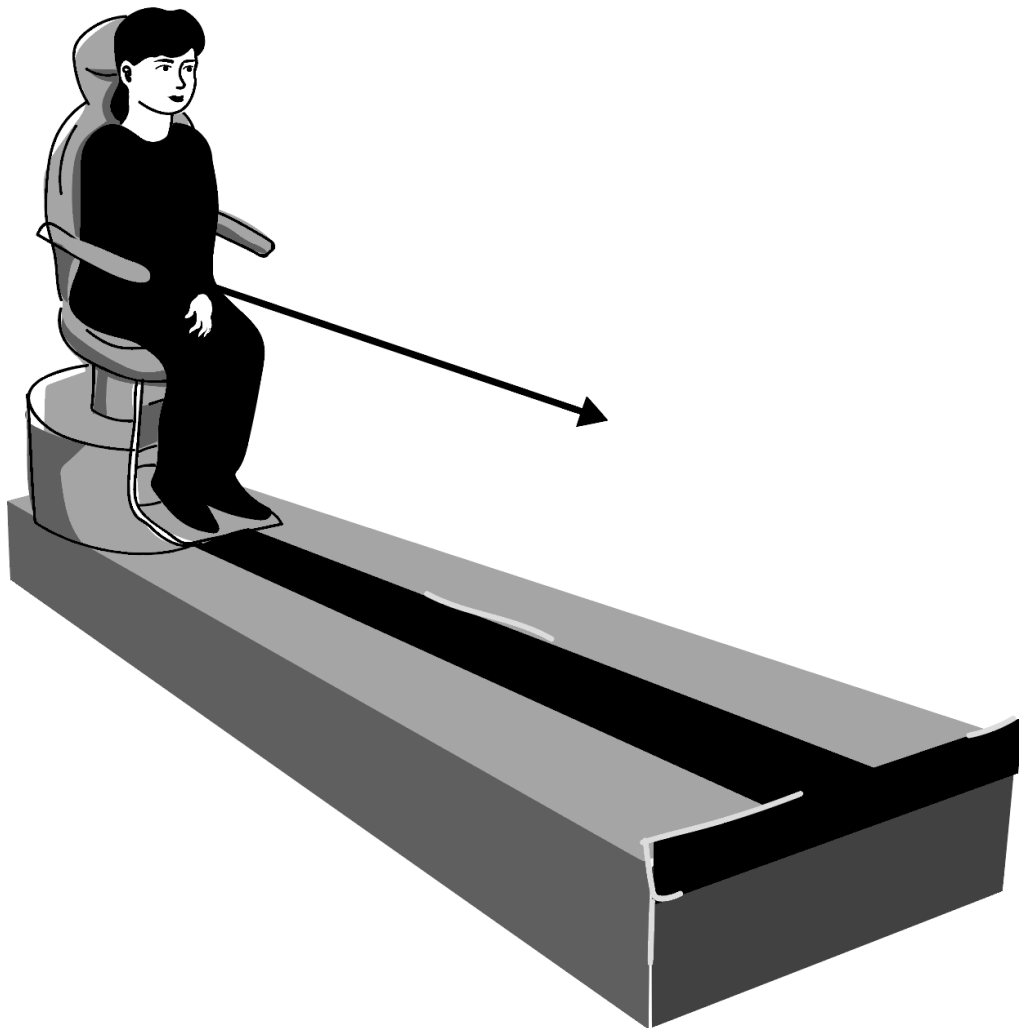
**Figure 36– Illustration of the rotatory chair, inclined with respect to gravity for OVAR and the variant of protocol.**



### 3. Linear sled

Linear sled is used for the dynamic harmonic linear acceleration stimulation of the otolithic system (Figure 37). Linear acceleration-deceleration creates sinusoidal modulation of the otolith activation.

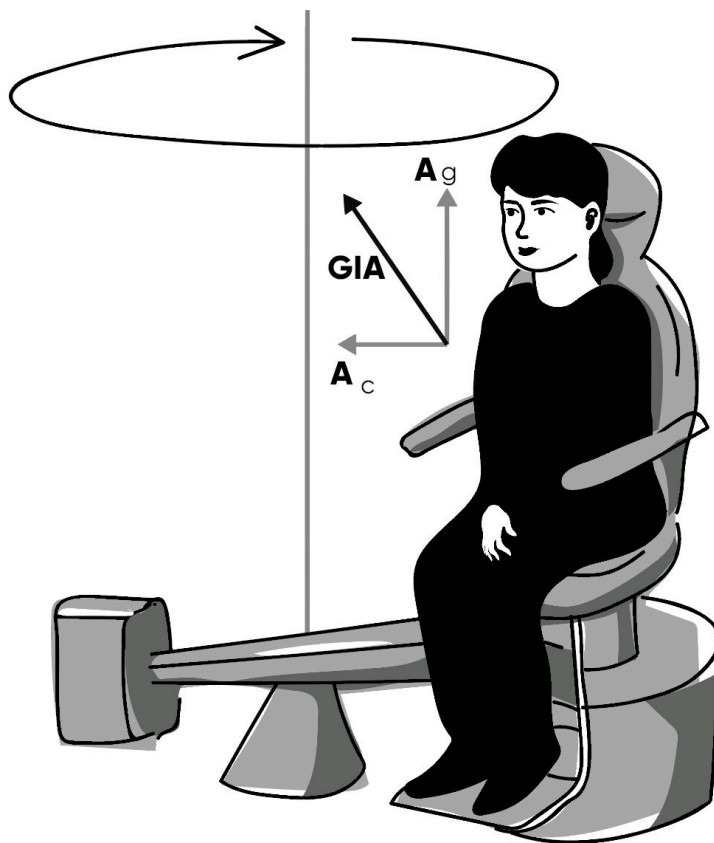
Subjects are seated on a chair mounted on a sled, that is usually controlled with a servodrive to create the stimulations with the required amplitude and frequency.



**Figure 37 – Illustration of the linear sled.**

## 4. Centrifugation

Centrifugation is a static method of stimulation of otolithic organs (Figure 38). It is used to simulate the hypergravity condition. The centrifuge represents a rotatory chair with the subject placed out of the axis of rotation. Rotation results in the centripetal acceleration applied to the subject, which changes the otolithic input. The resultant acceleration that stimulates the otolithic organs is the vector sum of gravitational acceleration and centripetal acceleration. The resultant acceleration acting on the vestibular system is constant and tilted with respect to the Earth-vertical, however it is perceived as a new vertical reference by the centrifuged subject.

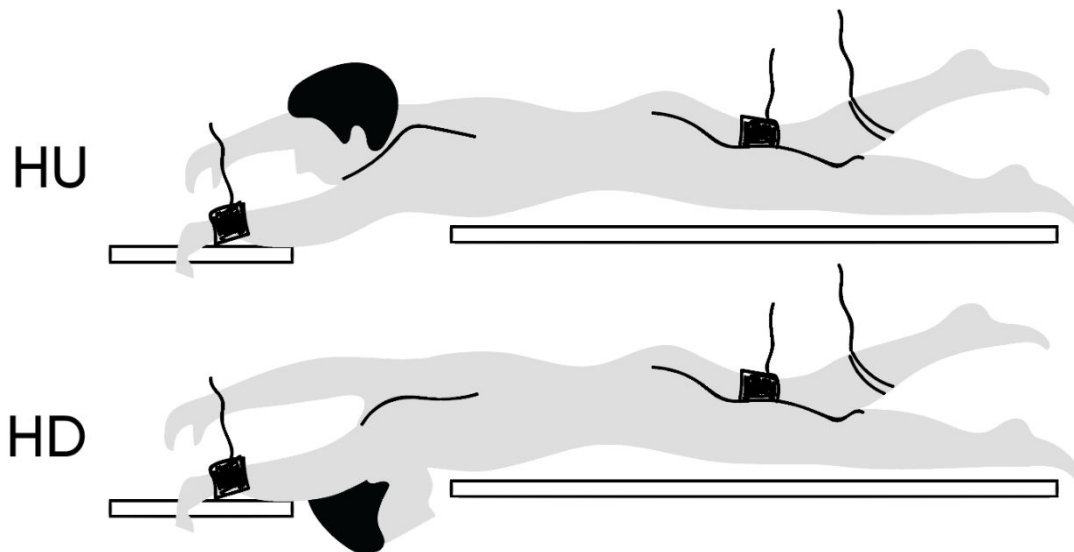


**Figure 38 – Illustration of the centrifugation.** Unlike for the rotatory chair, subject is out of the axis of rotation. GIA – gravito-inertial acceleration,  $A_g$  – gravitational acceleration,  $A_c$  – centripetal acceleration.

## 5. HDNF

The abbreviation stands for the Head-Down Neck Flexion manoeuvre, a method of otolith stimulation introduced by Essandoh (Essandoh, Duprez, & Shepherd, 1987; Essandoh et al., 1988). HDNF is a static stimulation of the otolithic system used when the body must be immobile (Figure 39).

The initial position is the subject lying ventrally prone with neck slightly extended and the chin supported by a soft-padded head rest. Then the support is removed and the head is lowered to achieve maximal neck flexion. The measurements are performed in the neck extension position and in the neck flexion position (or head-up and head-down positions).

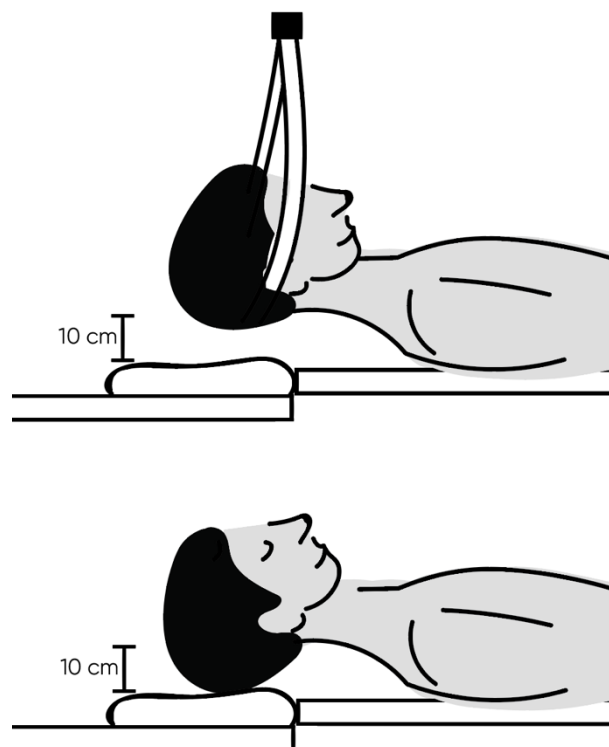


**Figure 39 – Illustration of the HDNF protocol.** HU – Head Up position, HD – Head Down position.

## 6. Head Drop

Head drop is a high-frequency short duration stimulation method that affects both the otolithic organs and semicircular canals. It is used when the rapid stimulation of the vestibular system is required, and the distinction between the canalar and otolithic stimulation is not important.

During the protocol subjects lie supine on a horizontal platform with their head suspended in a sling around the occiput and raised 10 cm above the surface (Figure 40). The sling is attached to a mechanical release. Activation of the release liberates the sling, causing the head to drop freely with an angular extension of the neck of about 45° until the fall is stopped by a cushioned surface. The drops can be self-released, released by an experimenter or automatically, driven by a hear beat as was the case in the study by Radtke and colleagues (Radtke et al., 2000, 2003).



**Figure 40** – Illustration of the HDNF protocol. HU – Head Up position, HD – Head Down position.

## **7. General notice**

The methods of stimulation described above create different patterns of firing in the vestibular nerve and result in vestibular-related responses. VOR, motion perception, cardio-vascular, respiratory and other parameters can be assessed during the stimulations.

It is important to mention, however, that each protocol has limitations. The indirect and non-invasive nature of protocols suggest that a complete elimination of other factors is impossible. Thus, other sensory systems can be involved in the generation of the response. For example, whole-body movement protocols also activate the proprioception and trunk graviceptors; the head down neck flexion activates neck receptors and possibly other sensors; cardiovascular changes can be induced by a slight redistribution of liquids or baroreceptor activation. Moreover, some motion protocols are able to evoke motion sickness symptoms.

These factors make the creation of a proper protocol for the vestibular evaluation challenging. Obviously, the list of methods of vestibular stimulation provided here is not exhaustive; the search of protocols that can help researchers to reveal some more knowledge about the vestibular function is a continuous and creative process.

## Objectives of the thesis

The literature review has summarized the highly integrative, largely distributed fine network of processing of vestibular signals. Vestibular afference is integrated at all levels, from the lowest levels to the cortex. The major processing of vestibular signals is based in the vestibular nuclei that receive, apart from the labyrinthine afference, multiple other sensory inputs. Vestibular reflexes and perception require this integration for a better performance. The integration is supposedly weighted (Fetsch et al., 2009; Zupan et al., 2002) and is highly variable between individuals (Mittelstaedt, 1992). In normal life, humans use vestibular information to a rather limited extent, in comparison to many animals. The velocity, intensity and directional variations of human mobility is lower than that of, for example, monkeys. However, some activities involve a stronger stimulation of the vestibular system, for example, some sports. It has been demonstrated that the vestibular function of individuals that are subject to intensive vestibular stimulations can differ from that of normal people, probably indicating the rearrangements in the central integrator. Another example of a dramatic change in vestibular afferent activity is the loss of vestibular function. Central mechanisms to counteract this loss are multiple, but the multisensory character of all of the vestibular reflexes suggests that the response recovery can also happen as a central integrator rearrangement, based on non-labyrinthine sensory afference, instead of lacking labyrinthine.

Based on the literature review we can conclude that the central processing of the vestibular signals has following characteristics:

- 1) Already at the level of secondary neurons, vestibular information is much more complex than just the relay of the vestibular sensory signals.
- 2) The weighted integration of multiple sensory signals is required for good performance.
- 3) Internal estimates of motion parameters are required for good performance.
- 4) Internal models that estimate these parameters store the previous experience and can be updated in order to conform to new sensory conditions.

- 5) This circuitry can rearrange the fine parameters of the estimation for a better performance, and it can reweight the elements of multisensory integration.

Considering this, we attempted to assess the role of the vestibular system in the orientation-related homeostasis. We aimed to examine how the central processing of vestibular and non-vestibular signals is happening in Human to generate vestibulo-respiratory responses, vestibulo-autonomic responses, subjective vertical perception and vestibulo-ocular responses and how this processing might change after the change in sensory afference.

Several hypotheses have been tested:

- We hypothesized that total bilateral vestibular loss would impair the control of blood circulation during postural changes.
- We hypothesized that the periodic activation of graviceptors in OVAR would lead to a preferred angle where the transition between inspiration and expiration occurs. We hypothesized that this transition would be synchronized with the position of the head of the subject, indicating the labyrinthine source of respiratory control.
- We hypothesized that the visual stimulation would drive the perception of the self-movement. We also hypothesized that the perception of self-movement including body inclination would induce a greater modulation of cardio-vascular parameters during OVAR than the perception of self-rotation without inclination.
- Finally, we hypothesized that aerobic pilots, as people experiencing unusual and intensive vestibular stimulations, present lower susceptibility to motion sickness and different vestibulo-ocular reflexes and verticality perception than normal subjects.

## **Part II: Experiments**





# Study I: Vestibulo-sympathetic reflex in patients with bilateral vestibular loss

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## 1. Background

The vestibulo-sympathetic reflex is the activation of sympathetic neural traffic via the vestibular organ. It was first evidenced by Tang and Gernandt (Tang & Gernandt, 1969) who showed that electric stimulation of the vestibular nerves in decerebrate cats affects the sympathetic portion of the autonomic system, increasing respiration depth and rate as well as blood pressure, without affecting parasympathetic outflow to the heart. Since then, numerous studies observed the effect of electric stimulation of vestibular afferents on sympathetic efferents (Ishikawa & Miyazawa, 1980; Kerman & Yates, 1998; Tang & Gernandt, 1969; Uchino et al., 1970; Yates, Goto, Kerman, & Bolton, 1993) and brainstem zones responsible for blood pressure control, in particular nucleus tractus solitarius, the lateral tegmental field, the subretrofacial portion of the rostral ventrolateral medulla, and the caudal medullary raphe nuclei (Yates, Balaban, Miller, Endo, & Yamaguchi, 1995; Yates, Goto, et al., 1993; Yates et al., 1994, 1991). Different protocols using electric stimulations caused both excitation and inhibition of the sympathetic efferents. This heterogeneity of effects could be explained by the difference in the protocols and the non-physiologic nature of the electrical stimulation that simultaneously engages afferents from both the otolith organs and semicircular canals.

The vestibulo-sympathetic link was also confirmed by using natural stimulations. The head-up tilt in anesthetized cats (Doba & Reis, 1974) and awake cats (Jian et al., 1999) caused a temporary drop of blood pressure followed by a recovery, while after bilateral transection of the VIIIth cranial nerve the drop of pressure was more pronounced and normal recovery was abated. Another study (Yates & Miller, 1994)

examined the effect of rotations around different axes on the splanchnic nerve activity in decerebrate cats. They found that the otolith sensors and not semicircular canals were involved in reflex. Rotations in pitch had the strongest sympathetic effect, the head up pitch led to the increase in the splanchnic nerve activity, while the head down pitch decreased it. Thus, the natural stimulation studies demonstrate the directional dependence of the vestibulo-sympathetic effect. In animal models the head up stimulations evoke the increase in the sympathetic activity and vascular tonus of the hind limbs. Physiologically this reflex could serve to maintaining stable blood pressure and proper blood distribution in the body during, for example, vertical climbing.

In Human, the head-down neck flexion (HDNF) in prone position has been used to investigate the vestibulo-sympathetic reflex. The method, also called head-down neck rotation, consists in passively changing the head position from extension to flexion in subjects lying in prone position and comparing static vascular responses between head positions. Head Up position is the otolithic analogue of the orthostatic position, and Head Down position is the analogue of either prone or inverse position. Using the method, Essandoh et al. (Essandoh et al., 1987, 1988) demonstrated an increased vascular resistance in the forearm and calf during HDNF. The head down position also increased muscle sympathetic nerve activity (MSNA) (Hume & Ray, 1999). Interestingly, the MSNA is increases proportionally to the degree of head rotation and remains elevated for a prolonged period of time (Hume & Ray, 1999). Normand et al. (Normand et al., 1997) employed a variation of HDNF protocol to exclude the role of neck receptors in the vascular response during the HDNF. Using this protocol, Ray et al. (Ray & Monahan, 2002) demonstrated that aging attenuates the vestibulo-sympathetic reflex.

As the vestibulo-sympathetic reflex is thought to be related to the activation of the otolithic organs, our aim was to assess the vestibulo-sympathetic reflex in a group of patients with bilateral vestibular loss. We hypothesized that the absence of vestibular signals will abolish the vestibulo-sympathetic response.

## 2. Materials and methods

### Participants

The patient group was composed of 9 adults (5 male and 4 female subjects, with a mean age of  $54 \pm 6$  years) suffering from total bilateral idiopathic loss of vestibular function (BVL) for  $7 \pm 2$  years but not from hearing loss or associated neurological symptoms. None of the patients complained of persistent oscillopsia. The diagnosis was based on the absence of abnormal responses to a battery of neuro-otological tests performed in the “Centre d’Explorations Fonctionnelles Oto-neurologiques” (Paris, France) before inclusion in the study. Abnormal canal function was evaluated using a bithermal caloric irrigation for the right and the left ear at both  $44^{\circ}\text{C}$  and  $30^{\circ}\text{C}$  (caloric testing), and by measuring the vestibulo-ocular reflex VOR during a low frequency rotatory test (0.05 Hz, period 20s). Absence of response or inferior to  $5^{\circ}/\text{s}$  for caloric testing was reported in BVL patients. The Video Head Impulse Test (VHIT, Otometrics, see (Halmagyi & Curthoys, 1988)) was performed with an automatic sensitive video camera system for each of the six canals. Moreover, the majority of these patients also had a deficit in high frequency tests with no compensatory eye movements and multiple catch up saccades. Otolithic (saccular) function was evaluated using cervical vestibular evoked myogenic potential (cVEMP) testing. Patients had no response to CVEMP or poor response with a weak amplitude ( $<100 \mu\text{V}$ ), characteristic of BVL (Chiarovano, Zamith, Vidal, & de Waele, 2011). The diagnosis was established before inclusion in the study following the criteria of the Barany society (Strupp et al., 2017): absence of response, or inferior to  $6^{\circ}/\text{s}$ , for bithermal caloric irrigation for the right and the left ear at both  $44^{\circ}\text{C}$  and  $30^{\circ}\text{C}$  (caloric testing); reduced horizontal vestibulo-ocular reflex gain ( $<0.1$ ) upon sinusoidal stimulation a low frequency on a rotatory chair (period 20 s). This study received ethical approval by the ethics committee (“Comité de Protection des Personnes” (CPP) Ile de France VI (No: 07035), Necker Hospital in Paris, France). All participants provided written informed consent after the study procedures were explained in detail.

### Experimental design

#### *Table position and head support*

The subjects lay on the examining table with the head resting comfortably on a mobile support. The support allowed placing the head at the desired height and at different positions for examination. To ensure good venous drainage, an articulated system was used to maintain the subject's right leg stable and above heart level. The table was covered with a soft mattress to ensure the subject's comfort.

#### *Blood flow*

Calf Blood Flow (CBF) was measured with a venous occlusion strain-gauge plethysmograph (Greenfield, Whitney, & Mowbray, 1963) with the gauges placed around the region of maximal circumference of the segment of the right calf. Venous occlusion was ensured by cuffs that were adapted to the size of the right thigh and rapidly inflated to 50 mmHg with a single compressor. The circulation of the foot was excluded by inflating a small cuff to 250 mmHg at the ankle just before the measurement. Blood flow was calculated using the initial part of the plethysmographic curve and expressed in  $\text{mL}\cdot\text{min}^{-1}\cdot 100\text{ mL}^{-1}$ .

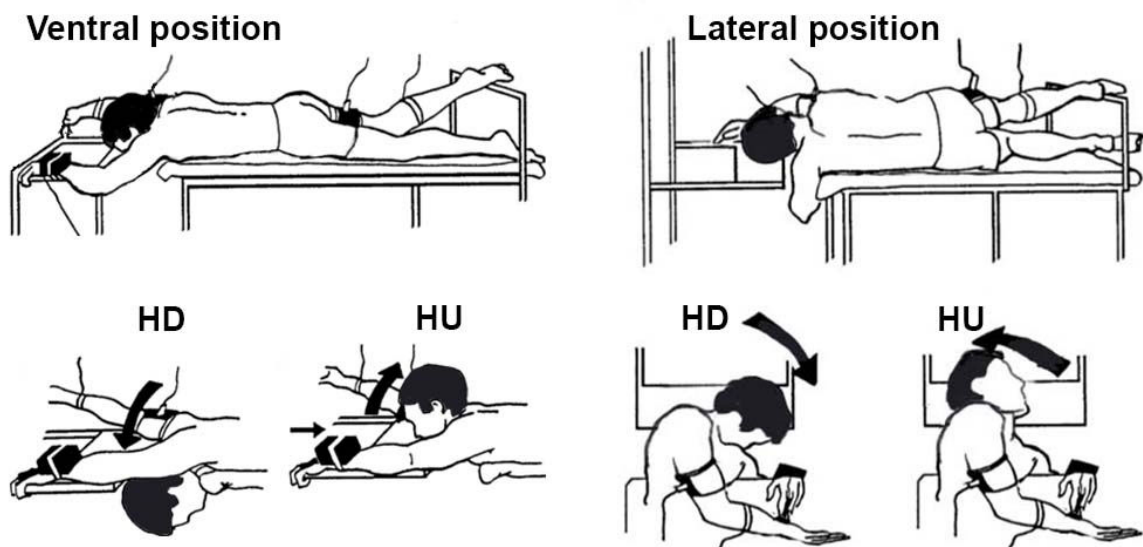
#### *Arterial pressure and heart rate*

Continuous arterial pressure and HR measurements were done with an automatic continuous noninvasive arterial pressure monitor (Finometer Pro, FMS, Amsterdam, The Netherlands) placed on the middle finger held at heart level. Pressure values provided by this system do not significantly differ from those taken directly from the radial artery in subjects in various physiological conditions (Parati, Casadei, Groppelli, Di Rienzo, & Mancia, 1989), and there is good agreement in the evaluation of beat-to-beat variations (Lindqvist, 1995). Mean arterial pressure (MAP) was calculated with the acquisition software (Notocord Hem 4.2, Notocord Systems, Croissy-sur-Seine, France) as the arithmetic mean of the continuous pressure signal. Calf vascular resistance (CVR) was calculated as MAP divided by CBF (Levine, Giller, Lane, Buckey, & Blomqvist, 1994).

#### *Protocol*

The experiments were performed at 2 or 4 PM in a room at  $24.2 \pm 0.8^\circ\text{C}$ . Each subject was examined lying prone and on the left side (Figure SI.1) The head support was adjusted to place the head in the Head-Up (HU) position. After the cuffs and sensors were set in place, the subject remained in this position for 10 min

before measurements were taken. Instruction was given to keep the eyes closed during the whole session in particular when the position of the head was changed. The studies of the two body positions were separated by 10 min. At each body position, the head was passively changed in the following sequence: Head Up (HU) – Head Down (HD) – Head Up. At each head position, CBF was measured twice after the new head position was taken. MAP measurements in the LP for the two HU positions were different and thus compared separately with the HD; the rest of the HU measurements were not different and thus averaged.



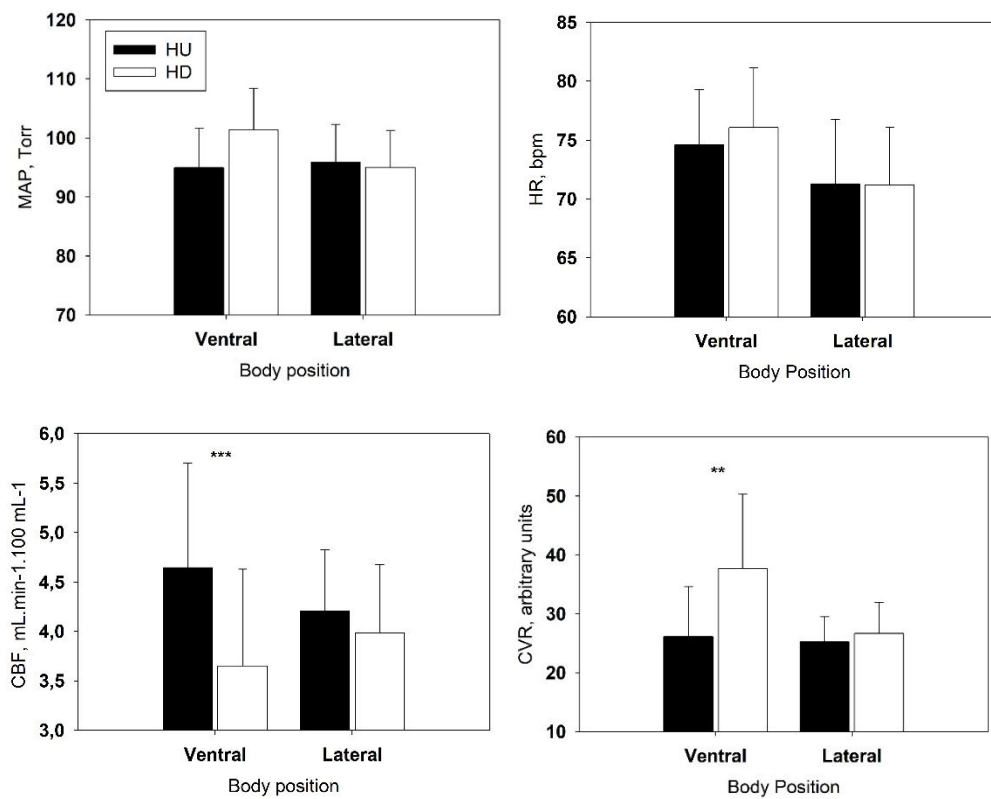
**Figure SI.1 – The HDNF protocol illustration for the ventral and lateral positions.**

### *Statistical analysis*

The overall calculations were carried out by using the statistical software SAS 6.08. Values are expressed as means  $\pm$  SEM. For each body position (prone, on left side, and prone minus on left side), the data were compared by two-way analysis of variance, testing for head position (Head-Up, Head-Down) and subject variability. The Wilcoxon Signed Rank Test, which is a variant of a non-parametric paired t-test, was used to compare head positions for each parameter in Ventral and Lateral positions separately.

### 3. Results

CBF in Ventral position decreased significantly in HD as compared to the HU position ( $4.64 \pm 0.71$  in HU to  $3.65 \pm 0.65$  in HD), while CVR increased in the same body position from HU to HD ( $26.12 \pm 5.63$  in HU to  $37.68 \pm 8.42$  in HD; Figure SI.2, Figure SI.3). MAP and HR did not demonstrate any significant change. No difference were found in the Lateral position in MAP, HR, CBF, CVR (Table SI.1).



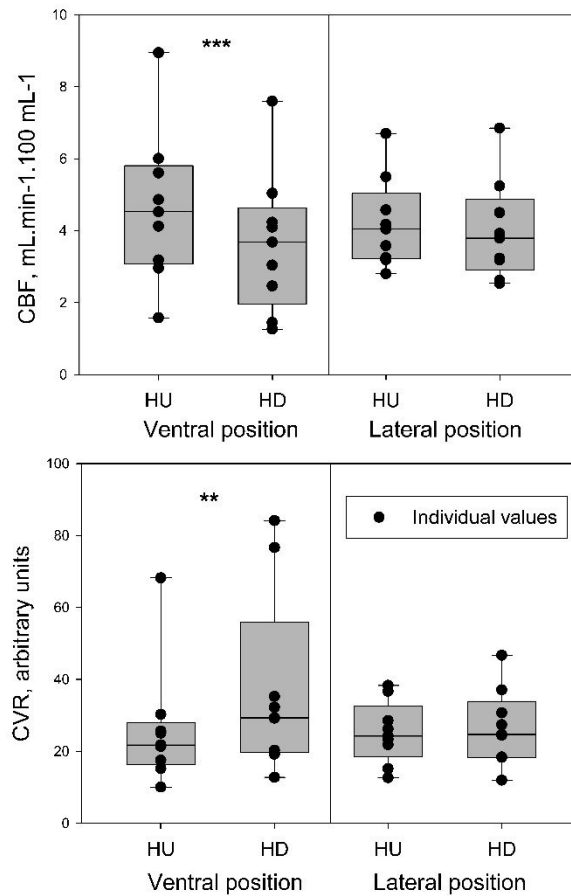
**Figure SI.2 – Effect of the HDNF on MAP (Mean Arterial Pressure), HR (Heart Rate), CBF (Calf Blood Flow) and CVR (Calf Vascular Resistance).**

**Table SI.1 – Cardiovascular effect of HDNF in BVL patients and the corresponding results from studies on healthy subjects.**

Mean  $\pm$  SE for 9 subjects, Values of the MAP (mean arterial pressure), HR (heart rate), CBF (calf blood flow) and CVR (calf vascular resistance) in HU and HD positions. Significance: \* $<0,05$ , \*\* $<0.01$ , \*\*\* $<0.001$ . The data from two studies on healthy subjects provided below for comparison. The significance in Normand et al. was calculated in relation to the intermediate head position, see (24).

Body Position	Ventral		Lateral		
	Head Position	HU	HD	HU	HD
MAP, Torr		94.94 $\pm$ 4.46	101.39 $\pm$ 4.66	95.93 $\pm$ 6.35	95.01 $\pm$ 6.29
HR, beats per min		74.57 $\pm$ 3.14	76.05 $\pm$ 3.37	71.29 $\pm$ 3.63	71.19 $\pm$ 3.23
CBF, mL.min <sup>-1</sup> .100 mL <sup>-1</sup>		4.64 $\pm$ 0.71 ***	3.65 $\pm$ 0.65	4.20 $\pm$ 0.41	3.99 $\pm$ 0.46
CVR, arbitrary units		26.12 $\pm$ 5.63 **	37.68 $\pm$ 8.42	25.24 $\pm$ 2.86	26.65 $\pm$ 3.51
<u>From Shortt and Ray (31):</u>					
MAP, Torr		96 $\pm$ 3 *	98 $\pm$ 3		
HR, beats per min		71 $\pm$ 2 *	76 $\pm$ 3		
CBF, mL.min <sup>-1</sup> .100 mL <sup>-1</sup>		4.63 $\pm$ 0.78 *	3.97 $\pm$ 0.60		
CVR, arbitrary units		24.0 $\pm$ 4.3 *	27.4 $\pm$ 4.7		
<u>From Normand et al. (24):</u>					
MAP, Torr		102.6 $\pm$ 5.9	105.7 $\pm$ 6.4	96.4 $\pm$ 6.2	102.4 $\pm$ 5.8 *
HR, beats per min		61.4 $\pm$ 2.6	62.8 $\pm$ 2.6	64.1 $\pm$ 2.2	65.9 $\pm$ 2.5 *
CBF, mL.min <sup>-1</sup> .100 mL <sup>-1</sup>		6.2 $\pm$ 0.7	5.2 $\pm$ 0.6 *	4.20 $\pm$ 0.4	4.2 $\pm$ 0.4
CVR, arbitrary units		18.9 $\pm$ 2.2 **	23.0 $\pm$ 2.7 *	25.6 $\pm$ 3.1	27.8 $\pm$ 3.3

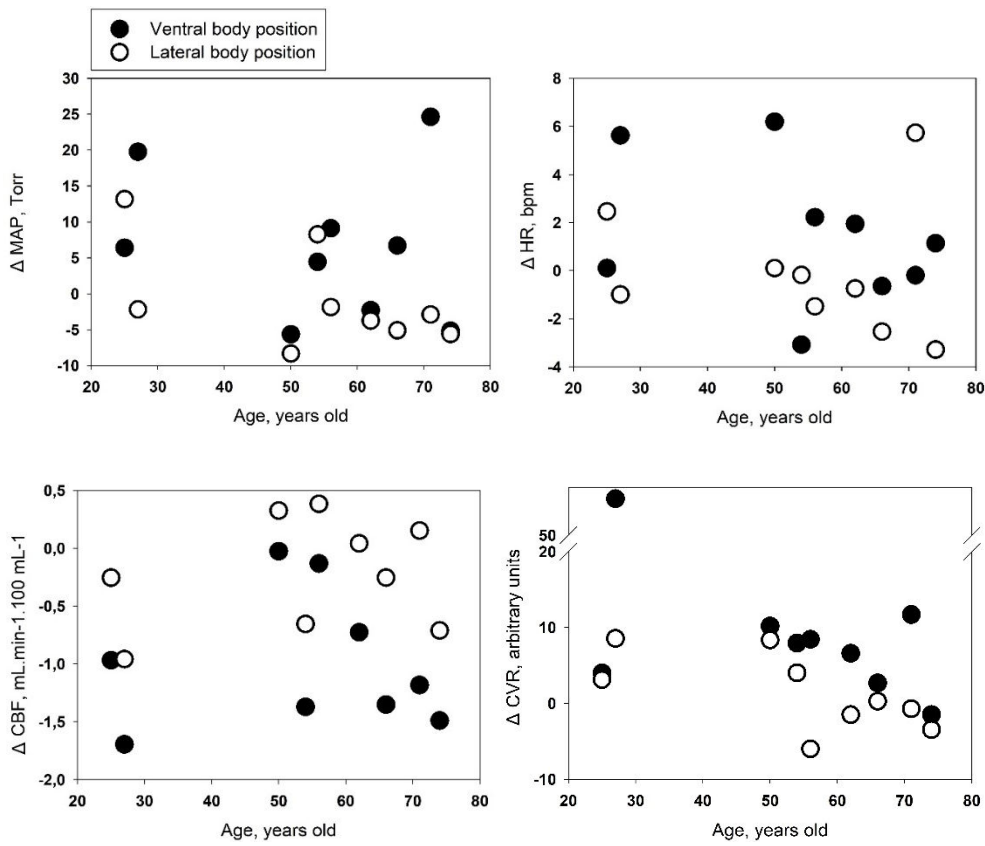




**Figure SI.3 – The detailed data representation for CVR and CBF in Ventral and Lateral positions of the body for HU and HD conditions.** Black dots represent individual values for every subject.

Age effect :

Linear regression of  $\Delta$  MAP,  $\Delta$  HR,  $\Delta$  CBF and  $\Delta$  CVR to age was calculated (Figure SI.4), where  $\Delta$  is a difference between values recorded in HD and HU positions. Statistically, no effect of age was revealed in any parameter. However, the CVR has a tendency to be significantly correlated to age ( $p= 0.105$  for Ventral and  $p=0.062$  for Lateral position).



**Figure SI.4 – Effect of age of patients on  $\Delta$  MAP (HD - HU),  $\Delta$  HR,  $\Delta$  CBF and  $\Delta$  CVR.**  $\Delta$  is a difference between values recorded in HD and HU positions. Individual values of  $\Delta$  for every subject are represented as black circles for ventral position, and white circles for lateral position.

## 4. Discussion

### *The vestibulo-sympathetic reflex in BVL patients*

The main result of this study is that the HDNF protocol elicits a vasoconstriction in patients with bilateral vestibular defect. The values for CBF and CVR obtained are almost identical to the data obtained using the same protocol in healthy subjects (Shortt & Ray, 1997). CBF decreased from  $4.64 \pm 0.71$  to  $3.65 \pm 0.65$  during the HDNF in our study and  $4.63 \pm 0.78$  to  $3.97 \pm 0.60$  mL·min<sup>-1</sup>·100mL<sup>-1</sup> during the same manoeuvre in healthy subjects. CVR also increased in both studies. However, in our study HR remained unchanged, as well as the MAP, while both

parameters increased in the study of healthy subjects. However, Shortt & Ray did not discuss or interpret the increase in these parameters, as it could simply be the result of the experiment participation excitation. To our knowledge, this is the only study using exactly the same protocol. Another study observed greater values of the CBF  $6.2 \pm 0.7$  and  $5.2 \pm 0.6 \text{ mL}\cdot\text{min}^{-1}\cdot 100 \text{ mL}^{-1}$  with no change in HR and MAP (Normand et al., 1997). The greater values could be explained by the difference in protocols as in the study of Normand et al (Normand et al., 1997), the circulation of the foot was not excluded. Nevertheless this study also showed a decrease in blood flow and increase in vascular resistance in the HD position. The difference observed in CBF, however, is even less than in the current study.

Basing on the decrease in the CBF and increase in CVR observed in the BVL patients with values identical to the one observed in healthy subjects, we could suggest that human subjects can fully recover the ability to adjust the blood pressure to the head position even after the loss of vestibular inputs. It might be the result of neural integration of signals from different non-labyrinthine sensors, participating in the reflex apart from the vestibular system. Otherwise, it is possible that the cardiovascular reflex elicited by the HDNF is mediated by some other receptor, for example pressure receptors in the head or changes in the anatomical configuration around the baroreceptors. Using another vestibular stimulation, which consists in an unpredictable head drop in prone position, Radtke et al. (Radtke et al., 2000, 2003) showed that labyrinthine defective patients still present a vascular response as normal subjects and a cardiac response, though delayed. In our study, as labyrinthine inputs were absent or negligible and the visual inputs were eliminated, the origin of the lower limbs vasoconstriction during HDNF is puzzling. We will discuss the two possibilities.

#### *Multisensory compensatory integration?*

Indeed, animal studies have revealed the possibility to recover from experimental bilateral vestibular loss. In awake cats bilateral peripheral vestibular lesions led to an impairment in controlling blood pressure. However, it has been shown that within a month animals are able to regain the ability to maintain stable blood pressure during body tilts even without visual inputs (Jian et al., 1999). This suggests that other, non-labyrinthine inputs participate in the cardiovascular adjustments, and when deprived from the labyrinthine inputs, animals learn to use non-labyrinthine cues regarding body position in space to regulate blood pressure.

It is known also that inputs from the trunk, including visceral graviceptors, can contribute to a sense of spatial orientation (Mittelstaedt, 1992, 1995, 1996) and influence respiration (Kuldavletova, Marie, Denise, & Normand, 2018). It has been demonstrated that after the vestibular loss in human somatosensory and proprioceptive signals take a bigger role in balance and postural control (Lacour et al., 1997; Pyykkö, Enbom, Magnusson, & Schalén, 1991; Yates & Miller, 2009).

The vestibular nuclei receive primarily, but not solely the inputs from the labyrinth. The activity of vestibular nuclei neurons is shown to be affected by multiple non-labyrinthine inputs. Neck, limb and trunk receptors are shown to affect the firing of the neurons from vestibular nuclei (Arshian et al., 2014; Boyle & Pompeiano, 1981; Brink, Hirai, & Wilson, 1980; Jian, Shintani, Emanuel, & Yates, 2002; Jian et al., 2002; Kasper, Schor, & Wilson, 1988; Pompeiano, 1972; Rubin, Liedgren, Ödkvist, Larsby, & Aschan, 1979).

Basing on physiological and anatomical studies, Yates et al (Yates et al., 2000) proposed a model of neural interactions for the vestibulo-vascular control that integrates the signals from multiple sensors. Vestibular nuclear complex receives inputs from the labyrinth, and viscera, cutaneous and proprioceptive inputs as well as optokinetic information. Posterior cerebellar vermis serves to modulate the integrative response of the vestibular nuclei. It should be mentioned that this modulation becomes particularly important in cases of deficiency of information, such as BVL, or the contradiction of signals from different sensors. Brainstem circuitry provides cardiovascular regulatory functions via sympathetic activity that increases peripheral vascular resistance.

Thus, multisensory integration taking place in the vestibular nuclei can substitute lost labyrinthine signals to recreate the vascular adaptation to changes in posture. The fact that the HDNF manoeuvre induces the same adaptive vascular responses in BVL patients as in normal subjects might indicate that the integration of inputs from non-vestibular origin should be able to rebuild the position of the head. This leaves the place for another hypothesis.

*Non-vestibular nature of the reflex observed during the HDNF?*

HDNF manoeuvre places the head below the level of the heart that can alter the cerebral pressure and intracranial blood volume. The increased intracranial pressure could stimulate the nonspecific pressure receptors. To our knowledge

only one study tried to eliminate this factor from consideration by using the Head Down Neck Extension (HDNE) protocol in the supine position (Hume & Ray, 1999). The idea was that the HDNF in prone and HDNE in supine position differently stimulate the otolithic system while placing the head similarly below the heart. The HDNE did not reveal any change in blood flow and the authors concluded that the cranial pressure receptors do not take a part of the vestibulo-sympathetic reflex. These results can be interpreted otherwise. Regarding the neck anatomy, the neck extension to the back cannot place the head far below the level of the heart. Therefore, there is no or negligible difference of levels relative to the heart, so the manoeuvre is not comparable to the HDNF in prone.

Another argument is that in supine position HDNE stretches the carotid artery, the area where the baroreceptors are situated, while the HDNF enlarges the carotid diameter independently of the pressure. Baroreceptors are not stimulated by the pressure itself but by the dilation of the carotid (Abboud & Thames, 2011). It might result a decrease in the stimulation of the carotid baroreceptors during HDNE, which would counteract the increase in hydrostatic pressure. This mechanism makes the comparison of both protocols impossible.

Therefore, we cannot eliminate the possibility that nonspecific pressure receptors in the head could be a source of vascular reaction during the HDNF manoeuvre.

#### *Age and the HDNF response*

The results of the current study did not reveal a statistically significant effect of age of the patients on the cardiovascular adjustment efficiency. However, the difference in CVR between HU and HD position ( $\Delta\text{CVR}$ ) has a tendency to be significantly correlated to age ( $p=0.105$  for Ventral and  $p=0.062$  for Lateral position). The literature demonstrates that in elderly the vestibulo-sympathetic reflex is significantly attenuated (Ray & Monahan, 2002). Physiological data are naturally highly variable, which often inhibits the power of the linear regression test, especially with small samples. However, changes induced by the HDNF manoeuvre are still much more pronounced in elderly population of our study, than in the subjects reported in the earlier study (Ray & Monahan, 2002). It is possible that in elderly this compensatory circuit performs more efficiently than the vestibular system, which is known to impair with age (Walther & Westhofen, 2007).

*Physiological significance of the human VS reflex*

Finally, the existing literature seems to have a gap in the physiological significance of the reflex, known as vestibulo-sympathetic. It has long been assumed in the literature that the vestibular-sympathetic reflex is aimed to anticipate the slower-acting baroreceptor reflex, acting immediately after the postural change.

The animal studies have clearly demonstrated a directional dependence of the sympathetic activation in animals. The sympathetic activity is increased in nose up and decreased in nose down pitch (Yates & Miller, 1994). In quadruped, the reflex might serve to maintaining blood pressure stability during vertical climbing.

In Humans, the physiological significance of the reflex is less clear. Most studies using the HDNF maneuver have revealed that the head down neck flexion increases the MSNA and the vascular resistance. It has long been assumed a vestibular-modulated compensation for orthostatism. However, regarding the otolith sensors position, the postural analogue of orthostatism is rather the head up than the head down position in the HDNF manoeuver. Thus, the vestibulo-sympathetic reflex does not act in line with the baroreceptor activation during orthostatism, being just the faster version of the same vascular adjustment, but, on the contrary, opposes the baroreceptor function. A recent study in microgravity, showing an increase of the carotid baroreflex at oG, supports this interpretation (Ogoh et al., 2018). With this, the vestibulo-sympathetic reflex should be considered as a limiting mechanism for the baroreflex.

## **5. Summary**

Patients with bilateral vestibular loss presented normal vascular responses during the HDNF manoeuver. Thus, the so-called vestibulo-sympathetic reflex either does not originate from the vestibular system during the HDNF or recovers after bilateral vestibular loss. If it is so, it results not only from activation of the vestibular apparatus, but also from other non-labyrinthine sensors, such as trunk graviceptors, proprioceptive and cutaneous inputs, and vision. These inputs are integrated to create the modulation of the vascular response. This integration is subject to plastic changes and reweighting of impact of different types of sensors

and can reestimate the position of the head following the BVL. Finally, there is evidence that the vestibulo-sympathetic reflex in humans acts in opposition to the orthostatic baroreflex, raising the question of its physiological significance.

# **Study II: Influence of graviceptors stimulation initiated by off-vertical axis rotation on ventilation**

*Published in Experimental Physiology (Kuldavletova, Marie, Denise, & Normand, 2018)*

## **1. Background**

Electric vestibular stimulation in cats alters the activity of the respiratory muscle nerves, including the phrenic, intercostal, abdominal nerves and upper airway muscle nerves (hypoglossal, recurrent and superior laryngeal, glossopharyngeal nerves and pharyngeal branches of the vagus nerve) (Siniaia & Miller, 1996; Yates, Jakus, et al., 1993). Also in cats, otolithic stimulation during head rotation in pitch, while keeping the position of the body, alters respiratory nerve activity; semicircular canal stimulation in yaw, on the other hand, shows no effect (Rossiter et al., 1996; Rossiter & Yates, 1996). In cats and dogs, linear vertical movements and pitching movements increase amplitude and frequency of breathing movements (Spiegel, 1936).

In humans, very few data could be found on the topic. It may be important in situations when strong externally whole body accelerations are imposed (Sung et al., 2011) especially in emergency transportation (Ambulances, medical helicopters, etc). For instance, increase in ventilation would decrease cerebral blood flow, which may alter further cerebral oxygenation. Although natural and caloric stimulations of the semicircular canals are proved to induce alterations in respiration (Jauregui-Renaud et al., 2001, 2000), very little is known about the physiological importance and functional characteristics of the relation between the otolithic and respiratory systems. The study of Omlin et al. (Omlin et al., 2016) shows that otolith stimulation by rocking movements along the longitudinal axis of a body affect human respiration frequency. Monahan et al. have found that



stimulation of semicircular canals, but not otolith organs, increases ventilation in humans (Monahan et al., 2002). However, these studies do not take into account the possible effect of non-labyrinthine graviceptors. Moreover, inducing an isolated otolithic stimulation in human is a difficult challenge: if the stimulation is provided by inertial acceleration, extra-labyrinthine graviceptors are also stimulated; if stimulation is provided by head-only tilt, neck mechanoreceptors and carotid baroreceptors are stimulated in addition to the labyrinthine ones. During such stimulation, the otolithic effect is at best brought out indirectly (Normand et al., 1997). Hence, the absence of ventilatory alteration during Head Down Neck Flexion (HDNF, a static otolithic stimulation), does not provide definitive proof of the lack of involvement of the otolithic system in respiratory control (Lee et al., 2001; Monahan et al., 2002).

During off vertical axis rotation (OVAR), in head-fixed coordinates, the component of the gravity vector perpendicular to the axis of rotation revolves around this axis and periodically stimulates the graviceptors (both otolithic and visceral). When the angular velocity is constant, after a while (30-60 seconds) only the graviceptors are stimulated, but not the semicircular canals. To our knowledge, only one study has investigated the OVAR effects on ventilation in humans, demonstrating that ventilation synchronizes with chair rotation (Kaufmann et al., 2002). However, only respiration rate was measured, but not ventilation per se. Moreover, since OVAR stimulates both labyrinthine and non-labyrinthine receptors, ventilatory modulation during OVAR could be due to activation of either one type or both types of receptors. Respiratory activity results from the interaction of two functional systems through various respiratory neurons: a “flow generator” which adjusts inspiratory flow as a function of metabolic needs; and a “time switch” which regularly interrupts the flow generator. If OVAR modifies ventilation, one or both of these systems are likely to be involved.

The aim of this study was to assess the OVAR effects on ventilation and to determine whether the OVAR effect on ventilation is due to the labyrinthine or the non-labyrinthine graviceptors. The stimulation of graviceptors possibly acts on the ramp neurons presumably responsible for the inspiratory flow. Ventilation and its components such as tidal volume and breathing frequency were thus compared in OVAR and EVAR. The specific effect of the otolithic system on the respiratory drive was deduced from calculating the mean inspiratory flow ( $V_{ti}/T_i$  ratio where  $V_{ti}$  is

inspiratory tidal volume and  $T_i$  is inspiratory time) at the maximum angle of occurrence of inspiration. In the event that the gravity receptors may also interrupt the inspiratory activity, for instance by activating the off-switch inspiratory neurons, the frequency histograms of transition between Inspiration and Expiration (I-E transition) as a function of angular chair position during OVAR and EVAR were analyzed. The periodic activation of graviceptors in OVAR should lead to a preferred angle where the I-E transition occurs.

## 2. Materials and Methods

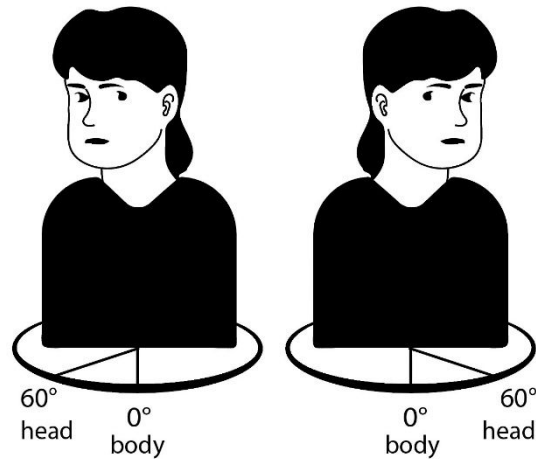
### *Ethical Approval:*

The study was conducted on Human subjects at the University of Caen Normandie and conformed to the standards of the Declaration of Helsinki. Subjects were informed of the protocol and familiarized with the instruments and the recording procedure before giving their written consent. The experiments were conducted during practical teaching sessions approved by the Dean of the School of Medicine who was at that time the President of the local Ethics Committee (CCP de Basse-Normandie).

### *Paradigm:*

To distinguish between vestibular and non-vestibular gravity receptors, we used the head-turn-on-trunk (HTOT) paradigm (Douglas, Clément, Denise, & Wood, 2017) analyzing the same parameters during two identical rotations, executed with different head positions in relation to trunk position: “head rightward” for one rotation, “head leftward” for another. The trunk position remains the same ( $0^\circ$ ) while the head is turned either to  $60^\circ$  or to  $-60^\circ$  relative to the trunk (Figure SII.1) either advancing (if head rightwards while rotating Clockwise) or retarding (if head leftwards while rotating Clockwise) relative to the trunk rotation. In this paradigm, if the otolithic receptors are solely involved in ventilatory synchronization, then the phase of I-E transition should shift by the same angle as HTOT; conversely, if the otolithic receptors are not involved in ventilatory synchronization, head shift should induce no change in the phase of I-E transition. To distinguish the specific effect of otolithic and non-labyrinthine receptors on the inspiratory flow we

compared the inspiratory tidal volume ( $V_{t_i}$ ) to inspiratory time ( $T_i$ ) ratio recorded at the same angle for the two head positions.



**Figure SII.1 – Head-Turn-On-Trunk (HTOT) paradigm.** Head is fixed at  $60^\circ$  to the left or to the right from the straight position, while the orientation of trunk remains straight ( $0^\circ$ ).

*Subjects:*

Twenty-one healthy subjects (five female and sixteen male; age  $23 \pm 3.2$  years) participated in the study. All were free of any documented cardiovascular, respiratory, cochlear, vestibular, or neurological diseases or conditions, as judged by clinical examination. The participants did not take any medication on a regular basis and refrained from alcohol and caffeine on the day of testing.

*Experimental protocol:*

Subjects sat on a motorized rotating chair in the middle of the experimental room. They were secured with a harness and wore anti-noise ear plugs. The protocol was divided into three parts (a baseline recording and two recordings of rotation), all conducted in darkness. Subjects were instructed to keep quiet and relax. They were able to stop the chair rotation at any time.

In the baseline recording, the subjects' relaxed spontaneous breathing frequency was measured over a five-minute period. To facilitate "rotation-ventilation" synchronization, the rotational frequency for OVAR and EVAR stimulations was individually chosen to be close to the subject's spontaneous breathing frequency. The individual breathing frequencies are shown on Table SII.1.

**Table SII.1** – Velocity and frequency of rotation for the 17 subjects who were taken for analysis. Data are presented in rising order of rotation frequency.

Subjects (S)	Rotation velocity (°/sec)	Rotation frequency (Hz)
S 14	35	0.10
S 8	54	0.15
S 15	54	0.15
S 1	60	0.17
S 13	60	0.17
S 16	60	0.17
S 2	65	0.18
S 10	65	0.18
S 12	65	0.18
S 5	66	0.18
S 9	74	0.21
S 7	75	0.21
S 17	75	0.21
S 4	80	0.22
S 11	80	0.22
S 6	84	0.23
S 3	85	0.24
<b>Mean</b>	<b>67</b>	<b>0.19</b>
<b>S.D</b>	<b>13</b>	<b>0.04</b>

The protocol was identical for the two rotational trials, except for the head positions: “head rightward” for one rotation, “head leftward” for the other; the order of the head position being randomized. The angular difference between head positions was approximately 120°. The chair was fitted out to make the subject comfortable, with head support in both positions. All rotations were clockwise. Each rotation recording began with EVAR sustained for 11 min, then the chair was tilted to 15 degrees and OVAR was sustained for 11 min. Finally, the chair returned to the upright position and EVAR continued for another 1 min, stopping when the chair came back to the initial position. After rotation, subjects remained in the dark for 1 min so as not to be confused by a sudden return of light. The final angular velocity in each recording was reached in 1 second and remained constant; its magnitude was set individually for each subject during baseline recording. After five minutes of rest, subjects underwent the second rotational trial. The protocol for this rotation was the same as for the first trial.

To make allowance for the inactivation time of the semicircular canals, the first minute of rotational phases 1 and 2 was ignored.

*Measurements and data analysis:*

Respiratory measurements were taken with a face mask using a Fleisch pneumotachograph (range 0 – 1.4 L.s<sup>-1</sup>) connected to a Validyne DP45 transducer (Validyne, Nothbridge, CA) and a Gould amplifier. Volume was calculated by integration of the flow signal. An acquisition card (LabPc, Nationals instruments) interfaced with a PC was used to control the rotational parameters and monitor data. Signals were acquired at 1000 Hz. Calibration of the pneumotachograph was performed with a one liter syringe at the end of the experiment.

*Ventilatory effects of OVAR:*

For each subject, the “head rightward” and “head leftward” ventilation data comprising tidal volume (L), mean frequency (breath<sup>-1</sup>) and ventilatory flow (L.min<sup>-1</sup>) were averaged for EVAR and OVAR minute by minute. A two-way repeated measures ANOVA was used to analyze both Inclination (EVAR, OVAR) and Time (1, 2, 3...10 min.) effects.

Data from subjects were averaged minute by minute, independently of head positions, in order to observe a global modulation of ventilation during OVAR in comparison with EVAR.

*Ventilatory synchronization:*

In OVAR and EVAR the 360° rotation circle was divided into 18 equal angular sections (20° each). To assess the effect of gravity on the timing of respiration, the number of transitions between inspiration and expiration (I-E transition) was counted in each section for every subject. The frequency of occurrence of I-E transitions in each section was taken as a function of a total number of I-E transitions.

*Distinction between labyrinthine and non-labyrinthine effects:*

Two head positions were used in the study to separate the effects of the labyrinthine and non-labyrinthine receptors. We assumed that if the otoliths had an effect on respiration, the phase of the I-E transitions would shift towards the direction of the head turn. We used a cross-correlation analysis on the mean frequency of occurrence of I-E transitions between “head rightward OVAR” and “head leftward OVAR” to recognize if the phase shift in I-E transitions exists depending on head position. The cross correlation factor  $r$ , between the two series, was computed with a step of 20 degrees. The maximum  $r$  value is plotted as function of the phase shift. In the absence of effect of the head position, we expect that the maximum  $r$  value occurs for a phase shift of 0° (or 360°). Individual cross-correlations were also performed for each subject to assess inter-individual variability.

To assess the effect of the head position change on ventilatory flow, we calculated the average inspiratory tidal volume ( $V_{t_i}$ ) to inspiratory time ( $T_i$ ) ratio for inspirations occurring for fixed chair positions (180° to 240°) during off vertical rotations. A paired t-test was used to compare “head rightward OVAR” and “head leftward OVAR” data.

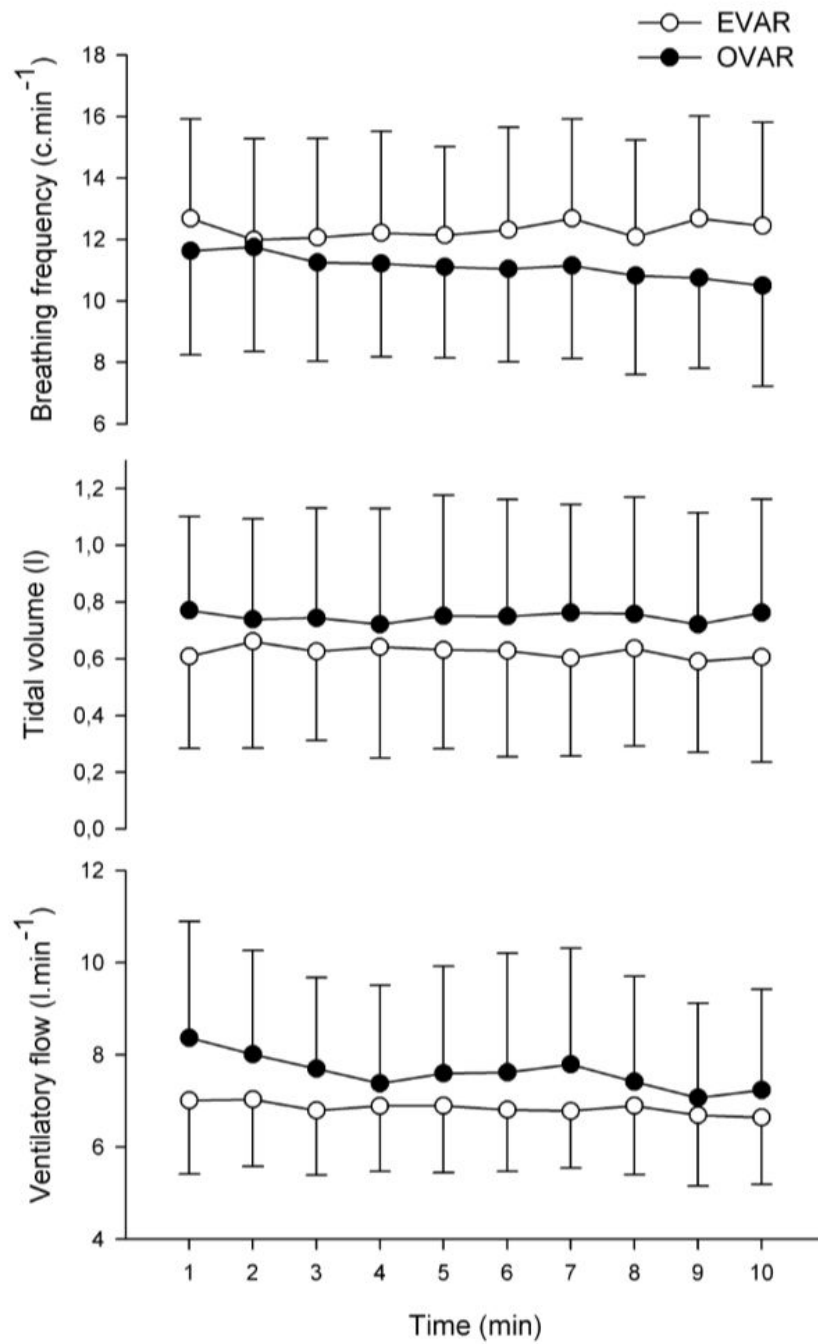
### **3. Results**

#### *Subjects:*

Owing to symptoms of motion sickness, 4 subjects preferred to stop the experiment before the end of protocol, their data were excluded from analysis. Thus data from only 17 subjects, with no or slight symptoms of motion sickness, (4 women and 13 men) were taken for the analysis. For one subject tidal volume calibration was not obtained. Accordingly, the ventilatory parameters (tidal volume, respiratory frequency, ventilation) were analyzed for only 16 subjects. However, the ventilatory cycle and the determination of I-E transition phases were calculated for 17 subjects.

#### *Ventilatory effects of OVAR and duration of the stimulation:*

We used the Scheirer–Ray–Hare test, a nonparametric two-way ANOVA with factorial design to assess the effect of type of stimulation represented as a two-level factor (“OVAR” and “EVAR”) and the effect of duration of the stimulation (10-level factor) on tidal volume, respiratory frequency and ventilator flow (Figure SII.2).



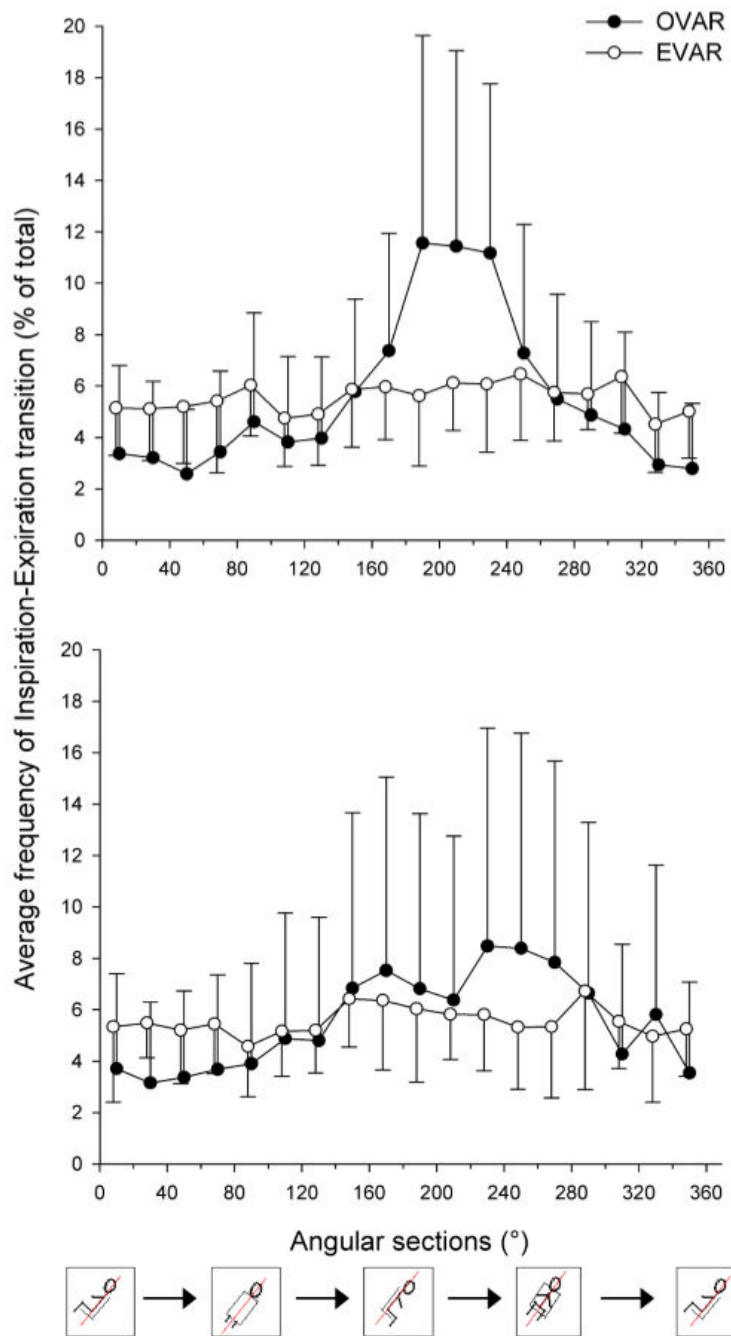
**Figure SII.2 – Tidal volume (bottom), respiratory frequency (middle) and ventilatory flow (top) observed during 10 minutes of EVAR (empty circle) and OVAR (full circle). n = 16. Error bars = S.D.**



We found a significant effect of axis inclination for all respiratory parameters ( $p < 0.001$  for tidal volume and respiratory frequency,  $p < 0.01$  for ventilator flow), while time did not influence respiration ( $p$ -values close to 1) and interaction between factors showed no effect on the respiratory parameters.

*Ventilatory synchronization:*

Angular position histograms of I-E transition phases, in EVAR and OVAR for both head positions, are given in Figure SII.3. Repeated measures ANOVA highlighted no significant difference between the 18 angular sections in the EVAR regardless of head position ( $p > 0.3$  for “head rightward”,  $p > 0.5$  for “head leftward”), while a significant difference between these sections was found in OVAR ( $p < 0.001$  for both head positions). Therefore, the occurrence frequency of I-E transitions is significantly depending on the angular position of the chair in OVAR, indicating that respiration is influenced by chair rotation. The fact that there is some difference seen between the head-leftward and head-rightward conditions might correspond to the well-known head-turning asymmetry (Ocklenburg & Güntürkün, 2009).



**Figure SII.3 – Effects of EVAR (empty circle) and OVAR (full circle) on the occurrence frequency of I-E transitions during “head rightward” position (top) and “head leftward” position (bottom).** n = 17. Error bars = S.D.

*Distinction between labyrinthine and non-labyrinthine effects:*

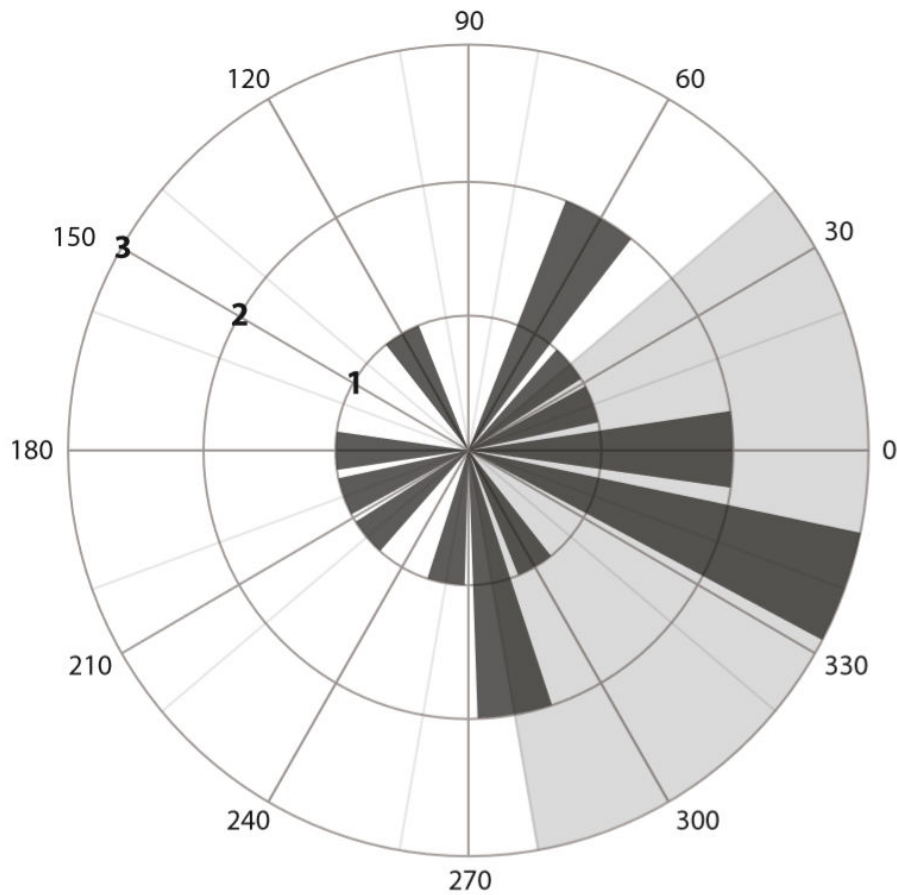
*Angular positions of I-E transitions*

The cross-correlation between the occurrence frequencies of I-E transitions in “head rightward” and “head leftward” OVAR conditions shows that the maximum correlation occurs for a phase shift between  $-40^\circ$  and  $-20^\circ$  with  $r(-40)=0.8$  and  $r(-20)=0.79$ . Thus phase difference in respiration between the “head rightward” and “head leftward” recordings is between  $20^\circ$  and  $40^\circ$  in average. It should be noted that the phase difference in I-E transitions between “head rightward” and “head leftward” OVAR conditions is about 4 times smaller than the angle difference between head positions (nearly  $120^\circ$ ).

However, efficiency of synchronization of the I-E transitions with OVAR was variable among subjects. Only 10 subjects out of 17 had more than 50% of their I-E transitions in a single  $120^\circ$  sector for both head positions.

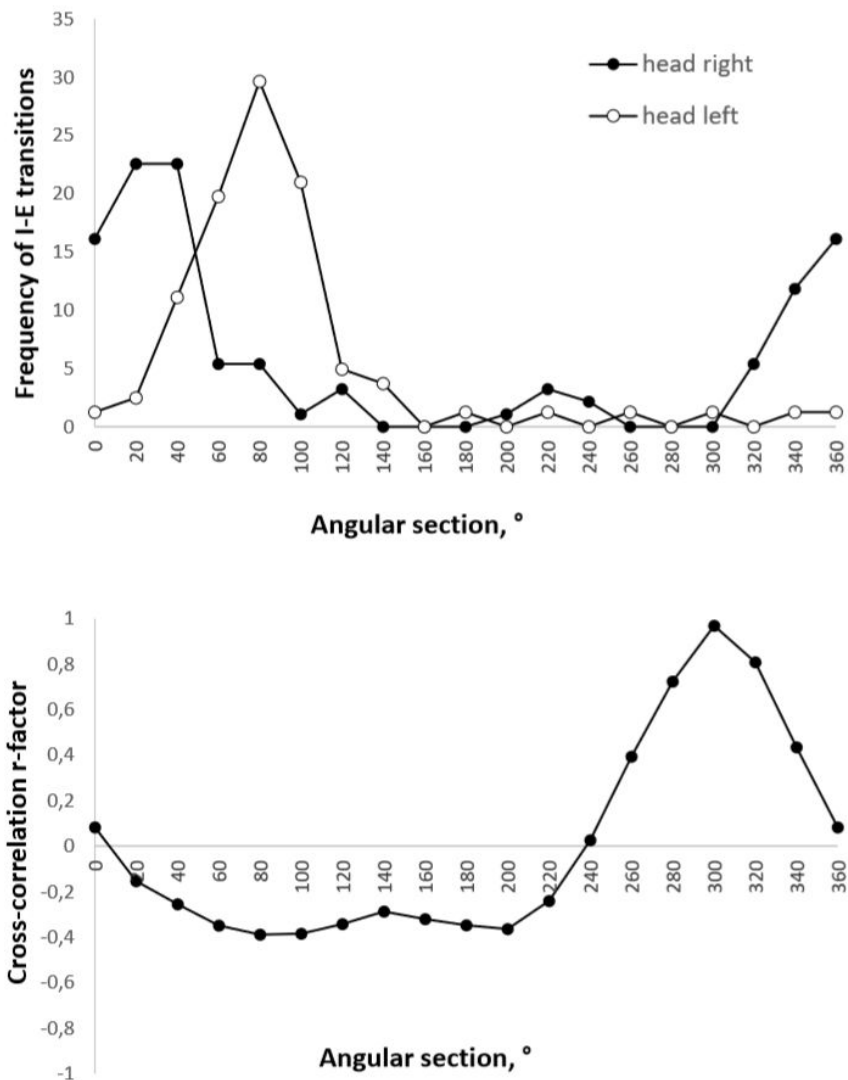
Moreover, the phase difference in respiratory timing had also a high inter-subject variability. Individual cross-correlation showed that the maximum value of  $r$  occurred between  $280^\circ$  and  $40^\circ$  only in 10 out of the 17 subjects (Figure SII.4). In the rest of the subjects the respiratory phase shift between the “head rightward” and “head leftward” positions was larger which can be seen in Figure SII.4.

Individual data from one of these subjects are given in Figure SII.5.



**Figure SII.4 – Number of subjects in each calculated phase shift between respiration transitions in head-leftward and head-rightward conditions.** Step =  $20^\circ$ . For each subject, the deemed phase shift is the one with the maximal value for  $r$ . The shaded sector includes the range of angles with most of the subjects' phase shifts. However, many subjects fall outside the shaded zone, which demonstrates a large intersubject variability.

Study II: Influence of graviceptors stimulation initiated by off-vertical axis rotation on ventilation



**Figure SII.5 – Individual data of one subject.** (upper) Effects of OVAR on the occurrence frequency of I-E transitions in function of head position, “head rightward” (filled circle) or “head leftward” (blank circle) in one subject. Each circle represents the moving average of the frequency of I-E transitions. As seen on the graph, the phase shift between positive peaks is  $\sim 60^\circ$ . (lower) Cross-correlation r factor for the same subject. The peak correlation is for the shift  $300^\circ$  which is  $-60^\circ$ .

*Ventilatory flow:*

The  $V_{t_i}/T_i$  ratios were calculated for the angular section  $180^\circ - 240^\circ$  during the “head rightward” and the “head leftward” OVAR. We were interested in this angular section because these are the chair positions at which most of the inspirations occurred during OVAR. As few inspiratory phases were observed in one subject for this angular section, the corresponding data were not used. Among the 15 subjects, the change of head position leads to no significant difference in the  $V_{t_i}/T_i$  ratio observed for the angular section  $180^\circ - 240^\circ$  (Head rightward =  $0.27 \pm 0.09$  L/sec vs. Head leftward =  $0.28 \pm 0.08$  L/sec, ns).

## 4. Discussion

*Differences between humans and animals:*

While it seems fairly certain that static otolithic stimulation causes modulation of respiratory activity in animals (Cotter et al., 2001; Rossiter et al., 1996; Rossiter & Yates, 1996), static or dynamic otolithic stimulation effect on ventilation in humans is less clear (Lee et al., 2001; Monahan et al., 2002). Conversely stimulation of the semicircular canals can apparently modulate respiratory functions in humans (Jauregui-Renaud et al., 2001; Monahan et al., 2002).

One possible reason for these differences is that animal studies are carried out on denervated preparations, with otolithic stimulation totally cut off.

*OVAR effects on ventilatory flow*

Our study shows that mean ventilatory flow increased significantly during OVAR as compared with EVAR. In particular, mean tidal volume increased significantly while ventilatory frequency was significantly less. On the contrary, during a complex vestibular Coriolis stimulation, Sinha found an increase in both ventilatory frequency and tidal volume (Sinha, 1968). The discrepancy in breathing rate arises perhaps from the different stimulations used in the 2 studies: purely

graviceptive in the present one, both graviceptive and rotatory in Sinha's (Sinha, 1968).

#### *OVAR and ventilatory synchronisation*

The occurrence of I-E transition phases is independent of angular chair position during EVAR, while I-E transitions appear mainly in a certain angular chair position during OVAR, regardless of head position.

In line with our own experiment, one study showed that ventilation tends to be synchronized with chair rotation during dynamic graviceptor stimulation in OVAR (Kaufmann et al., 2002). The maximum of thoracic expansion (a sign of inspiration ending) occurred cyclically in the nose-down position. Nevertheless, the authors were unable to pinpoint what kind of graviceptors might be mediating this ventilatory synchronization. A mechanical hypothesis can probably be ruled out. Indeed, functional residual capacity (FRC) is affected by body position being 30% less in supine than in upright position (Lumb & Nunn, 2010) and in head-down body position FRC is close to supine position. During OVAR, body position changes regarding gravity may periodically affect FRC which would result in periodic change in volume expansion. However, Rodriguez-Nieto et al. (Rodriguez-Nieto et al., 2002) showed no difference in FRC and tidal breathing in prone and supine positions, thus it is unlikely that volume expansion results from a mechanical effect.

#### *Function of the otolithic receptors*

There is no doubt that OVAR causes ventilatory modifications, acting both on ventilatory flow, with tidal volume and respiratory frequency modifications, and on the ventilatory cycle, with modulation of the I-E transition phases.

However, these ventilatory effects can originate from the stimulation of either the otolithic, the non-labyrinthine graviceptors, or other stimulations.

The primary hypothesis of this study focused on whether the phase of the I-E transition shifted towards alignment with the head. We found that the phase of I-E transition shifted during HTOT only by approximately  $\frac{1}{4}$  of the amplitude of the head turns ( $30^\circ$  for the phase shift *vs.*  $120^\circ$  for the head turn). Thus, besides the

otoliths, it seems likely that other stimulations play a part in ventilatory regulation in OVAR.

$V_{ti}/T_i$ , that is the mean inspiratory flow, was not affected by head position, indicating that the otolithic system probably does not influence the respiratory drive.

#### *Visceral graviceptors*

In humans, visceral graviceptors, which play a major role in the perception of body position (Mittelstaedt, 1998), may by the same token influence respiratory centers as well. In this study, in accordance with the results of the Kaufmann study (Kaufmann et al., 2002), we show that Inspiration-Expiration transitions mainly occurred in the forward-pitch chair position during OVAR, regardless of head position. Thus activation of the visceral graviceptors in this body position would be conducive to Inspiration-Expiration transitions, and possibly the cause of the ventilatory change.

#### *A synergic action of graviceptors*

In fact, if activation of the otolithic receptors has limited effect on ventilation in the majority of subjects during OVAR, it would most likely be because the otolithic stimulation acts indirectly, by assessing the subject's position during cortical reconstruction. The estimation of the position of the body depends both on the otolith and on somatic graviceptors but with a greater influence for somatic graviceptors, 60% *vs.* 40% for the otoliths according to Mittelstaedt (Mittelstaedt, 1996). It has also been found that there are large interindividual differences in the weighting between these receptors: 3 subjects out of 31 relied only on somatic graviceptors and 1 relied only on the otoliths (Mittelstaedt, 1996). The same phenomenon is observed in our result: in most subjects, respiration is mainly influenced by non otolithic stimulation but for a minority of subjects the main influence is otolithic.

This hypothesis could also explain why the I-E transition histograms are significantly different even when the phase shift is taken into account, with a lower amplitude for "head rightward": because the change in the head position induces a 120° phase shift in the otolithic response, otolithic and non otolithic responses might act synergistically in one head position and antagonistically in the other one.



### *Other stimuli*

Other factors must also be taken into account. In particular, it is possible that the “head rightward” and the “head leftward” positions cause stimulation of the tonic neck receptors. The ways in which these sensors influence the respiratory system have been reported (Bolton et al., 1998). Although in theory their action is symmetrical, they might not be stimulated in the same way in the two head positions. Symptoms of motion sickness, which vary from subject to subject, could also be a factor impacting the results.

It can also be noted that the skin pressure caused by OVAR could possibly contribute to the response. However, this stimulation acts in the same way in both head positions. The effect may however override graviceptors stimulation depending on the weight of the subject and the integration of the signal, participating in the interindividual differences.

Also, it is known that some vestibular responses like VOR and perception depend on frequency of stimulus (Clément & Wood, 2014; Denise et al., 1996). Otolithic input is considered to be lowpass-filtered. However, not much is known about the importance of otolith stimulation frequency over respiration. The frequency range of the stimulation used (related to the spontaneous breathing) is close to the filter cut-off frequency for which the stimulation is ambiguously perceived as translation or inclination (Denise et al., 1996), therefore the otolith stimulation may be also ambiguous in term of synchronization stimulus and participate in the inter-subject variability. However, we analyzed the correlation of frequency of rotation to the phase shift between two head positions and found no dependency ( $R^2=0.159$ ).

### *Limitations of the study*

#### *Motion sickness caused by OVAR*

In case of any possible nausea sensation and its persistence after the stimulation ceased, we decided against randomized rotation recording between OVAR and EVAR. Since motion sickness symptoms only occur during OVAR, this rotation was made each time during the second phase of the protocol, in order to collect maximum data and limit the length of exposure to OVAR. Thus, subjects were able to stop the experiment whenever they needed, with no repercussions on EVAR.

It is known that OVAR, with large inclination angles, enhances motion sickness (Graybiel & Miller, 1970; Miller & Graybiel, 1973). We thus chose an OVAR tilt of  $15^\circ$  allowing both graviceptors stimulation and a reduced probability of nausea. Though such a small angle of inclination might decrease the ability of the respiratory system to synchronize with chair rotation, there is no definitive proof that this potential effect might have had more impact on either head position. The choice of an angle was also determined by the protocol. Since the rotational frequency was close to the relaxed spontaneous respiratory frequency in order to facilitate “rotation-ventilation” synchronization, several subjects with a high respiratory frequency approached  $105^\circ/s$ , the most provocative velocity for OVAR (Denise et al., 1996; Miller & Graybiel, 1973). Despite the low inclination, 4 subjects stopped the experiment before the end and their data were excluded from analysis.

Controlled breathing patterns can delay motion sickness symptoms occurrence, while spontaneous breathing evokes motion sickness symptoms faster (Denise, Vouriot, Normand, Golding, & Gresty, 2009). It is possible that motion sickness was affected by the strength of breathing synchronization in our study.

#### *Different OVAR velocities*

The stimulation of the otolithic and visceral graviceptors was identical in both head rotations, except for their phase. It was, however, different between subjects because of the varying speeds of chair rotation that were set according to individual breathing frequency at rest. Depending on the absolute effect of the otolithic stimulation on respiration, our protocol might thus have introduced a variability that would contribute to the inter-subject variability (Figure 4). Except for one subject with a low breathing frequency, the stimulation nonetheless remained within a narrow range from 0.15 to 0.24 Hz

## **5. Summary**

In conclusion, this study shows that OVAR can synchronize ventilation, affecting the occurrence of I-E transition phases, and modify ventilatory parameters thereby increasing ventilatory flow. However, the study demonstrates a high intersubject

variability both in the ability of OVAR to synchronize breathing and in the influence of labyrinthine stimulation.

Stimulation of the otolithic receptors does not seem to be the predominant source of ventilatory modifications. Based on the fact that, in a small number of subjects, the change of head position leads to a clear phase difference between frequency peaks of I-E transition phases in OVAR while in the others it does not, we can assume that there might be a difference in an individual gain of each signal when integrated in the brain.

We thus conclude that the respiratory response to changes in orientation of the body with respect to the vertical involves labyrinthine and non-labyrinthine stimulation and that their respective weight varies significantly between individuals.

# Study III: Effect of self-motion perception on autonomic control

*To be finished and submitted in 2020*

## 1. Background

### *Perception of passive self-movement*

Off-Vertical Axis Rotation (OVAR) in the dark can evoke different perceptions of self-movement, often at a conical or cylindrical pattern (Wood, Reschke, Sarmiento, & Clément, 2007), sometimes variations of these, like a flower-shaped pattern or inverse conical pattern (Denise, Darlot, Droulez, Cohen, & Berthoz, 1988). These motion perceptions increase with the increase in angle or velocity of rotation (Denise et al., 1988).

OVAR stimulates principally the otolithic system, whose input is always ambiguous. The otolithic organs detect the gravito-inertial acceleration (GIA), the sum of the linear motion acceleration and gravitational acceleration that are physically indistinguishable by any accelerometer, as stated in Einstein's Equivalence Principle (Einstein, 1907). The brain has the capacity to distinguish the two sources of acceleration, based on the characteristics of the signal (Clément & Wood, 2014; Paige & Tomko, 1991; Wood et al., 2007) and the information integrated from other sensors (Oman, 1982; Oman & Cullen, 2014; Zupan et al., 2002). It is possible, that the perceptions during OVAR are reconstructed from the estimates of translation and tilt, obtained in the course of processing of the otolithic information (Denise et al., 1988). As this processing is individual, the perception varies between individuals.

If the multisensory integration hypothesis is correct, the visual input would probably alter the perception of movement, even when the real physical body movement remains the same. This assumption seems likely, because it is known that visual motion can induce the perception of the self-movement calledvection

(Rosenblatt & Crane, 2015). It was demonstrated that the perceptions of cone and cylinder during OVAR depend on the frequency of the stimulus, the low frequency, which is associated with the gravitational portion of the GIA, leads to the perception of moving along the conical pattern, while the cylindrical upright pattern is perceived at a higher frequency (Wood et al., 2007). It might be the result of filtering of the otolithic input, where the estimation of tilt with respect to gravity is derived from the low-frequency components of the GIA, while the translation is reconstructed from the high frequency component. The crossover frequency ( $\sim 0.3\text{Hz}$ ) (Clément & Wood, 2014), being the most ambiguous from the perceptual perspective, would then probably facilitate the switching between the conical and cylindrical self-motion pattern perceptions.

If visual input changes the output estimates of the internal vestibular processing, it can possibly affect the modulation of vestibular responses, in particular autonomic modulation.

The link between the vestibular activation and sympathetic modulation has been well established in the literature. In animals, the electric stimulation of vestibular nerves has been demonstrated to activate the sympathetic efferents, as well as brainstem zones responsible for blood pressure control (Yates, Balaban, et al., 1995; Yates, Goto, et al., 1993; Yates et al., 1994, 1991). Natural stimulations revealed that head-up tilt activated the sympathetic nervous system, helping to stabilize pressure during the postural changes, which was perturbed following the transection of the VIIIth cranial nerve (Doba & Reis, 1974; Jian et al., 1999; Yates et al., 1994). In Human, the sympathetic activation and the increase in the limb vascular resistance has also been demonstrated (Essandoh et al., 1987, 1988; Hume & Ray, 1999; Kaufmann et al., 2002; Normand et al., 1997).

The effect of visual information on the cardio-vascular control was reported by Jian et al (Jian et al., 1999). The absence of visual cues aggravated the blood pressure disturbances during postural changes in vestibular-lesioned cats.

The aim of the study is to know whether different visual input, in presence of the same graviceptors stimulation (otolithic and visceral), can differently modulate the cardio-vascular response in healthy human subjects.

The main objective of the study is to assess the effect of self-motion perception on cardio-vascular control during OVAR.

Secondary objectives of the study are (1) to assess the effect of OVAR on cardiovascular control (2) to estimate the effect of the visual stimulation during OVAR on the self-movement perception and the occurrence of symptoms of motion sickness; and (3) to assess the possible link of the perceptive strategy (visual field dependence/independence) on the perception and cardiovascular modulation.

We hypothesize that the visual stimulation would drive the perception of the self-movement. We also hypothesize that the perception of self-movement including body inclination (cone perception) would induce a greater modulation of cardiovascular parameters during OVAR than the perception of self-rotation without inclination (cylinder perception).

## **2. Materials and Methods**

### *Subjects*

We recruited 48 healthy adult volunteers (15 female, 21 male;  $24 \pm 5$  years old) with normally functioning vestibular system. Subjects, who did not finish the protocol on the rotatory chair due to motion sickness (9 subjects), and technical issues (3 subjects) were excluded from analysis and their data are not reported. Therefore, the data from 36 subjects were used.

The subjects were included based on a questionnaire about their history of vestibular and neurologic diseases. Informed consent was obtained from all participants.

### *Methods*

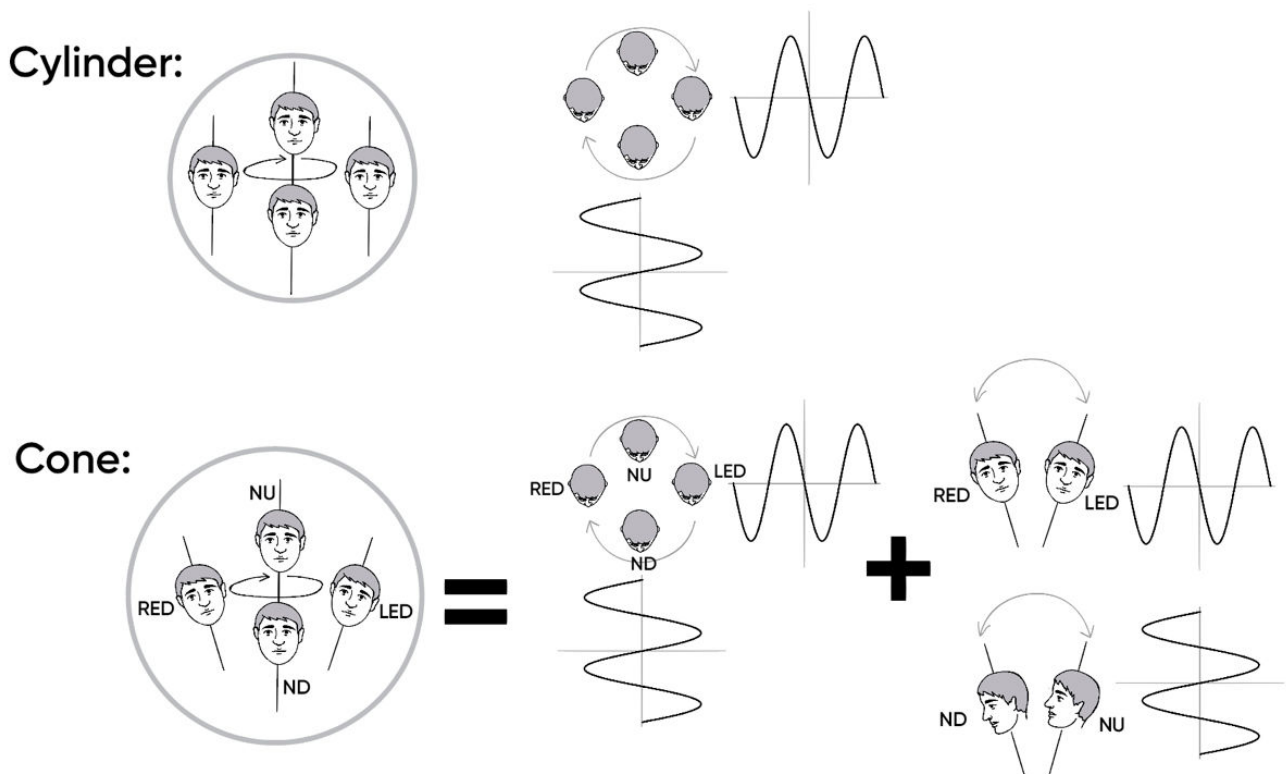
#### *Vestibular stimulation*

We used the Off-Vertical Axis Rotation (OVAR) protocol to stimulate the otolithic system. Rotatory chair with the axis of rotation inclined at  $10^\circ$  with respect to gravity was used for the stimulation. The velocity of rotation was  $60^\circ/\text{s}$ . The tilt

and velocity parameters were selected to evoke minimal motion sickness, while sufficiently stimulating graviceptors.

*Visual stimulation*

Visual stimulation was induced with the Virtual Reality goggles (HTC Vive). Subjects found themselves in a virtual room with furniture to give reliable visual cues for verticals. The rotation of the virtual visual environment, was synchronised with the rotation of the chair with the help of an integrated accelerometer. Two visual motion patterns were created: moving along a “cylinder” or a “cone” with an apex below the body, with the same direction of the gaze. The cylindrical motion pattern was created as a circular upright movement, or as a sum of harmonic oscillations along the interaural and naso-occipital axes. The conic path was composed of the same oscillations of lower amplitude with the addition of periodic tilt around the same axes (Figure SIII.1).



**Figure SIII.1 – Cylinder and Cone visual stimulation representation as a sum of oscillations.** Cylindric movement includes the oscillations of in the interaural and naso-occipital axes, conic movement includes those with the oscillations pitch and raw.

*Evaluation of autonomic control*

Continuous arterial pressure measurements were done with an automatic continuous noninvasive arterial pressure monitor (Finometer Pro, FMS, Amsterdam, The Netherlands) placed on the middle finger held at heart level. Pressure values provided by this system do not significantly differ from those taken directly from the radial artery in subjects in various physiological conditions (Parati et al., 1989), and there is good agreement in the evaluation of beat-to-beat variations (Lindqvist, 1995). Mean arterial pressure (MAP) was calculated with the acquisition software (Notocord Hem 4.2, Notocord Systems, Croissy-sur-Seine, France) as the arithmetic mean of the continuous pressure signal.

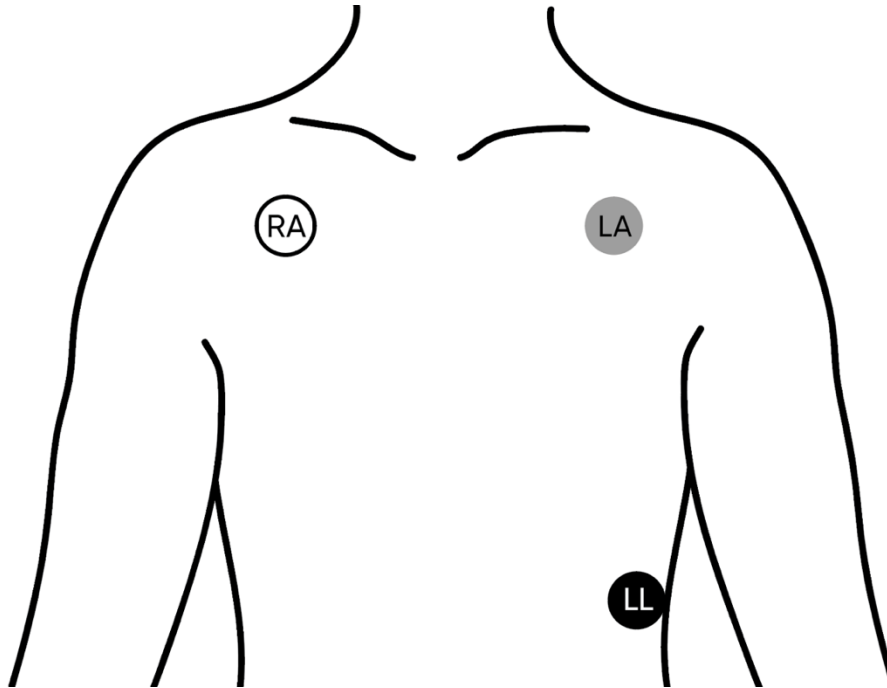
As parameters we assessed the heart rate (HR, in beat/min), mean, systolic and diastolic arterial pressure (MAP, SAP, DAP, in Torr), stroke volume (SV, in mL), cardiac output (CO, in L/min), end-tidal volume (EtCO<sub>2</sub>, in Torr) and breathing frequency (BF, in cycles/min).



**Figure SIII.2 – Installation of the device for arterial pressure tracking and nasal prongs for respiratory measurements.** Blood pressure sensor placement on the middle finger and arm, the hand is fixed at the level of the heart.



Heart Rate (HR) was measured through a 3-leads ECG (Contact Precision Instruments, Cambridge, USA). Stroke volume (SV) was calculated from the arterial pressure signal using the Modelflow method (Sugawara et al., 2003). Cardiac output (CO) was calculated as SV multiplied by HR.



**Figure SIII.3 – Placement of electrodes for the electrocardiogram tracking.**

Breathing frequency (BF) and the end-tidal CO<sub>2</sub> (EtCO<sub>2</sub>) were measured with the help of a commercial monitor and nasal prongs (Oridion, Microcap monitor CO<sub>2</sub>, Jerusalem, Israel).

#### *Evaluation of perception*

Evaluation of perception of movement and the “persuasiveness” of the visual stimulation were performed with the help of a questionnaire, developed for this experiment (Annex 4). Four questions with a continuous scale were scored from 0 to 10.

After each rotation trial, subjects were asked to show the movement that they have been submitted to with a little puppet. When the movement shown with a puppet matched the visual stimulation the subject has seen, it was scored “1”, when it did

not match, it was scored “0”, when the match was not perfect, the score was “0.5” (the perception-vision “match”). The “match” was multiplied by the score obtained with the the questionnaire, to obtain the overall “persuasiveness” parameter, which was calculated as:

$$\text{Persuasiveness} = \text{match} * (Q1 + Q2 + (10 - Q3) + (10 - Q4))/40.$$

Where Persuasiveness is a continuous score between 0 and 1; match = 0 or 0.5 or 1; Q1, Q2, Q3, Q4 – the continuous scores for each question (from 0 to 10).

#### *Motion Sickness evaluation*

The level of MS evoked by the rotatory chair stimulation was assessed with a diagnostic criteria proposed by Graybiel and colleagues (Graybiel, Wood, Miller, & Cramer, 1968). The symptoms were divided in categories with varying symptom intensities. The subject could underline only one level of intensity per category.

Self-reported childhood (part A) and current (part B) history of MS susceptibility in subjects was collected with the help of Motion Sickness Susceptibility Questionnaire (MSSQ) (Golding, 1998).

#### *Visual field dependence evaluation*

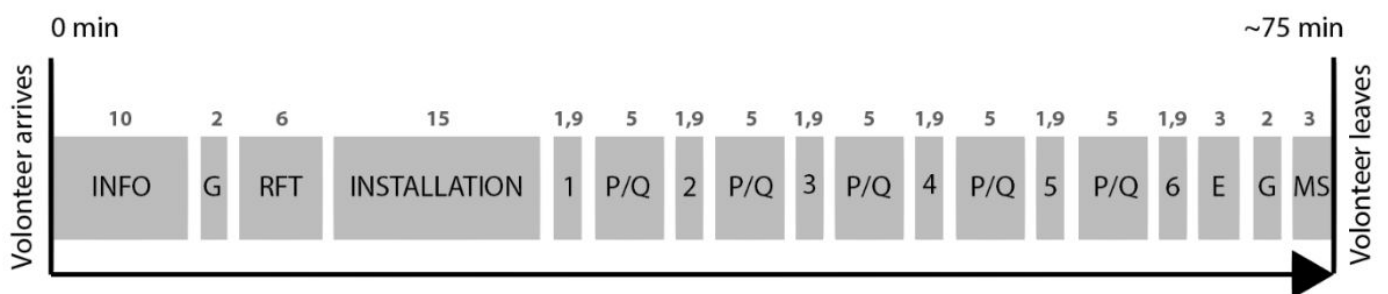
We used the Rod-and-Frame test (RFT) to evaluate the visual field dependence for each subject, using the original device and the original protocol proposed by Witkin and Ash (Asch & Witkin, 1948; Witkin & Asch, 1948). Individuals who were able to ignore the misleading context of the frame, setting the rod upright, were classified as “visual field-independent.” Individuals who tended to align the rod with the visual frame were classified as “visual field-dependent.”

#### *Procedure*

Subjects sat on a rotatory chair in darkness. The subjects were restrained so that they could not move their heads while rotating on the chair to prevent the cross-coupling stimulation. During all the experimental trials they wore HTC Vive Virtual Reality goggles.

The axis of rotation of the chair was inclined at 10° respective to the vertical. The rotations were performed at a frequency of 0.16 Hz, which is 6 seconds per full revolution, or 60°/s in counterclockwise (CCW) direction.

The duration of every rotation trial was 114 seconds, pauses were made between trials (Figure SIII.4).

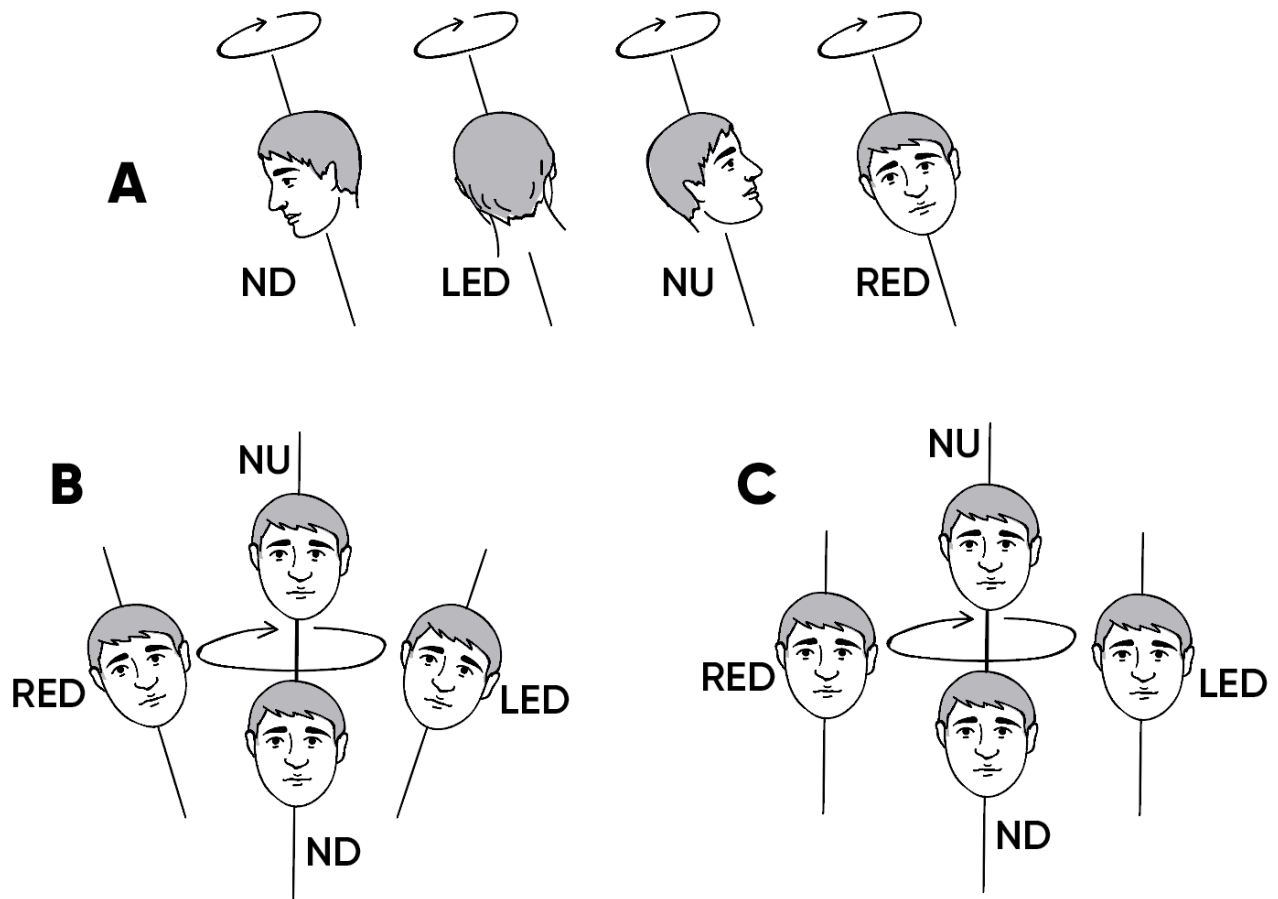


**Figure SIII.4 – The procedure timeline of one-time passage of a volunteer.** The overall protocol takes in average 1h 15min. The gray blocks represent one test or one event with the estimated duration indicated above each block (in minutes). INFO – instructions, reading and signing an information consent; G – Graybiel diagnostic criteria; RFT – Rod and Frame Test; Installation – installation on the rotatory chair, fixing the ECG electrodes, nasal prongs, blood pressure monitor, starting and verifying the recording of data; 1, 2, 3, 4, 5, 6 – rotatory or non-rotatory stimulations in the individual order according to the protocol; P/Q – Pause or/and the perception questionnaire (only after the tests including rotation); E – the end of recordings, deinstallation of a volunteer; MS – Motion Sickness Susceptibility Questionnaire (MSSQ).

### Protocol

Three visual stimuli were shown, one per trial: (**A**) elimination of visual stimulus (darkness), (**B**) self-rotation along cylindrical path, and (**C**) self-rotation along conical path, with the unchanging direction of gaze (Figure SIII.5). Visual stimulations in combination with rotation were rather nauseogenic. To minimize

the possibility of motion sickness, the visual stimulation was turned on after 1 minute of OVAR, the first minute of rotation was not included in the analysis or included separately.



**Figure SIII.5 – Real OVAR movement (A), conical movement perception during OVAR (B), cylindrical movement perception during OVAR (C).**

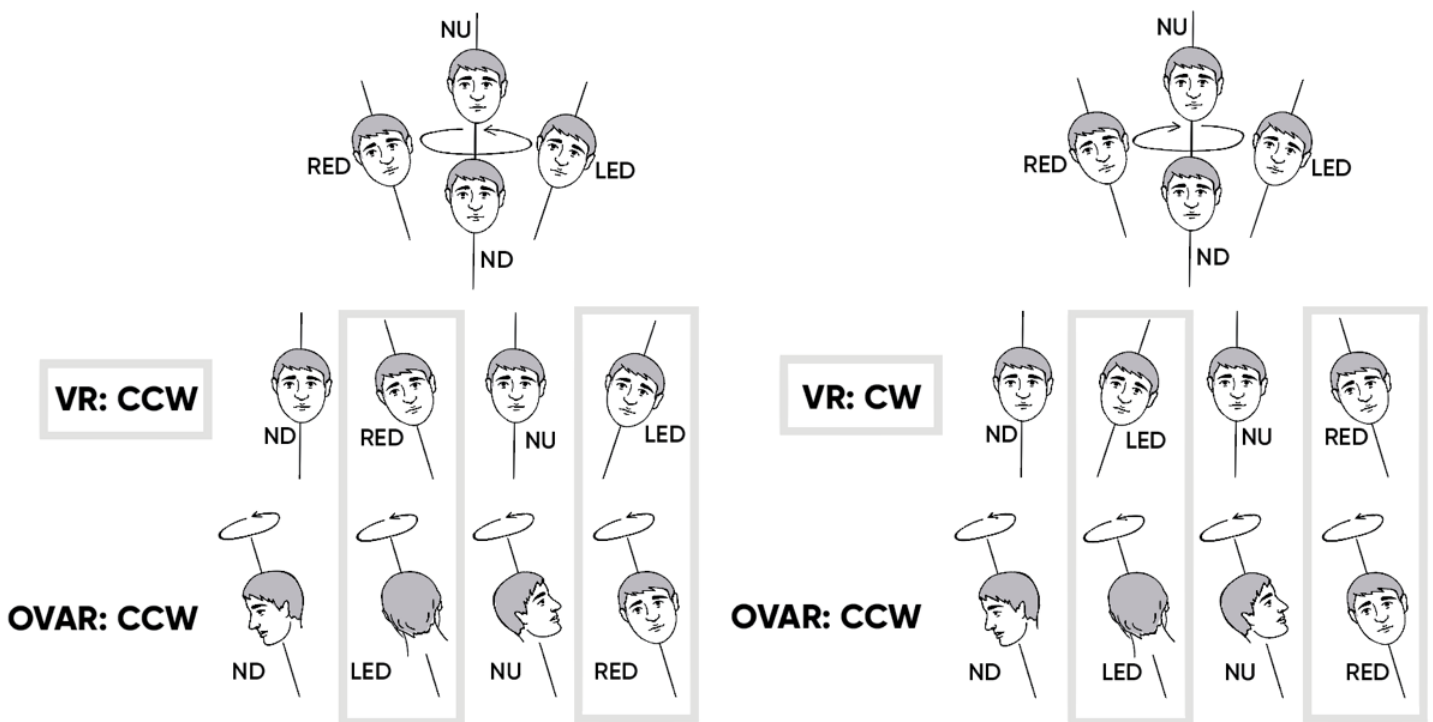
Every subject made 6 trials with different combinations of virtual reality visual stimulation: no-stimulation (Darkness), conical path self-movement (Cone) and cylindrical path self-movement (Cone) (Figure SIII.5 **B, C**) and actual rotatory stimulation: OVAR and non-OVAR. The trials were interchanging OVAR/non-OVAR to diminish the possibility of motion sickness. Visual-only conditions were matched in pairs with the corresponding visual-vestibular stimulations (3 pairs:

Darkness/OVAR in Darkness, Cone/OVAR with Cone, Cylinder/OVAR with Cylinder). With this, subjects were divided into 2 groups, 6 people each: for each pair, subjects of one group systematically began with visual alone stimulation and subjects of the other group began with vestibular + visual stimulation. Therefore, we had 12 different combinations of order of testing conditions (Table SIII.1). The number of subjects tested is thus a product of 12.

**Table SIII.1 - Twelve different protocols as combinations of vestibular and visual combinations (lines).** Cone, Cylinder – the visual stimulation shown in the virtual reality goggles. Darkness – no visual stimulation. OVAR – Off-Vertical Axis Rotation on the rotatory chair, vestibular stimulation.

	<b>Trial 1</b>	<b>Trial 2</b>	<b>Trial 3</b>	<b>Trial 4</b>	<b>Trial 5</b>	<b>Trial 6</b>
<b>Subject 1</b>	Darkness	Darkness + OVAR	Cone	Cone + OVAR	Cylinder	Cylinder + OVAR
<b>Subject 2</b>	Cylinder	Cylinder + OVAR	Darkness	Darkness + OVAR	Cone	Cone + OVAR
<b>Subject 3</b>	Cone	Cone + OVAR	Cylinder	Cylinder + OVAR	Darkness	Darkness + OVAR
<b>Subject 4</b>	Cylinder	Cylinder + OVAR	Cone	Cone + OVAR	Darkness	Darkness + OVAR
<b>Subject 5</b>	Cone	Cone + OVAR	Darkness	Darkness + OVAR	Cylinder	Cylinder + OVAR
<b>Subject 6</b>	Darkness	Darkness + OVAR	Cylinder	Cylinder + OVAR	Cone	Cone + OVAR
<b>Subject 7</b>	Darkness + OVAR	Darkness	Cone + OVAR	Cone	Cylinder + OVAR	Cylinder
<b>Subject 8</b>	Cylinder + OVAR	Cylinder	Darkness + OVAR	Darkness	Cone + OVAR	Cone
<b>Subject 9</b>	Cone + OVAR	Cone	Cylinder + OVAR	Cylinder	Darkness + OVAR	Darkness
<b>Subject 10</b>	Cylinder + OVAR	Cylinder	Cone + OVAR	Cone	Darkness + OVAR	Darkness
<b>Subject 11</b>	Cone + OVAR	Cone	Darkness + OVAR	Darkness	Cylinder + OVAR	Cylinder
<b>Subject 12</b>	Darkness + OVAR	Darkness	Cylinder + OVAR	Cylinder	Cone + OVAR	Cone

However, conical or cylindrical rotation path with same gaze direction are not perfectly compatible with the OVAR pattern. If the direction of visual rotation corresponds to the real movement, the body inclination on the sides would be inverted. If the body positions are matched in the visual and real rotations, the direction of rotation would be inverted (Figure SIII.6).



**Figure SIII.6 – Two cone patterns partly match the real OVAR movement.** The circular motion at a conic pattern, largely perceived during OVAR, cannot be perfectly matched to the real OVAR. To the left, the direction of rotation corresponds to the real one; however, the inclination of the body in the coronal plane is inverse. To the right, the inclination of the body corresponds to the real one, however, the direction of rotation is opposite. ND – Nose Down, NU – Nose Up, LED – Left Ear Down, RED – Right Ear Down.

As there is no perfect match to the visual and vestibular stimulation patterns, and the two possibilities are conforming to one parameter and not conforming to the other, it was decided to try both types of stimulation. Two protocols were

implemented, each partly conforming to the characteristics of the real OVAR movement. The first protocol matched the directions of rotation (Figure SIII.6 left). A sub-group of 24 subjects performed this protocol. The second protocol matched real and virtual body tilt directions (Figure SIII.6 right). A sub-group of 12 subjects performed this protocol.

### **3. Preliminary results**

#### *Motion sickness and perception*

The mean unsigned error made with the RFT (Witkin & Asch, 1948) was  $1.9^\circ \pm 1.7^\circ$ . As a limit to divide the frame dependent and frame independent subjects, we used the 95% quantile of the mean error of every subjects. From 36 subjects only two had the mean error more or equal to the 95% quantile. Therefore, we can state that two subjects had visual frame dependency, while 34 were field independent.

The general MS susceptibility scored with the MSSQ (Golding, 1998) has shown the mean score of  $3.7 \pm 3.9$  for the part A (childhood, before 12 y.o.), and  $2.5 \pm 2.8$  for the part B (the last 10 years).

The scores for the diagnostic criteria of Graybiel were not different between two protocol groups and were averaged. The mean score for 36 subjects was  $4.5 \pm 4.1$  points, which corresponds to the moderate malaise (Graybiel et al., 1968). However, the result is obtained in exclusion of 9 subjects that have not finished the protocol due to the motion sickness.

The overall score for “persuasiveness” of the visual stimulus for the “Cone” stimulation was  $0.69 \pm 0.26$ , while it was  $0.68 \pm 0.23$  for the “Cylinder”. These two evaluations were calculated for both protocols (see Figure SIII.6) together, as the t-test did not reveal a statistical difference between the perception efficacies of the two protocols. For the protocol, where the direction of visual rotation did not correspond to the actual direction of rotation, subjects were additionally asked about the direction of rotation. While the real OVAR rotation was CCW, and the visual rotation was CW, for the “Cone” visual stimulation, all the 12 subjects reported CW, for the “Cylinder” all except one reported CW, and for the OVAR in

darkness, two subjects reported CW rotation, while all the rest reported the actual CCW rotation.

### *Cardio-vascular evaluation*

#### *Mean values*

The cardiovascular and respiratory values were averaged for the duration of each stimulation and the mean values (Table SIII.2) were compared with the two-way repeated measures ANOVA with two factors: 2-level vestibular stimulation (OVAR, non-OVAR) and 3-level visual stimulation (Darkness, Cylinder, Cone). The significant effect of OVAR was found for the mean HR ( $p = 0.028$ ), SAP ( $p < 0.001$ ), MAP ( $p = 0.033$ ), CO ( $p < 0.001$ ), SV ( $p < 0.001$ ), BF ( $p < 0.001$ ). No effect was found for the DAP and the EtCO<sub>2</sub>. ANOVA showed the effect of the visual stimulation on the mean values of breathing frequency ( $p = 0.006$ ), but not for the other parameters.

**Table SIII.2 – Mean values of cardiovascular parameters for each stimulation, averaged for all the sample of 36 subjects.** Heart Rate (HR) in beats per minute, Systolic Arterial Pressure (SAP), Diastolic Arterial Pressure (DAP), Mean Arterial Pressure (MAP) in Torr, Stroke Volume (SV) in mL, Cardiac Output (CO) in L/min, Volume of CO<sub>2</sub>, EtCO<sub>2</sub> in Torr and breathing frequency in breaths/min. The highlighted mean values are significantly different in OVAR/non-OVAR conditions according to the two-way RM ANOVA.

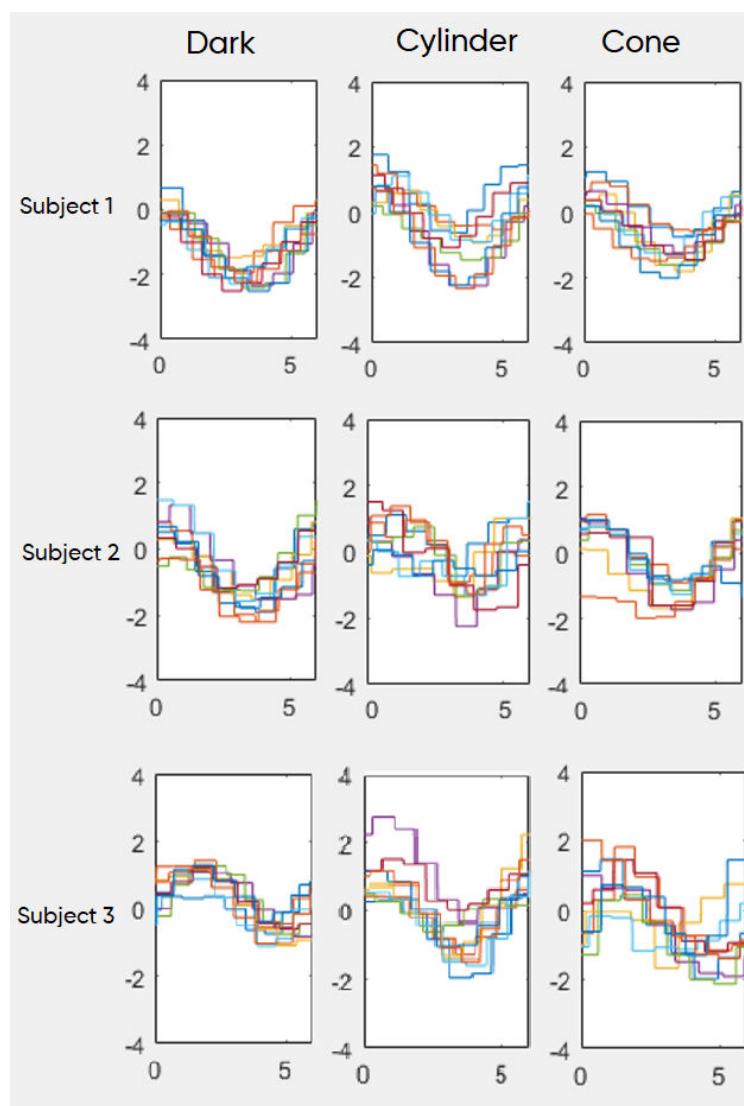
	<b>Dark</b>	<b>Cylinder</b>	<b>Cone</b>	<b>OVAR + Dark</b>	<b>OVAR + Cylinder</b>	<b>OVAR + Cone</b>
<b>HR, beat/min</b>	76.0 ± 12.9	76.7 ± 11.5	78.4 ± 12.1	79.1 ± 16.6	79.3 ± 14.5	79.1 ± 14.8
<b>SAP, Torr</b>	116.9 ± 13.0	115.5 ± 12.2	114.7 ± 13.4	122.1 ± 13.2	122.0 ± 13.7	119.9 ± 15.3
<b>DAP, Torr</b>	74.0 ± 10.1	72.5 ± 10.7	72.5 ± 11.1	73.5 ± 11.0	72.8 ± 10.7	72.1 ± 12.1
<b>MAP, Torr</b>	91.3 ± 10.5	89.6 ± 10.9	89.5 ± 11.9	92.8 ± 11.1	91.9 ± 11.5	91.0 ± 12.7
<b>SV, mL</b>	53.5 ± 13.3	53.5 ± 14.1	52.4 ± 13.2	58.8 ± 13.2	58.8 ± 15.5	59.1 ± 15.3
<b>CO, L/min</b>	4.03 ± 1.06	4.08 ± 1.11	4.08 ± 1.05	4.63 ± 1.30	4.65 ± 1.45	4.62 ± 1.25
<b>EtCO<sub>2</sub>, Torr</b>	34.2 ± 4.7	33.8 ± 5.6	34.0 ± 4.6	33.8 ± 4.7	33.7 ± 4.7	34.2 ± 4.7
<b>BF, cycle/min</b>	14.8 ± 2.2	15.5 ± 2.6	15.6 ± 2.9	16.0 ± 3.3	17.4 ± 2.9	16.6 ± 2.9



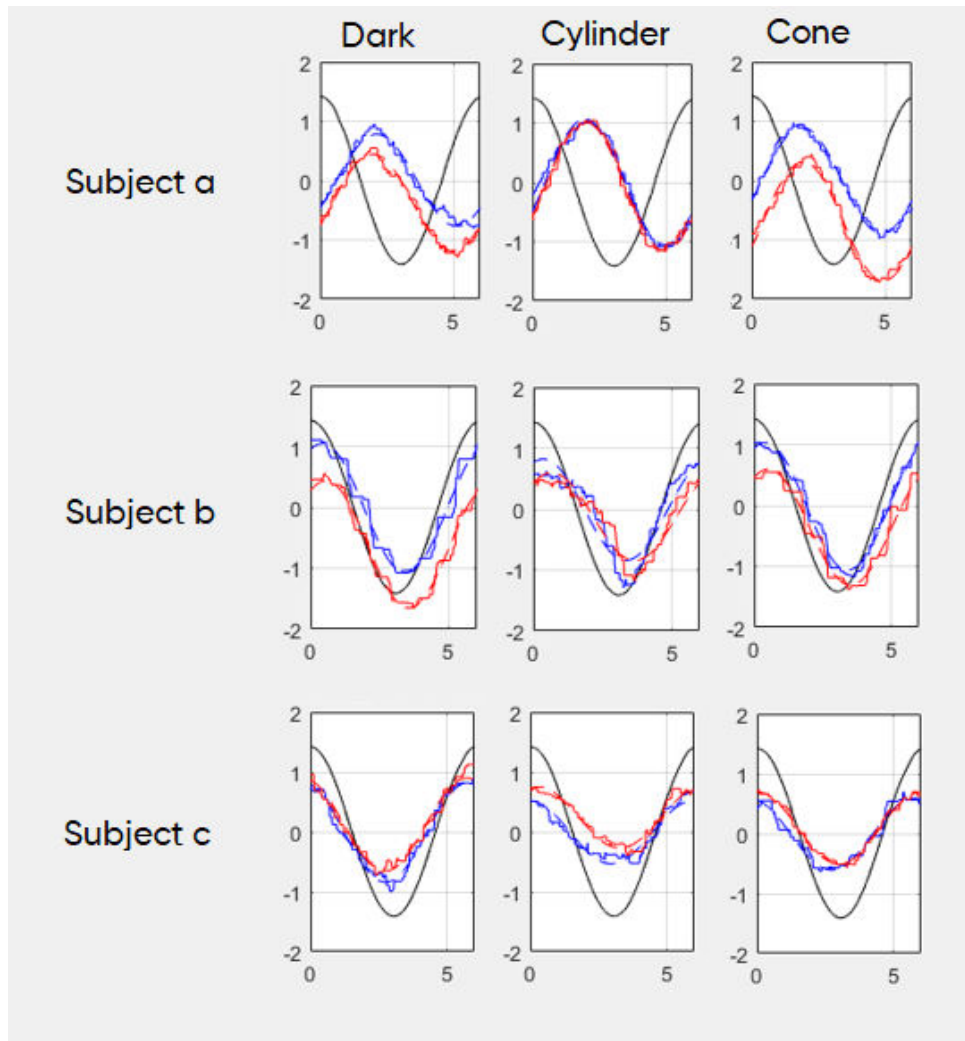
### *Modulation*

Apart from the mean values, modulatory parameters needed to be calculated in order to assess the effect of vestibular and visual stimulation on modulation of cardiovascular parameters. We started this analysis with the arterial pressure (MAP). To analyze the modulation during rotations in every visual condition, the data were normalized and then cut and superimposed cycle-by-cycle (Figure SIII.7).

It is visible in Figure SIII.7 that MAP is well-synchronised within a subject.



**Figure SIII.7 – Cycle-by-cycle superimposed normalized data of MAP during OVAR in three visual conditions: Dark, Cylinder, Cone.** The figure shows examples of data from three subjects. The modulation of arterial pressure through cycles is visible.



**Figure SIII.8 – Cycle-by-cycle averaged normalized cycle of the MAP during OVAR in three visual conditions: Dark, Cylinder, Cone.** The intersubject difference in phase seems to be very variable between subjects, being stable within the trials of the same subject. The blue curve is the average of the 1-10 cycles; the red curve is the average of the 11-19 cycles (pure otolithic stimulation, and the visual stimulation); the black curve is the actual rotatory cycle.

The cycles for every condition were averaged for every subject (Figure SIII.8). The values of the amplitude, phase and offset were calculated for the averaged modulation of every condition per subject. Repeated measures one-way ANOVA was applied to amplitude, phase and offset, with the visual condition as a factor. No significant effect of visual stimulation on the phase and offset of modulation

has been found ( $p = 0.7$  for the phase,  $p = 0.18$  for the offset). However, the amplitude parameter has shown a significant difference ( $p = 0.039$ ). Post-hoc Tukey test located the difference between the “Darkness” and “Cone” visual conditions with the median amplitudes of 0.82 for the “Darkness” and 0.69 for the “Cone”.

## 4. Discussion

The study has attempted to detect the effect of visual information and perception of self-movement on cardiovascular adjustment during otolithic stimulation in healthy humans.

Significant effects of OVAR were found for the mean values of Heart Rate, Arterial Pressure, Cardiac Output, Stroke Volume, respiratory frequency. The effect of visual stimulation was not observed for the mean values.

However, the hypothesized effect of visual stimulation on modulation of cardiovascular parameters would rather be expressed not in the mean, but in the amplitude of modulation of the parameter along the rotation. We hypothesized that the translatory and gravitational components of GIA would be calculated differently depending on the visual cue. A tilt would result in a greater estimate of gravity component, than the translation only. Therefore, we expected that the amplitude of modulation in “Cone” visual condition, which combines translation and tilt, would be greater than in “Cylinder” condition, representing only translation in horizontal plane. To verify the hypothesis, we averaged the response over the cycles of OVAR to get an individual averaged 6-seconds cycle for each condition. Indeed, the effect of visual stimulation on the amplitude of modulation has been found. However, surprisingly, the modulation in the visual “Cone” condition was lower than in “Darkness”, which is contrary to what was expected. This effect is not clearly visible when looking at the individual modulation results. However, the visual inspection of the data attracts attention to another parameter – the phase of modulation.

The phase switch seems to be constant for all the rotatory trials within a subject, but different between subjects (Figures SIII.7 and SIII.8). This might indicate that

the modulation of arterial pressure observed is not just a consequence of mechanical issues like hydrostatic pressure changes. The interindividual differences in phase shift from the rotational phase speaks in favor of the neural nature of the modulatory regulation.

Only two out of 36 subjects were classified as visual field dependent, while 34 were field independent. It does not seem that these two subjects had a specific cardiovascular modulation among other subjects, and they were not more convinced by the visual stimulation than the other subjects, according to their score in the questionnaire of perception.

The general MS susceptibility scores were rather low, which demonstrates that the sample of subjects was not highly susceptible for motion sickness. Mean score for motion sickness among subjects indicated moderate malaise (Graybiel et al., 1968). However, the results are obtained in exclusion of 9 subjects that have not finished the protocol due to the motion sickness, so the scores cannot serve as a descriptive of the nauseogenicity of the stimulus.

Multiple limitations can affect the results of the study. First, the assessment of individual perceptions of self-movement without pre-given cues is necessarily subject to individual bias and the difficulty to reconstruct the perceptual experience. Anecdotally, the reports often included descriptions such as “strange, hard to describe”. Moreover, as it has already been mentioned, the real OVAR movement is impossible to relay perfectly with the visual conic movement (Figure SIII.6). This fact possibly impairs the level of persuasiveness of the visual stimulus.

Other factors such as tiredness, motion sickness, stress, could interfere in regulation of cardio-vascular parameters. To account for the time-dependent effects, such as the motion sickness, which can augment by the end of the experimental session, or the initial excitement before the experiment, we have counterbalanced the order of experimental trials between subjects.



# **Study IV: Vestibulo-ocular responses, visual field dependence and motion sickness in aerobatic pilots**

*Accepted for publication in Aerospace Medicine and Human Performance Journal*

## **1. Background**

Vestibular processing in the CNS is adjusted during lifetime by everyday movements. Unusual and unnatural passive stimuli cause the mismatch between the actual sensory input and an expected input formed basing on previous experience. This sensory mismatch is the most commonly cited to be the cause of motion sickness (Reason, 1978). Moreover, the same previously unusual stimulus, that is applied repetitively, can lead to adaptation and/or habituation that change the responses and diminishes the risk of occurrence of motion sickness symptoms.

Vestibulo-Ocular Reflex (VOR) implies the eye rotations that compensate for the movements of the head, serving to stabilize the gaze. The VOR can originate from both semicircular canals system and otolithic system and the two parts of the reflex are separate: Canal-Ocular Reflex (COR) and Otolith-Ocular Reflex (OOR).

VOR is plastic and can habituate under repetitive prolonged stimulus and is characterized by a bidirectional or unidirectional decrease of response, which was demonstrated by numerous studies employing habituation protocols (Clément, Deguine, Bourg, & Traon, 2007). Habituation was demonstrated in sportsmen experiencing intensive vestibular stimulations (e.g. figure skaters, ballet dancers, gymnasts) (Tanguy et al., 2008). Adaptation can appear, for example, if one uses spectacles that magnify or miniaturize the visual scene, inducing adaptive increase or decrease in gain in COR (Paige & Sargent, 1991).

Mental effort can also evoke modifications in COR gain: Jones et al. (Jones et al., 1984) used a mental suppression paradigm to observe a decrease in COR gain after 3h of training. Attention mechanisms and alertness are also crucial factors in regulating the COR; for example, mental arithmetic has been demonstrated to enhance COR gain (Collins & Guedry, 1962).

Only a few studies have dealt with the plasticity of the human Otolith-Ocular Reflex (OOR). OOR was modified along with COR after visual-vestibular mismatch habituation protocols (Koizuka, Katsumi, Hattori, Okada, & Kato, 2000). In the study on the OOR of figure skaters, the OOR amplitude of modulation was found to be lower than in the control group, and the bias corresponded more to the actual stimulus (Tanguy, Quarck, Etard, Gauthier, & Denise, 2008).

Aviation is a challenge to the vestibular system of pilots. Such a strong stimulus is likely to drive the development of adaptive changes in the vestibular processing of pilots. Moreover, because there are different aviation kinds and purposes, the stimulus differs a lot in the total peak linear acceleration magnitude, rotatory stimulus, concentration primarily on the instrument panel or on the environment, and other factors. This suggests that different types of pilots might be affected differently by their activity and the vestibular adaptive changes in aerobatic pilots might differ from those in civil passenger aviation, for example. Thus, while sportsmen usually demonstrate a decrease in the VOR time constant (TC) and gain which indicates habituation, the existing data from pilots are less clear.

The study of Fisher in 1919 reported the results of post-rotatory nystagmus assessment studies in approximately 1500 veteran pilots and concluded that the duration of after-turning nystagmus in aviators is not affected by flying (Fisher & Babock, 1919). In contrast, another study reported reduced Canal-Ocular Responses (COR) among 100 Swedish Air Force pilots (Aschan, 1954). It was mentioned however, that the variability of results on pilots was large. Interestingly, the author stated that the differences in vestibular responses were more pronounced in highly experienced pilots, while pilots flying to a very limited extent did not differ from controls. In addition, they reported that the nystagmus parameters often had a directional preponderance. It was also noted that the absence from flying for at least several months leads to normalization of the status. Unlike the previous findings, Schwarz and Henn (Schwarz & Henn, 1989) found that in military student pilots the time constant of the nystagmus response after

vestibular stimulation was shorter ( $p$  less than 0.001;  $t$ -test), whereas the gain tended to be higher ( $p$  less than 0.025) (Schwarz & Henn, 1989). One more study demonstrated that during vestibular stimulation on rotatory chair at a frequency range of 0.01 Hz – 0.32 Hz there was little difference in fighter pilots and controls except for frequency 0.16 Hz. In a consequent experiment they showed that after four successive velocity-step tests at 0.16 Hz there was little modification in the COR gain in pilots ( $0.64 \pm 0.04$  to  $0.58 \pm 0.032$ ), while it significantly increased in non-pilots ( $0.59 \pm 0.03$  to  $0.78 \pm 0.06$ ) (Ahn, 2003). Lee investigated COR by slow harmonic acceleration in Korean Air Force pilots and found that for frequencies 0.04 – 0.32 Hz the gain of COR of pilots was significantly higher than that of the control subjects (Lee et al., 2004). A more recent study evaluated the function of all the six semicircular canals in active fighter pilots (1000-3000 hours of training), using the video head impulse test (vHIT), and found the decrease in gain only in the left posterior canal (Zuma e Maia, Mangabeira Albernaz, Cal, Brusco, & da Costa, 2015).

The literature on aviators is very heterogeneous and provides contradictory results. Some studies report modifications in the vestibular reflexes of pilots, while some studies report no differences. Different studies reported the COR gain to increase and to decrease in comparison with control subjects. Most of the studies were assessing solely lateral semicircular canals function except for one (Zuma e Maia et al., 2015). However, no study was held on the otolithic response in pilots. Moreover, all the studies have been performed on military pilots. No vestibular studies have been held on aerobatic pilots.

Literature shows that motion sickness (MS) occurrence is likely to be linked with vestibular habituation. Shupak et al. (Shupak et al., 1990) in the study on sailor students demonstrated simultaneous diminution of MS severity and diminution of VOR gain at 0.01 Hz after 6 months of sailing. They conclude that VOR gain can serve as a physiologic correlate helping to predict seasickness susceptibility. A more recent study by Clement used a short-term vestibular training to assess short-term habituation (Clément et al., 2007). It demonstrated that after the training, MS and VOR peak velocity and time constant declined in all subjects. Another study showed that the time constant of COR was reduced due to the habituation protocol which was in line with MS symptoms reduction (Dai et al., 2003). Most literature demonstrates a positive correlation between the TC of the VOR (Quarck



et al., 1998; Shupak et al., 1990), however there is also evidence for a negative correlation (DiZio & Lackner, 1991). Both MS and VOR habituation were shown to involve the velocity storage mechanism (Cohen et al., 2003; Dai et al., 2003; DiZio & Lackner, 1991).

Literature shows a decrease or a complete cessation of symptoms of MS in pilots after several sessions of training (Syburra, Huber, & Suter, 2009). One study described three symptomatic peaks during aerobatic training, that occurred at the first three flights, the seventh flight (on which there was an abrupt increase in aircraft acceleration), and the first three flight of the phase in which aerobatics was introduced (Tucker, Hand, Godbey, & Reinhardt, 1965). For these pilots, every introduction of a new stimulus evoked MS, which then decreased with training.

Vestibular processing modifications can also affect the sense of self-orientation in space. It has been shown that prolonged exposure to altered conditions like microgravity, leads to changes in the perceived orientation of vertical (Harris, Jenkin, Jenkin, Zacher, & Dyde, 2017), so do the habituation protocols (Clément et al., 2007). Thus, adaptation of vestibular reflexes can be linked to perturbations in spatial orientation and rearrangements in visual-vestibular interactions. Rod-and-Frame Test (RFT) that serves to reveal the perceptual strategy (visual field dependence-independence) is a tool, that helps to assess the subjective vertical assessment and the influence of the visual field cues in this process. There is some evidence of a link between the field independence and a greater susceptibility to simulator sickness (Barrett & Thornton, 1968) but the topic is debated (Mirabile, jr., Glueck, & Stroebel, 1976).

The aim of the current study was to investigate whether aerobatic pilots, as individuals who experience an intense vestibular stimulation, present a modification of the vestibular function and MS susceptibility in comparison to normal volunteers. We hypothesized that the aerobatic pilots might develop a vestibular adaptation to their activity and thus present altered VOR and visual vertical estimation and a lower MS susceptibility.

## 2. Materials and Methods

### *Subjects*

31 subjects participated in the study. The population consisted of a group of pilots (11 subjects: 10 male, 1 female, age  $30.3 \pm 14.4$  y.o.) and a control group (18 subjects: 16 male, 2 female, age  $25.6 \pm 11.3$  y.o.). All the pilots were undergoing the same intensive course on aerobatic piloting in Caen, France, at the time of the study.

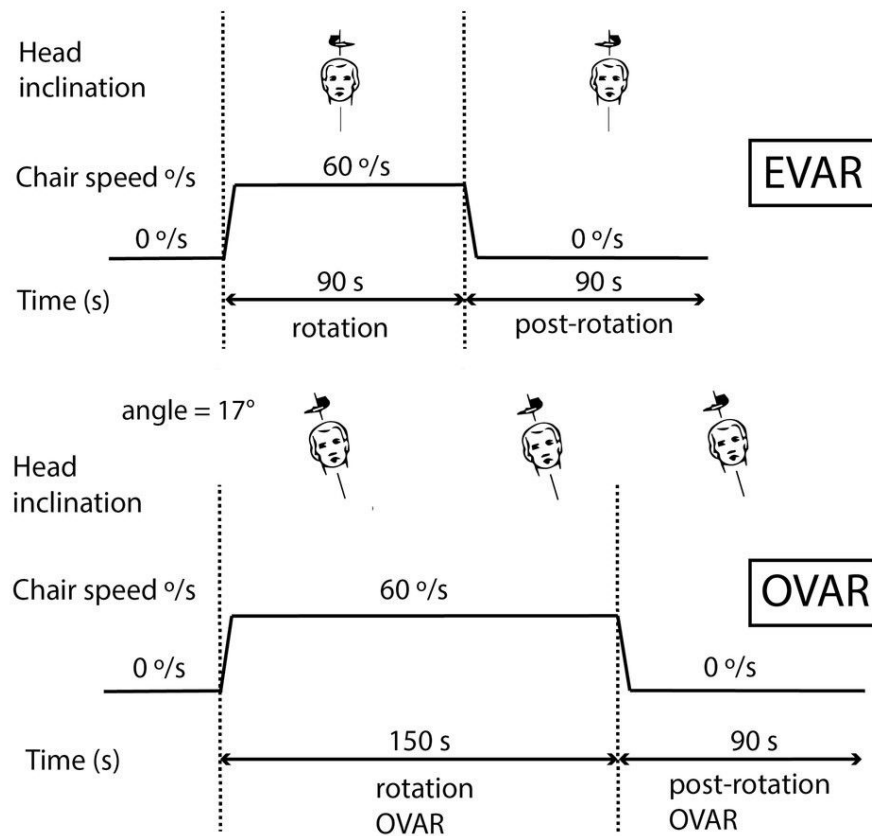
Subjects, who did not finish the protocol on the rotatory chair due to motion sickness, were excluded from analysis. Datasets for any test, when the data were absent, incomplete or of bad quality, were excluded from the analysis. In particular, in MSSQ (Golding, 1998) the data from one pilot and three control subjects are absent, COR recordings from one control subject and one pilot are also missing; for OOR, Diagnostic Criteria of Graybiel (Graybiel et al., 1968) and Rod-and-Frame Test (RFT) (Asch & Witkin, 1948) the datasets are complete.

All participants were clinically normal according to a screening battery that included a combined neurologic and otologic physical examination, performed by MD, PhD. Ethics committee approval N°: CCPPRBN 2004-03 and informed consent from all participants were obtained.

### *Materials*

To assess visual-vestibular interactions (visual field dependence) Rod-and-Frame test (RFT) was applied, using the original device and the original protocol (Asch & Witkin, 1948).

The VOR was evaluated using a rotatory chair that can be tilted with respect to gravity. We used two protocols – Earth-Vertical Axis Rotation (EVAR) and Off-Vertical Axis Rotation (OVAR) to stimulate the semicircular canals and otoliths accordingly. Figure SIV.1 illustrates the protocols for both types of stimulation.



**Figure SIV.1 – The protocols for EVAR (above) and OVAR (below).**

Eye movements induced by VOR for the Left eye were recorded by a video oculograph (Chronos 3D, Chronos Vision, Berlin), sampled on line at 100 Hz. Each experimental session started with a calibration, accomplished using sequentially illuminating LED.

The level of MS evoked by the rotatory chair stimulation was assessed with a diagnostic criteria proposed by Graybiel and colleagues (Graybiel et al., 1968). Apart from that, the self-reported childhood (part A) and current (part B) history of MS susceptibility in subjects was collected with the help of Motion Sickness Susceptibility Questionnaire (MSSQ) (Golding, 1998).

### *Procedure*

The visual field dependence test was held before the rotation session. Individuals who were unable to set the rod upright, and instead set it tilted (more than  $5^\circ$ ), were classified as “field-dependent.” Individuals who were able to ignore the misleading context of the frame, setting the rod upright, were classified as “field-independent.”

The diagnostic criteria of Graybiel were applied after the EVAR and OVAR rotatory chair session. The nauseogenic part of the protocol are the two OVAR stimulation sequences. In the criteria, symptoms were divided in categories with varying symptom intensities. The subject could underline only one level of intensity per category. The subject also completed the MSSQ, reporting the history of motion sickness susceptibility during childhood (before 12 y.o.) and adulthood (the last 10 yrs).

The participants sat upright on the rotatory chair having their head immobilized in the straight position. All stimulations were carried out in darkness with the participants' eyes open.

The EVAR protocol for assessing COR consisted of two sequences with counterbalanced directions of rotation (CW and CCW). The axis of rotation was vertical, the subjects were accelerated in 1 second to a velocity of rotation of  $\pm 60^\circ/\text{s}$  and after 90 seconds of rotation, they were decelerated in 1 second. The ocular responses were recorded from the beginning of the rotation until 90 seconds after the stop.

Eye movement velocity was calculated digitally using the two-point central difference algorithm (50 ms step size) (Denise, Darlot, Ignatiew-Charles, & Toupet, 1996). The saccadic eye movements were removed from the eye velocity signal and replaced by a linear interpolation, resulting in a slow phase velocity (Denise, Darlot, et al., 1996). Then it was manually verified and corrected as required.

For COR recordings, an exponential curve was fit on the slow phase velocity curve (SPV) of the per- and post-rotatory eye movements. The variables studied were the peak phase velocity ( $V_i$ ,  $^\circ/\text{s}$ ) and time constant (TC, s) of the exponential decrease of SPV (Denise, Darlot, et al., 1996).

The protocol for the OOR assessment was also composed of two sequences identical except for the direction of rotation. OVAR started with an axis tilted at 17° to the Earth-vertical. Subjects were accelerated during one second to a constant velocity of rotation of ±60°/s. Rotation continued for 150 seconds and then a subject was decelerated during one second. The stimulation parameters (60 °/s, 17° tilt) were chosen to induce a sufficient otolithic stimulation and a slight motion sickness (Denise et al., 1996). For OOR recordings, the eye movements were analyzed when OOR was well established (60 seconds after the onset of movement).

The slow phase velocity curve of OOR nystagmus was modeled according to the formula:

$$SPV(t) = B + A \cos(2\pi/T + \varphi)$$

t as time (s); T as the period of rotation (6 s). Magnitudes B, A and  $\varphi$  are the bias (°/s), the amplitude of modulation (°/s) and the phase (°), respectively. The variables compared were bias and modulation.

In the results, CW and CCW refer to the Clockwise and Counterclockwise directions of rotation, not of the eye movements.

### *Statistical analysis*

To perform analysis and graphs we used SigmaStat 3.5 and SigmaPlot 10.0 (Systat Software, Inc). Groups were compared with bilateral unpaired t-test; asymmetry was assessed with bilateral paired t-test. When the data were not normally distributed, the non-parametric analogue of t-test was used (Wilcoxon Signed Rank test for the paired data and Mann-Whitney Rank Sum test for the non-paired data). The results are presented as Mean ± SD. The threshold of statistical significance was set at 0.05.

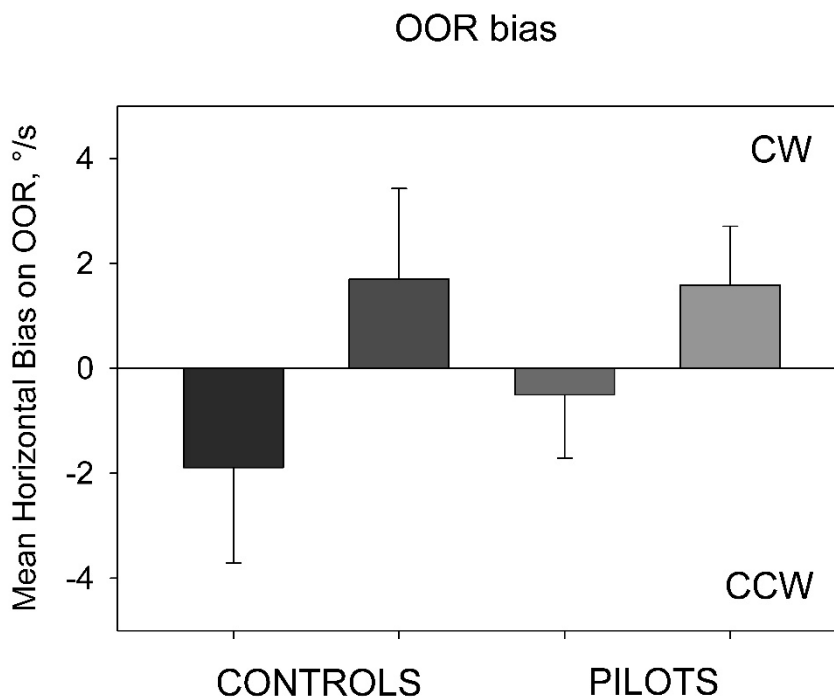
## **3. Results**

During EVAR the COR gain in pilots did not show significant difference from the control group (0.59 ± 0.11 vs. 0.61 ± 0.1; t = 0.53; 25 degrees of freedom (df); p =

0.6). There was no significant difference ( $t = -1.37$ ;  $df = 25$ ;  $p = 0.18$ ) detected in TC between the groups either ( $12.4 \pm 1.9$  sec *vs.*  $11.3 \pm 2$  sec).

The amplitude of OOR was not found to be different between groups ( $1.54 \pm 1.15$  °/s in pilots *vs.*  $1.17 \pm 0.66$  °/s in controls;  $t = -1.12$ ;  $df = 27$ ;  $p=0.27$ ). The bias along the horizontal axis has a tendency to be lower in pilots than in control subjects ( $1.05 \pm 0.93$  °/s *vs.*  $1.8 \pm 1.2$  °/s), though not statistically significantly ( $t = 1.77$ ;  $df = 27$ ;  $p = 0.09$ ).

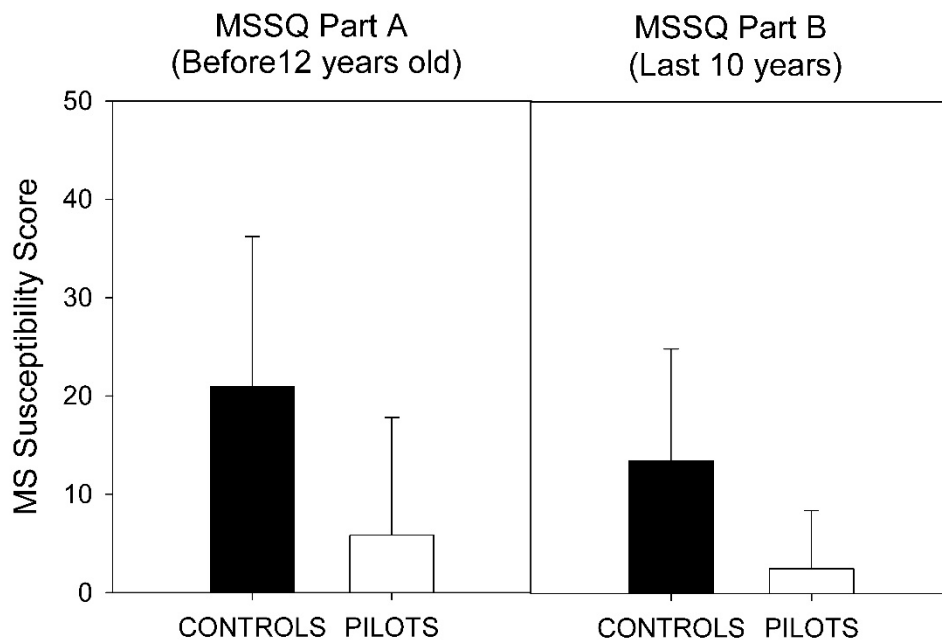
However, the pilots presented asymmetric OOR bias, while the control subjects are not (-CW *vs.* CCW:  $0.50 \pm 1.21$  °/s *vs.*  $1.59 \pm 1.12$  °/s, ( $t = -2.26$ ;  $df = 10$ ;  $p = 0.03$ , paired t-test) in pilots and  $1.89 \pm 1.82$  °/s *vs.*  $1.7 \pm 1.73$  °/s, ( $Z = 0.46$ ;  $n = 81$ ;  $p=0.67$ , Wilcoxon signed rank test) in control group; Figure SIV.2).



**Figure SIV.2 – Horizontal bias in the otolithic response in Clockwise and Counterclockwise rotations in pilots and control group**

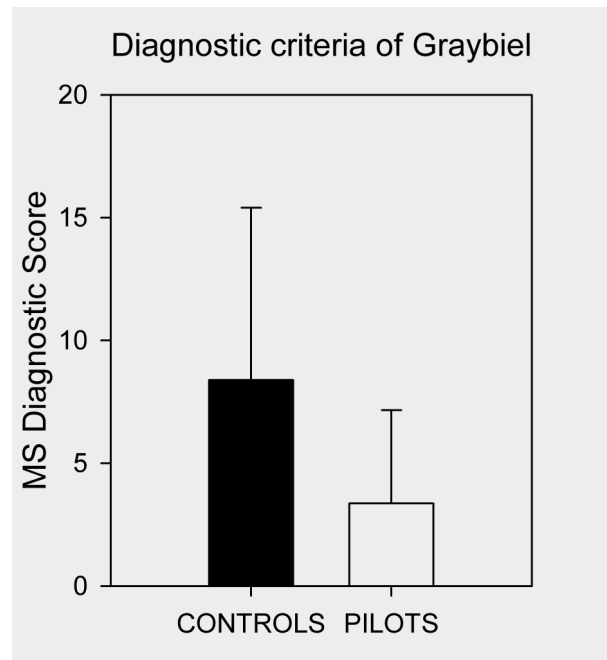
The unsigned mean error in subjective vertical with respect to the real vertical, revealed with the RFT, is not different between groups ( $1.66 \pm 1^\circ$  for control subjects *vs.*  $1.7 \pm 1.17^\circ$  for pilots;  $p = 0.89$ , U Statistic = 102.5; Mann-Whitney Rank Sum test). Both groups are field independent as the mean error was not more than normal physiological value.

Self-reported history of MS susceptibility (MSSQ score) was found to be significantly less in pilots than control group during the last ten years ( $2.52 \pm 5.59$  *vs.*  $13.5 \pm 11.36$ ;  $p = 0.003$ , U Statistic = 126.5; Mann-Whitney Rank Sum test) and before the age of 12 ( $5.85 \pm 11.35$  *vs.*  $20.96 \pm 15.26$ ;  $p = 0.02$ , U Statistic = 117; Mann-Whitney Rank Sum test); see Figure SIV.3.



**Figure SIV.3 – Motion sickness susceptibility scores in childhood (Part A) and adulthood (Part B) in pilots and control group.**

The symptoms score obtained with the diagnostic criteria of Graybiel (Figure SIV.4) are also significantly different in the effect of the vestibular stimulation of the study in two groups ( $3.36 \pm 3.81$  *vs.*  $8.39 \pm 7.01$ ; U Statistic = 148;  $p = 0.03$ , Mann-Whitney Rank Sum test).



**Figure SIV.4 – Scores of motion sickness diagnostic criteria of Graybiel in pilots and control group.**

## 4. Discussion

The mean unsigned errors made by both groups in the Rod and Frame Test do not differ statistically in average. Normal range of deviation from the real vertical without the field tilt influence is  $0 \pm 2^\circ$  (Zwergal et al., 2009). For both groups the mean error is less than 2 degrees, which shows that the subjects are field independent. These results suggest that from the perspective of perception, no alteration is induced in pilots by their activity.

The pilots presented less history of susceptibility to MS than control participants. This finding is consistent with the data on other types of pilots and supports the observations of the MS susceptibility habituation (Syburra et al., 2009; Tucker et al., 1965). However, it might be the result either of habituation, or of the fact that people, who are less susceptible to motion sickness are more likely to choose aviation as an activity. The second explanation seems more likely, as long as the score of the part A of the MSSQ suggests that even in childhood MS experience in



pilots was significantly less than in the control group. The rotatory chair stimulation was less nauseogenic for pilots than for control subjects (the score of 3.4 for pilots corresponds to slight-to-moderate malaise, while 8.4 is interpreted as a moderate-to-severe malaise (Graybiel et al., 1968)), which corresponds to the general susceptibility of groups. It should be mentioned that the analysis of motion sickness of subjects in this study is limited. First, the choice of the stimulus intensity was made to be optimal between the sufficient otolithic stimulation and the low nauseogenicity. Therefore, due to the low nauseogenicity, the differences between groups might seem not as pronounced as they are in the reality. Second, subjects that have not finished the protocol due to motion sickness were excluded for the analysis, which could influence the mean score. However, even with these limitations the difference is detectable.

Literature suggests that the habituation to MS is linked with the habituation of the COR (Dai et al., 2003; Shupak et al., 1990) as well as with a change in the subjective vertical (Clément et al., 2007) none of which we observe in the group of aerobatic pilots in this study.

Indeed, contrary to what has been observed in sportsmen like figure skaters (Tanguy et al., 2008), we have not found a significant change in pilots' canal function. Aerobatic pilots perform rotations differently than figure skaters or gymnasts. First, many rotations are performed with orientation changing with respect to gravity, which implies otolithic inputs together with canal inputs. This might be interpreted in the brain differently than a pure canal stimulation. Second, unlike figure skaters that suppress their compensatory eye movements to perform the rotations better, pilots should have precise ocular compensations to better orient in space and keep the visual attention. This suggests active attention and usage of all the sensory cues that might help to build a robust representation of their position. Unlike many other pilots, the aerobatic pilots dominantly concentrate not on the instrument panel, but on their perception of the environment and orientation in space, in particular by using the visual information. It was shown in velocity steps habituation in cats, that visual suppression during the secondary nystagmus prevented the full development of the habituation (Courjon et al., 1985). This suggests that the aerobatic pilots are less likely to diminish the gain of the VOR.

The investigation of the otolithic system with the OVAR indeed revealed an alteration in otolith-ocular reflex in pilots. Comparing to control subjects, otolith-driven eye movements of pilots had a significant decrease in bias for the rightward head movements, while for the leftward it remained the same as observed in the control group. That is, pilots demonstrated a significant asymmetry in bias of the horizontal otolith-ocular response. The bias asymmetry suggests a unilateral habituation. This is surprising because this asymmetry could lead to spatial orientation alteration, which we do not observe indirectly, according to the results of the RFT test. The habituation is usually caused by repetitive stimulus. In this case it can possibly be explained by the directional preferences of the aerobatic maneuvers performance. According to the anecdotal data from the pilots, this preference indeed takes place due not only to the subjective habits, but also to the construction of the vehicle that pilots use for their training and performances. Aerobatic aircrafts have propellers that rotate clockwise. This facilitates and accelerates leftward rotations. In addition, the cockpit is constructed in such a way that the stick is usually controlled with right hand and it is physically much easier to push it leftwards. These constructive features explain the fact that, according to the anecdotal estimations by pilot instructors, more than 2/3 of rotations are performed leftwards. Such unequal and asymmetric conditions could have induced asymmetric habituation in the OOR of pilots, concerning leftward rotation. However, the results show the opposite. We could suggest that during intense stimulations there are not only accelerations that should be taken into account, but also decelerations. It is likely that during aerobatic maneuvering decelerating is even more abrupt. Therefore, it might be the termination of leftward maneuvers that contributes the most to the vestibular signaling.

However, the observed asymmetry remains unclear suggesting the necessity of further research of otolithic function in pilots, and aerobatic pilots in particular. It should be noted, that the design of airplanes can affect the vestibular system of pilots.

## **5. Summary**

Our study demonstrates that aerobatic pilots have a significant asymmetry in the horizontal eye movements driven by otoliths, while the control subjects are symmetric. It might be the result of habituation to rapid decelerations during the manoeuvres, which could possibly lead to disturbances in spatial orientation. However, pilots were equally successful in visual vertical estimation as control subjects and all subjects tested were field independent. We found no change in the ocular responses driven by semicircular canals in pilot group. Pilots were found less susceptible to motion sickness.

## **Part III: General discussion**



## The overall view

Vestibular signals play a role in a great variety of functions in the body. They drive motor functions such as Vestibulo-Ocular Reflexes, Vestibulo-Collic and Vestibulo-Spinal reflexes. Vestibular system adds to autonomic control mainly through the vestibulo-sympathetic reflex. It was shown to influence vascular tonus, cardiac rhythm and respiration. Vestibular inputs are involved in cognitive functions such as navigation in space, distinguishing self-motion and object motion, perceiving the vertical, bodily self-consciousness, and even circadian rhythms and emotions. Vestibular system is responsible for generation of motion sickness.

Vestibular system can be found in almost any species. The simplest vestibular reflexes in human keep the basic three-neuron structure. However, upon these simple reflex arcs, a complex structure that uses vestibular signals is elaborated in the human CNS.

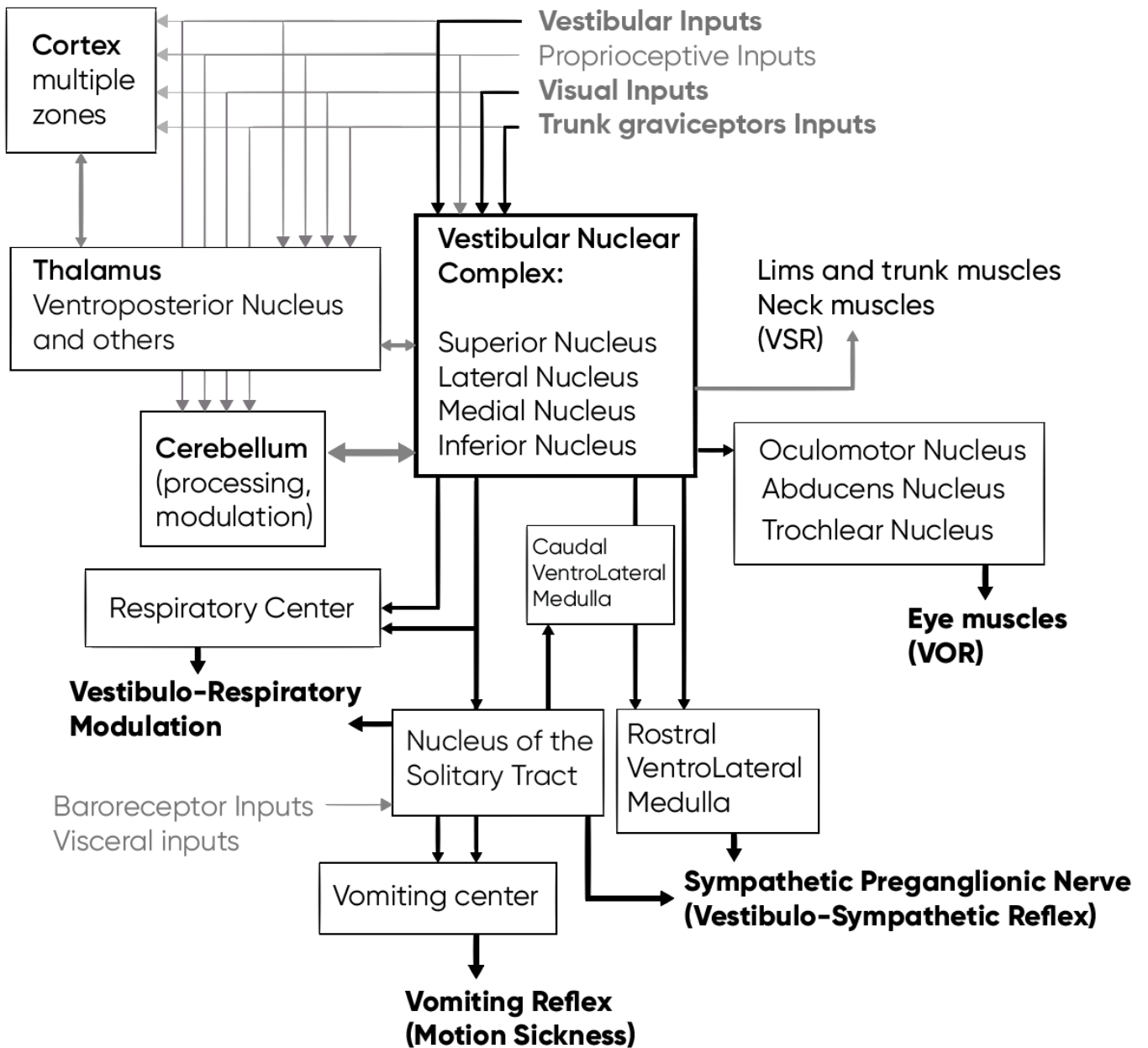
Vestibular afferent signals are sent in the brainstem, cerebellum, numerous thalamic and cortical areas, creating a fine network of processing. Unlike other sensory systems, the vestibular system does not have a unique assigned zone for processing. The vestibular pathways are largely distributed, and since the first stage of processing, neural fibers carry transformed and integrated signals, instead of pure sensory afference. The major locus of processing the vestibular and corresponding sensory information, necessary for the generation of a response, is contained in the brainstem and the cerebellum.

Vestibular sensory inputs undergo transformation and integration with multiple sensory modalities already at the level of secondary neurons. The ambiguous and head-referenced nature of vestibular signals require central involvement for distinguishing tilt from translation, head-on-body from head-and-body orientation changes, passive movement from active one (Angelaki & Dickman, 2003; Boyle & Pompeiano, 1981; Cullen & Roy, 2004; Merfeld et al., 1999). An elaborated circuitry integrates vestibular signals with information from other sensors, probably in a weighted manner to reduce the sensory noise (Zupan et al., 2002). The internal model of sensory dynamics helps to derive the best estimate of the real motion parameters to generate adequate responses. These internal models are based on previous experience and can be updated in order to conform to new

sensory conditions (Gonshor & Jones, 1976; Yates et al., 2000). Any persistent change in sensory afferents that can cause a “sensory conflict” and impair the precision of responses, is a potential cause for adaptive changes in this central integrator.

We would like to emphasize several points in this text. First point is that the integrator is constantly updating, driven by the persistent sensory experience. As a direct consequence of this assumption, the integration weighting and the estimation parameters should be quite individual, differing between the subjects. Another point is that plastic changes are caused not by the stimulus itself, but by the necessity to improve the precision of the response. In other words, the processing strategies are updated when the change in the response is crucial for normal living and performance.

In this thesis, we concentrated on multiple vestibular-driven responses. We examined cardio-vascular and respiratory variations, ocular movements and motion sickness that are induced primarily by vestibular inputs (Figure GD.1).



**Figure GD.1 – Schematic representation of the vestibular interactions with their major pathways.** Black arrows show the inputs and responses we investigated in the studies of this thesis.



## Our studies

The results of the Study I demonstrate that subjects having a total bilateral vestibular loss still present the vascular response to change of the position of the head with respect to gravity. One of the ways to interpret these data is that BVL subjects restore the capacity to adjust vascular resistance to postural changes even in the absence of vestibular inputs, integrating the information provided by other sensory modalities. This interpretation is supported directly by the study by Yates and colleagues (Jian et al., 1999). They demonstrated that within a month after the BVL animals, that at first have lost the blood pressure stability during body tilts, were able to regain the proper cardiovascular control, even in dark. Yates (Yates et al., 2000) proposed a model for the possible compensation for the absence of vestibular inputs to restore the cardiovascular response for changes in the orientation in space.

The results of the Study II show the synchronizing effect of OVAR on respiration. In attempt to localize the graviceptors that make a dominant effect on respiration, we faced a large intersubject variability. We have noticed that some subjects tended to synchronize their respiration cycle to the position of the trunk graviceptors, while others tended to synchronize more with the labyrinthine graviceptors. The synchronization has been found quite individual. The finding is supported by the literature: Mittelstaedt attempted to separate the roles of otolithic and somatic graviceptors on estimation of the position in space (Mittelstaedt, 1996, 1999). He concluded that the contribution of otolithic and somatic graviceptors in average is 40% *vs.* 60% in the perception of body position. However, the interindividual variance in the proportion of receptors contribution was also remarkable. Therefore, we suggest that the two sources of sensory information are combined with an individual weighting for every source to synchronize the respiration during the graviceptors stimulation by rotatory chair.

The results of the Study III show the effect of OVAR on the mean values of cardiovascular parameters – Mean Arterial Pressure, Heart Rate, Cardiac Output, Stroke Volume and respiratory frequency. All the values increased in OVAR conditions in comparison to non-OVAR conditions. This finding is in line with other observations with OVAR. However, the major question of the study is the effect of

visual stimulation on modulation of cardio-vascular parameters. The mean values were not significantly affected by the visual stimulation. The normalized modulation of arterial pressure was quite pronounced. The effect of the visual stimulation on the modulation amplitude of the MAP was observed, however, it was inverse from what was expected: the amplitude of modulation in “Cone” was smaller than in “Darkness” and not different from the “Cylinder”. The phases of modulation seemed to be very variable between subjects, however stable for different trials for every subject. This speaks in favor of the neural nature of this modulation, rather than mechanical or hydrostatic reasons. As in the study II, the individual strategy of the modulation is observed, with large difference between individuals.

The results of the Study IV indicate that the aerobatic pilots who participated in the study did not develop the expected habituation. Canal-Ocular Reflexes did not differ from those of the control group. The subjective vertical estimation was also similar and both groups were visual field independent. However, we have found an asymmetry of the otolith-ocular reflex, not present in the control group. We could suggest this asymmetry to be developed due to the construction specificities of the airplane the pilots use in their practice. The pilot group was also found less susceptible to motion sickness in their childhood and adulthood experience and during the rotational test in the laboratory. The difference in motion sickness susceptibility is an important issue that permits the pilots perform their activities. Whether it precedes or results from piloting, it indicates a different treatment of vestibular information within an integrator, leading to the less generation of the sensory conflict. We suggest that the pilots do not develop habituation, as they require unsuppressed responses for a better performance.

## **Our studies within the overall context**

There is a considerable amount of literature using neuronal and functional approaches that attempt to reveal how the vestibular system interacts with other sensory systems to generate the responses. The subjective visual vertical is considered to be driven primarily by the labyrinthine inputs, so does the VOR

compensation to movement. At the same time, the perceived verticality of the position of body is assessed differently than visual vertical, and includes the integration of otolithic inputs with visceral graviceptor inputs. The proportions of impact of the two types of graviceptors on the body orientation perception is individual with the predominance of the visceral graviceptors in average (Mittelstaedt, 1996, 1999). The compensatory ocular movements in the dark can be evoked by other sensory inputs in the absence of labyrinthine, but in normal population the major system driving the ocular reflex is vestibular. The vestibulo-sympathetic reflex, as the vestibulo-respiratory reflex, can also be supported by other sensory sources, but the literature is lacking. The motion sickness generation is thought to be due to the labyrinthine inputs (probably, both otolithic and canalar), since people having lost their vestibular afference do not experience motion sickness.

In this thesis, we aimed to specify the role of the vestibular system in the orientation-related homeostasis. The studies of this thesis were performed in attempt to evaluate the type of graviceptors that contribute to the respiratory control, as well as the role of the vestibular afference in generating the cardiovascular responses to orientation changes. The possible influence of visual input or perceptual response on the cardio-vascular control during rotations was evaluated. Finally, the possible alterations of the vestibular responses of the “vestibular experts” – aerobatic pilots, experiencing intense vestibular stimulations, were evaluated.

We have demonstrated that autonomic orientation-related reflexes in Human can be functional even after the loss of the vestibular signals that were considered as the primary and necessary source. We also have shown that the vestibular system is probably not the dominant source of information about the self-orientation in space for synchronizing respiration. Visceral graviceptors divide the contribution to the orientation-related responses with the otolithic system, taking in average a bigger role for controlling respiration. However, the proportion of the contribution of graviceptors of both types is individual. The phase of neural modulation of arterial pressure during OVAR also seems to be individual and variable between subjects. We suggest that this individual difference is based on previous experience and successful estimation and response strategies. In some situations, the strategies need to be changed in order to keep the response adequate. In one case,

it may happen due to the loss of sensory inputs. The cardio-vascular regulation is a crucial task for normal performance; the recovery of the proper response is necessary and we do observe it in patients. In the other case, the trigger to adapt sensory processing can be a change in activity. However, the changes observed in the aerobatic pilots were minor. We suggest that the rearrangement of sensory processing is not caused by the stimulus itself, but by the necessity to change the responses for a better performance, or by the need to suppress the unnecessary responses. Aerobatic pilots, unlike the figure skaters, need unsuppressed responses to perform their activities and get the all the sensory information about their position that is available. Therefore, the development of vestibular habituation might be hampered.

## Perspectives

First, the cognitive perceptual involvement in the regulation of the vestibular orientation-related responses stays an interesting question.

Another interesting question to follow in the topic of this thesis is the internal estimation of gravity. Literature on the topic proposes multiple models, suggesting the constant recalculation of gravity vector by the CNS. Several models have been created to explain perceptual perturbations in the conditions of altered gravity. A utricular shear model (Schoene, 1964), a tangential model (Correia, Hixson, & Niven, 1968), Mittelstadt's idiotropic vector model (Mittelstaedt, 1983), modified observer model (Clark et al., 2015) aim to explain the perception of tilt in hypergravity. Interestingly, according to the model published by Clark (Clark et al., 2015), an illusory perception of vertical linear acceleration might occur in hypergravity. This results from the presumption that the CNS uses an internal model of the physical law  $a = GIA - g$  where the gravity is fixed to  $1g$ . How does it function in human? No sustainable linear translation illusion has been reported in hypergravity. We suggest that the estimate of the gravity vector updates not only its direction, but also its magnitude. At some moment, the CNS must adapt the estimated vector of gravity to limit the illusory translation component. So, how does the estimate of gravity update its magnitude in the conditions of altered

gravity? What is the dynamics of this process? To address these questions we have proposed a protocol for a parabolic flights experiment, assessing the perceptive responses during sinusoidal translation in microgravity, normal gravity and hypergravity.

Finally, writing the article on the Study I have lead us to question the physiological significance of the vestibulo-sympathetic response in human. While the response measured in animals is physiologically justified, the one in human subjects is not as clear. On the one hand, the methods used in studies on human subjects are less direct and more challenging, that can surely bias the results. On the other hand, it is also possible that in human the response has a different physiological significance than in animals. The circuitry involved in processing of the response might be much more complex and elaborated in human, which would probably explain the discrepancies and controversy between the results of the experiments using different experimental approaches. Thus, as this question remains unanswered and poorly investigated, it would be interesting to reveal the underlying mechanisms and significance of the responses. It has been shown that in microgravity, in absence of vestibular inputs, the baroreflex is stronger than in normal gravity conditions (Ogoh et al., 2018). The multiple studies using HDNF protocol show that the head-down position, and not the head-up, which would be closer to orthostatism, augments the sympathetic activity in human, contrary to the animal studies. This directional controversy in the vestibulo-sympathetic reflex evoked by the HDNF method is puzzling. However, we see the same pattern in the study of Radtke et al. (Radtke et al., 2000, 2003): the head drop (thus taking the prone position) causes the acceleration of the heart which would lead to the increase in blood pressure. We are left with a question, if the response is indeed driven directly by the vestibular influence on any branch of the autonomic nervous system, would the motion stimulus in the other direction give the opposite effect on the cardiac rhythm? In other words, would a head up push, equal in characteristic to the head drop performed by Radtke and colleagues, increase the RR interval of the first heartbeat following the stimulus? If it is the case, then the direction of the stimulus is of importance to the autonomic control. In this case, the next piece of a puzzle would be to understand why in human the vestibulo-sympathetic reflex acts controversially to the orthostatic logic and the response observed in animals. Another possibility is that the head push would result in the same cardiac response as the head drop. In this case, probably the directional

orientation of the stimulus does not play a significant role in human, and so the response serves as a trigger for the following responses, for example the baroreceptor reflex. Also, as the experiments in human are brought out indirectly, with the stimulations that do not definitively isolate to the vestibular activation, so there is a possibility, that the sympathetic effect is rather due to the activation of some other type of receptors, for example situated in the blood vessels. The cardio-vascular response in the BVL subjects, equal to the response in normal subjects, which has been found out in the Study I works along with this hypothesis.



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# **Annexes**

**Annex 1: Poster “Vestibulo-ocular responses, visual field dependence and motion sickness in aerobatic pilots”.**

O. Kuldavletova\*, S. Tanguy, P. Denise, G. Quarck

*Presented at*  
**FENS, October 2017**, Pecs, Hungary;  
**JED 2018**, Rouen, France.

# Vestibulo-ocular characteristics and motion sickness susceptibility of aerobatic pilots in comparison with control participants

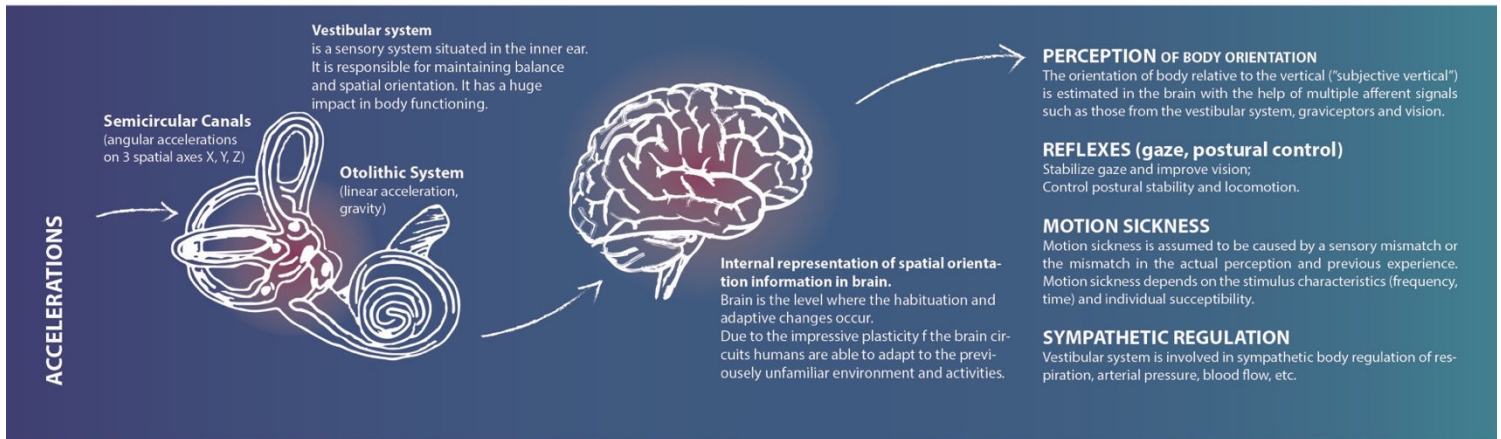
O. Kuldavletova, S. Tanguy, H. Normand, P. Denise, G. Quarck

University of Caen Normandy  
Lab COMETE INSERM U1075, PFRS,  
2 avenue des Rochambelles

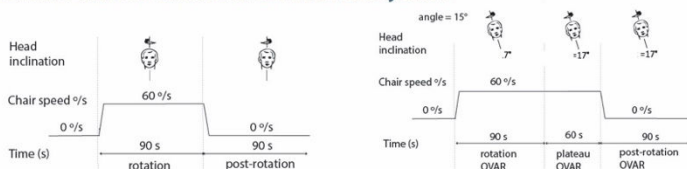
Pilots of aerobatic aircrafts are regularly subjected to linear accelerations of +4.5 g to -3 g during their flights. These stimulations probably require the vestibular system to "optimize" or "adjust" its responses for Canal-Ocular Reflex (COR) and Otolith-Ocular Reflex.

The aim of this study is to evaluate the functional plasticity of the vestibular system in aerobatic pilots. We want to investigate whether the aerobatic pilots, as individuals who experience an intense vestibular stimulation, present a modification of the vestibular functioning as compared to normal volunteers.

We hypothesized that the aerobatic pilots present a higher VOR gain due to the adaptation mechanisms, more accurate perception of the real vertical and smaller sensitivity to motion sickness compared to the control group participants.



## STIMULATION : EVAR and OVAR on rotary chair



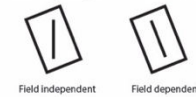
**Earth-vertical axis rotation (EVAR)**  
EVAR is rotation in yaw with the constant orientation relative to gravity. For this reason EVAR is used to assess the function of Semicircular Canals that detect angular accelerations. We used the protocol called Step-Stimulation.

**Off-vertical Axis Rotation (OVAR)**  
OVAR is rotation in yaw, around the axis inclined relative to gravity. Due to the constant changing stimulation of graviceptors OVAR is used to assess the otolith function (linear acceleration detectors). After some period of constant velocity rotation the semicircular canals signals decay and we can obtain almost pure otolith effect. Known to be nauseogenic.

## TESTS

### ROD AND FRAME TEST

Used to assess the Field-dependence on the perception of the vertical.



### MSSQ

**Motion Sickness Susceptibility Questionnaire** is a questionnaire used to assess the susceptibility of a subject to Motion sickness. It includes the history of a subject, covering a wide range of subject's experience in nauseogenic environments (e.g. different kinds of transport).

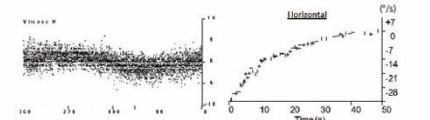
### GRAYBIEL QUESTIONNAIRE

Also referred to as Penacola Diagnostic Index. Used to assess the current Motion sickness symptoms of a subject.

### VIDEONYSTAGMOGRAPHY

A method to record the 3D eye movements. Used to assess Vestibulo-Ocular Reflexes. We assessed the Canal-Ocular Reflex with the EVAR Step-Stimulation and Otolith-Ocular Reflex with the OVAR stimulation. We also assessed the suppression of nystagmus by lighting a visual target during 5 seconds with the Step-stimulation motion protocol.

Video-recordings of the eye movement were transformed into the 3D of 2D eye tracks, containing Horizontal, Vertical and Torsional (if 3D) components of the eye movement.



Parameters for **OOOR** assessment:

- the bias velocity (a steady-state compensatory horizontal component of the eye response to OVAR)
- the amplitude (modulation of the oscillatory eye response)

Parameters for **COR** assessment:

- the time constant
- the maximal velocity of the slow-phase of the per-rotational and post-rotational nystagmus evoked by EVAR step-stimulation.

### STATS

Student t-test was used as a statistical tool. Paired, when assessing asymmetry, non-paired, when comparing pilots vs control groups. For Rod and Frame Test a method suggested by Nyborg (1974) was used.

## RESULTS

### ROD AND FRAME TEST

We assessed the field dependence of subjects on the perception of the vertical and the asymmetry. **Field dependence:** both Pilots and Control groups were found to be field-dependent.

**Asymmetry:** Pilot group showed the constant error to the **Left**.

### MSSQ

We found that Pilots ( $2.1 \pm 5.19$ ) are significantly ( $p = 0.002$ ) less susceptible to motion sickness than control subjects ( $14.9 \pm 12.45$ ).



### GRAYBIEL SCALE

Despite the differences in susceptibility, the MS symptoms evoked by the stimulation were not significantly different ( $p = 0.3$ ).  
Pilots:  $7.33 \pm 10.64$   
Control:  $12.06 \pm 13.03$



### CANAL-OCULAR REFLEX

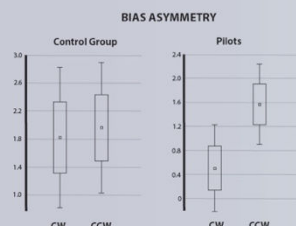
The COR did not show any significant difference between groups neither in time constant ( $p = 0.25$ ) nor in gain ( $p = 0.57$ ).

### NYSTAGMUS SUPPRESSION by visual target

Both pilots and control groups were **equally** successful in suppression of nystagmus by a LED-target ( $90\% \pm 7\%$  in Control vs  $88\% \pm 4\%$  in Pilots).

### OTOLITH-OCULAR REFLEX

No significant difference was found in the amplitude of modulation ( $p = 0.2$ ). The difference in bias is on the threshold of statistical commonly used significance ( $p = 0.055$ ). Asymmetry CW vs CCW bias was noticed in Pilots ( $p = 0.03$ ), but not in the control group ( $p = 0.86$ ).



## DISCUSSION

This study showed that pilots are significantly less motion sick than non-pilot population. However, the Graybiel scale showed no significant difference for motion sickness symptoms for the two groups. This could result from the parameters of the stimulation, that did not have the nauseogenic effect. Furthermore, the Graybiel questionnaire includes symptoms like somnolence, that could be due to the fatigue of the subject, but not due to motion sickness.

We expected pilots to have significant changes in canal-ocular regulation, but no significant difference was found in the study. This could be due to the fact that pilots are generally subjected to high levels of linear acceleration, but not the angular acceleration (as is the case of figure skaters, for example).

OOR on the contrary presents some change. There were two parameters assessed in the horizontal direction of the eye movement. **Modulation** component, that is generated from changes in otolith afferents induced by reorientation of the head with respect to gravity and **bias** component, that is generated by the so-called velocity storage mechanism and compensates for the head angular velocity reconstructed from otolith activation. Modulation component showed no change, whereas the bias was at the threshold of significance ( $p = 0.055$ ). This parameter needs to be deeper investigated. Moreover, the groups varied in the compensatory bias to different directions of rotation. A significant asymmetry (towards counterclockwise) was observed in pilots, while the control group presented no asymmetry.

The perception of verticality was equally field-dependent (subjects tended to rely on the visual frame when estimating the verticality), but the pilots again presented a significant asymmetry towards left. The reason for such leftward lean could probably be found in the training protocols and the aerobatic maneuvers technique.

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- Tanguy, S. et al. (2008) Vestibulo-ocular reflex and motion sickness in figure skaters.
- Lee, M. et al. (2004) Adaptation of the horizontal vestibuloocular reflex in pilots.
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Laboratory COMETE

**Annex 2: Poster “Influence of graviceptor stimulation initiated by off- vertical axis rotation on ventilation”.**

O. Kuldavletova, S. Marie, P. Denise, H. Normand

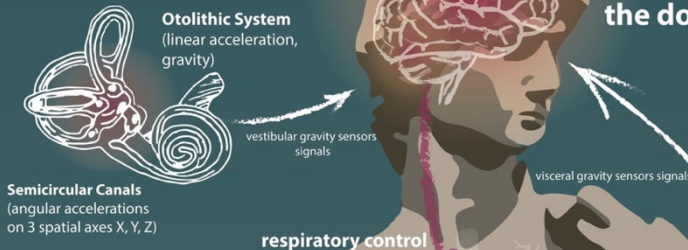
*Presented at*  
**JED 2019**, Caen, France.

# Influence of graviceptor stimulation initiated by off-vertical axis rotation on ventilation

Kuldavletova O<sup>1</sup>, Marie S<sup>1</sup>, Denise P<sup>1,2</sup>, Normand H<sup>1,2</sup>  
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## Vestibular system

is a sensory system situated in the inner ear. It is responsible for maintaining balance and spatial orientation. It has a huge impact in body functioning.



? How does the brain integrate signals of different nature to modulate the respiratory functions? Which sensor is the dominant one?

It is known that respiration is affected by graviceptors, but it remains unclear to what extent labyrinthine and non-labyrinthine graviceptors are involved in this process.

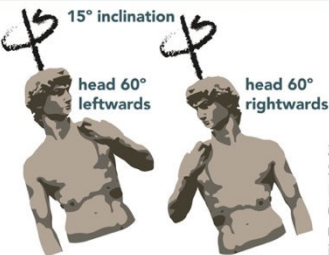
Off-Vertical Axis Rotation (OVAR; description below) stimulates both labyrinthine and non-labyrinthine receptors, ventilatory modulation during OVAR could be attributable to activation of either one type or both types of receptors.

We use a HTOT (see below) method to distinguish between two types of receptors.

## Visceral graviceptors

Visceral graviceptors refer to the sensory receptors that contribute to providing a neural representation of the direction of gravity with respect to an organism and of motion of the organism with respect to the gravity vector together with the otolithic system. Located in the body trunk, suggesting the liver.

## Results & Discussion



## Methods

21 subjects  
 Stimulations: Off-vertical and Earth-vertical Axis Rotations (OVAR and EVAR) using a rotatory chair with vertical or inclined axis of rotation HTOT method

### OVAR / EVAR

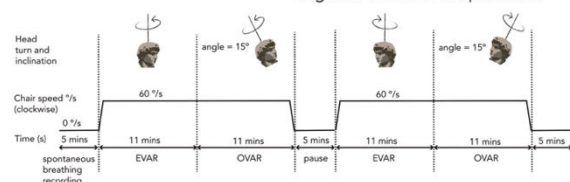
During off-vertical axis rotation (OVAR), in head-fixed coordinates, the component of the gravity vector perpendicular to the axis of rotation revolves around this axis and periodically stimulates the graviceptors (both otolithic and visceral). When the angular velocity is constant, only the graviceptors are stimulated and not the semi-circular canals.

The velocity of rotation was individually selected for every subject to match spontaneous breathing rate (measured during baseline receding over 5 mins).

### Parameters measured :

- Respiration frequency
- Tidal volume
- Ventilatory flow

### Protocol:



### Vestibular graviceptors (otoliths)

### Visceral graviceptors



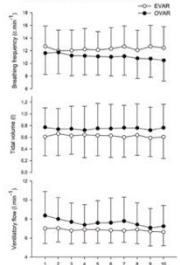
### gains are individual :

Our results suggest that the modulation of respiration is not a result of a simple reflex arc, but that it involves a higher integration of different types of receptors with variable contributions of either type of graviceptor among subjects.

We used the Scheirer-Ray-Hare test, a non-parametric two-way ANOVA with factorial design, to assess the effect of axis inclination ('OVAR' vs 'EVAR'; 2-level factor), and the effect of the duration of the stimulation on tidal volume, respiratory frequency and ventilator flow. We found a significant effect of axis inclination for all respiratory parameters ( $P < 0.001$  for tidal volume and respiratory frequency;  $P < 0.01$  for ventilator flow), whereas the duration of stimulation did not alter respiration ( $P$  values close to one), and interaction between factors showed no effect on the respiratory parameters.

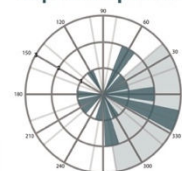
Inclination (OVAR vs EVAR) increased average ventilatory flow and tidal volume.

### OVAR vs EVAR



The estimation of the position of the body depends both on the otolith and on somatic graviceptors, but with a greater influence of the somatic graviceptors, 60%, compared with 40% for the otoliths according to Mittelstaedt (1996). It has also been found that there are large inter-individual differences in the weighting between these receptors; three subjects out of 31 relied only on somatic graviceptors, and one relied only on the otoliths (Mittelstaedt, 1996). The same phenomenon was observed in our study; in most subjects, respiration was influenced mainly by non-otolithic stimulation, but for a minority of subjects the main influence was otolithic. This hypothesis could also explain why the I-E transition histograms are significantly different even when the phase shift is taken into account, with a lower amplitude for 'head rightward'; because the change in the head position induces a 120 deg phase shift in the otolithic response, otolithic and non-otolithic responses might act synergistically in one head position and antagonistically in the other one.

### HTOT : inspiration position



In OVAR, the transition between inspiration and expiration occurred mainly at the forward pitch position. The phase of this transition in most subjects was driven mostly by the body position rather than by head position, suggesting that respiratory control during OVAR mainly involved non-labyrinthine receptors. However, the study demonstrates a high intersubject variability both in the ability of OVAR to synchronize breathing and in the influence of labyrinthine stimulation. We conclude that the respiratory response to changes in orientation of the body with respect to the vertical involves both labyrinthine and non-labyrinthine stimulation, with the gain of each signal varying individually.

## **Annex 3: Poster “Vestibulo-sympathetic reflex in patients with bilateral vestibular loss”.**

O. Kuldavletova, P. Denise, G. Quarck, M. Toupet, H. Normand

*Presented at*  
**SfN Neuroscience 2019, October 2019, Chicago, Illinois, USA.**

# Vestibulo-sympathetic reflex in patients with bilateral vestibular loss ...

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Patients with bilateral vestibular loss presented normal vascular responses during the HDNF manoeuvre. Thus, the so-called vestibulo-sympathetic reflex either does not originate from the vestibular system during the HDNF or recovers after bilateral vestibular loss. If it is so, it results not only from activation of the vestibular apparatus, but also from other non-labyrinthine sensors, such as trunk graviceptors, proprioceptive and cutaneous inputs, and vision. These inputs are integrated to create the modulation of the vascular response. This integration is subject to plastic changes and reweighting of impact of different types of sensors and can reestimate the position of the head following the BVL. And finally, there is evidence that the vestibulo-sympathetic reflex in humans acts in opposition to the orthostatic baroreflex, raising the question of its physiological significance.

## Methods

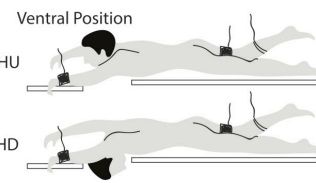
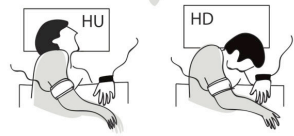
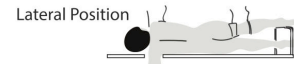
**Subjects**  
 9 adults (5 male and 4 female; mean age 54 ± 6 yrs) total bilateral idiopathic loss of vestibular function (BVL) for 7 ± 2 years

**Protocol : HDNF**  
 Eyes closed, (10 minutes)  
 Ventral Body Position (VP): Head Up (HU) – Head Down (HD) – HU, (10 minutes)  
 Lateral Body Position (LP): HU – HD – HU.

At each head position, CBF was measured twice after the new head position was taken. MAP measurements in the LP for the two HU positions were different and thus compared separately with the HD; the rest of the HU measurements were not different and thus averaged.

HDNF consists in passively changing the head position from extension to flexion in subjects lying in prone position. Suggestingly, it induces a different activation of the vestibular otolithic organs.

## Natural stimulation of the otolithic organs: Head-Down-Neck-Flexion (HDNF) manoeuvre



## Measurements

Continuous Arterial Pressure and Heart Rate (beats per minute) were measured with an automatic continuous noninvasive arterial pressure monitor (Finometer Pro, FMS, Amsterdam, The Netherlands) placed on the middle finger held at heart level.

Mean arterial pressure (MAP; Torr) was calculated as arithmetic mean of the continuous pressure signal.

Calf Blood Flow (CBF; mL.min<sup>-1</sup>.100mL<sup>-1</sup>) was measured with a venous occlusion strain-gauge plethysmograph

Calf vascular resistance (CVR) = MAP/CBF

## Statistical analysis

The Wilcoxon Signed Rank Test, which is a variant of a non-parametric paired t-test, was used to compare head positions for each parameter in VP and LP separately.

Vestibulo-sympathetic reflex is the activation of sympathetic neural traffic via the vestibular organ. Demonstrated in animals and Human with the use of multiple techniques. Helps to maintain stability of blood pressure during postural changes.

We have examined the vestibulo-sympathetic reflex in subjects without the functioning vestibular system.

We measured the cardiovascular changes, with the help of the HDNF protocol.

We have found that cardiovascular reaction to HDNF in patients that have no peripheral vestibular function...

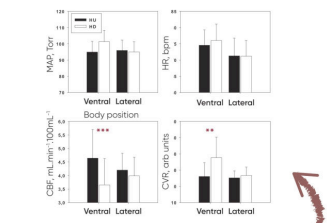
## Results and comparison with normals

Mean ± SE for 9 subjects. Values of the MAP (mean arterial pressure), HR (heart rate), CBF (calf blood flow) and CVR (calf vascular resistance) in HU and HD positions. Significance: \* $<0.05$ , \*\* $<0.01$ , \*\*\* $<0.001$ . The data from two studies on healthy subjects provided below for comparison. The significance in Normand et al. was calculated in relation to the intermediate head position.

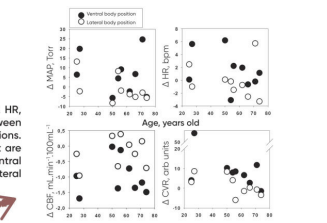
Body Position	Ventral HU	HD	Lateral HU	HD
MAP, Torr	94.94 ± 4.46	101.39 ± 4.66	95.93 ± 6.35	95.01 ± 6.29
HR, beats per min	74.57 ± 3.14	76.05 ± 3.37	71.29 ± 3.63	71.19 ± 3.23
CBF, mL.min <sup>-1</sup> .100 mL <sup>-1</sup>	4.64 ± 0.71***	3.65 ± 0.65	4.20 ± 0.41	3.99 ± 0.46
CVR, arbitrary units	26.12 ± 5.63**	37.68 ± 8.42	25.24 ± 2.86	26.65 ± 3.51

From Shortt and Ray:  
 MAP, Torr: 96 ± 3\*  
 HR, beats per min: 71 ± 2\*  
 CBF, mL.min<sup>-1</sup>.100 mL<sup>-1</sup>: 4.63 ± 0.78\*  
 CVR, arbitrary units: 24.0 ± 4.3\*  
 For the references see the publication, the link in the QR code or doi: 10.1111/EJN.14035

From Normand et al.:  
 MAP, Torr: 102.6 ± 5.9  
 HR, beats per min: 61.4 ± 2.6  
 CBF, mL.min<sup>-1</sup>.100 mL<sup>-1</sup>: 6.2 ± 0.7  
 CVR, arbitrary units: 18.9 ± 2.2\*\*  
 For the references see the publication, the link in the QR code or doi: 10.1111/EJN.14035



Mean Arterial Pressure, Heart Rate, Calf Blood Flow and Calf Vascular Resistance in BVL patients with Head Up and Head Down in Ventral and Lateral positions. In Ventral position the HDNF evokes cardiovascular response.

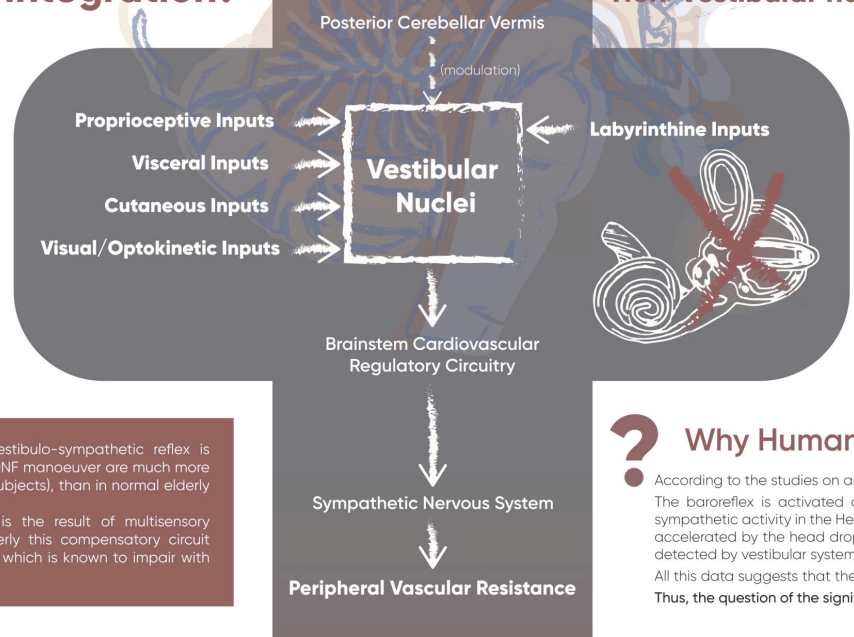


Effect of age of patients on  $\Delta$  MAP,  $\Delta$  HR,  $\Delta$  CBF and  $\Delta$  CVR.  $\Delta$  is a difference between values recorded in HD and HU positions. Individual values of  $\Delta$  for every subject are represented as black circles for Ventral position, and white circles for Lateral position.

...IS THE SAME AS IN NORMALS  
**How?**

## Multisensory compensatory integration?

Indeed, animal studies have revealed the possibility to recover from experimental bilateral vestibular loss. Blood pressure control, impaired after the vestibular loss, could restore within a month. This suggests that when deprived from the labyrinthine inputs, animals learn to use non-labyrinthine cues able to restore the body position in space, to regulate blood pressure. (The model provided in the center was proposed by Yates and colleagues (Yates et al., 2000) for an analogous process in animals). Inputs from the trunk, including visceral graviceptors, can contribute to a sense of spatial orientation and influence respiration. In human, somatosensory and proprioceptive signals take a bigger role in balance and postural control after the BVL. Thus, multisensory integration taking place in the vestibular nuclei can substitute lost labyrinthine signals to recreate the vascular adaptation to changes in posture. The fact that the HDNF manoeuvre induces the same adaptive vascular responses in BVL patients as in normal subjects, might indicate that the integration of inputs from non-vestibular origin should be able to rebuild the position of the head in the absence of vestibular cues.



## Non-vestibular nature of the reflex observed during the HDNF?

We cannot eliminate the possibility that nonspecific pressure receptors in the head could be a source of vascular reaction during the HDNF manoeuvre.

HDNF places the head below the level of the heart that can alter the cerebral pressure and intracranial blood volume. The increased intracranial pressure could stimulate the nonspecific pressure receptors. To our knowledge, only one study tried to eliminate this factor from consideration by using the Head Down Neck Extension (HDNE) protocol in the supine position. The idea was that the HDNF in prone and HDNE in supine position differently stimulate the otolithic system while placing the head similarly below the heart. The HDNE did not reveal any change in blood flow. However, we consider the protocols incomparable, because of:  
 1. Neck anatomy: the neck extension to the back cannot place the head far below the level of the heart. We consider the manoeuvre hardly comparable to the HDNF in prone.  
 2. Opposite effect on baroreceptors: In supine position HDNE stretches the carotid artery, while the HDNF enlarges the carotid diameter mechanically. Baroreceptors are not stimulated by the pressure itself but by the dilation of the carotid. It might result in a decrease in the stimulation of the carotid baroreceptors during HDNE, which would counteract the increase in hydrostatic pressure. This mechanism makes the comparison of both protocols impossible.

## Age and the cardiovascular response to HDNF

The literature demonstrates that in elderly the vestibulo-sympathetic reflex is significantly attenuated. Changes induced by the HDNF manoeuvre are much more pronounced in elderly population of our study (BVL subjects), than in normal elderly subjects. If the cardiovascular response during the HDNF is the result of multisensory integration rearrangement, it is possible that in elderly this compensatory circuit performs more efficiently than the vestibular system, which is known to impair with age. However, this speculation is to be tested.

## Why Humans have VSR?

According to the studies on animals, the VSR is thought to anticipate the baroreflex mechanism. However, is it true for Human? The baroreflex is activated as a response to orthostatism. Most of the studies demonstrate that HDNF increases the sympathetic activity in the Head Down position, which is a positional analog of lying, not of orthostatism. Heart rate was also accelerated by the head drop (again the opposite of orthostatism). Moreover, in weightlessness, in the absence of gravity, detected by vestibular system, the carotid baroreflex was shown to increase, not decrease. All this data suggests that the VSR acts opposite to the baroreflex mechanism, probably hampering it. Thus, the question of the significance of the VSR in Human is left open.



## Annex 4: Questionnaire of self-movement perception used in the Study III

CODE SUJET :

### Questionnaire de la Perception

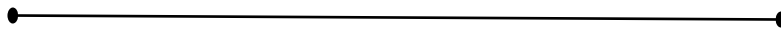
- Dans quel sens avez-vous tourné ?

Veillez dessiner / montrer le mouvement que vous avez perçu :

Veillez répondre aux questions en faisant une marque sur une échelle continue allant de « Absolument faux » à « Absolument vrai ». Dans ce questionnaire, veuillez considérer la **perception** du mouvement, pas le mal des transports.

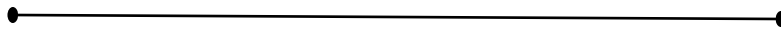
- 1) Le mouvement que j'ai ressenti était le même que celui que j'ai vu dans les lunettes.

Absolument faux Absolument vrai



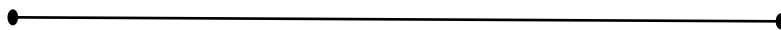
- 2) Le mouvement que j'ai ressenti était naturel et ne m'a pas dérangé.

Absolument faux Absolument vrai



- 3) La façon dont mon corps s'est déplacé était différente de celle du mouvement que j'ai vu.

Absolument faux Absolument vrai



- 4) Le mouvement m'a semblé étrange.

Absolument faux Absolument vrai



## Annex 5: Publications

- Kuldavletova O, Marie S, Denise P, & Normand H. (2018). Influence of graviceptor stimulation initiated by off-vertical axis rotation on ventilation. *Experimental Physiology*, 103(7), 1010- 1019. <https://doi.org/10.1113/EP087035>
- Kuldavletova O, Denise P, Quarck G, Toupet M, & Normand H. (2019). Vestibulo-sympathetic reflex in patients with bilateral vestibular loss. *Journal of Applied Physiology*, japplphysiol.00466.2019. <https://doi.org/10.1152/japplphysiol.00466.2019>
- Kuldavletova O, Tanguy S, Denise P, Quarck G. Vestibulo-ocular responses, visual field dependence and motion sickness in aerobatic pilots. (accepted for publication in *Aerospace Medicine and Human Performance Journal*)
- Kuldavletova O, Denise P, Etard O, Quarck G, & Normand H. Effect of self-motion perception on autonomic control. (further data analysis required)
- Kuldavletova O, Pasquier F, Bigot L, Denise P, Gautier A, Quarck G. Effect of physical activity on balance and vestibulo-ocular reflex in aging population. (in progress)









# Functional multisensory integration and plasticity of vestibular reflexes

## Abstract

The aim of this thesis was to specify the role of the vestibular system in the orientation-related homeostasis. We evaluated vestibular responses to changes in orientation in space (1) in normal population to reveal in what proportion different sensory systems are implicated in the generation of the cardio-vascular and respiratory responses, and (2) in populations with altered vestibular afference: bilateral vestibular loss patients and aerobic pilots.

The results indicated that the vestibular system cooperates with trunk graviceptors to evoke respiratory response to changes in orientation during Off-Vertical Axis Rotation protocol (OVAR). The contribution of each sensory source was found to vary between individuals. Another study tested the hypothesis that the vestibular modulation of cardio-vascular parameters can be influenced by visual input during OVAR. Preliminary results from this study have demonstrated that the OVAR stimulation has an effect on the mean cardio-vascular parameters. The modulatory effect of OVAR on the arterial pressure has also been shown. The phases of modulation were varying between individuals which can indicate the neural nature of the observed modulation. The effect of visual stimulation on modulation has been detected, however further analysis is required. In another study, subjects presenting bilateral vestibular loss were shown to have the same cardio-vascular response to changes in the position of the head during Head-Down-Neck-Flexion protocol (HDNF) as normals. This reconstruction of the vestibulo-sympathetic reflex in human seems to originate from the sensory sources other than labyrinthine. Finally, we studied aerobic pilots as humans experiencing intense and unusual vestibular stimulations. We have not revealed the expected vestibular habituation in the study using the OVAR and EVAR (Earth-Vertical Axis Rotation) stimulations, but were significantly less susceptible to motion sickness. We suggest that the pilots do not develop habituation, as they require unsuppressed responses for a better performance.

We conclude that to generate the orientation-related responses, the Central Nervous System integrates the vestibular and non-vestibular signals and is subject to plastic changes in altered sensory conditions, if the response needs to be changed or restored. This multisensory processing is individually tuned, with the variable portion of vestibular impact in this processing, depending on activities, sensory state and the requirements to the response.

**Key-words:** Vestibular system, orientation, multisensory integration, adaptation, plasticity, cardio-vascular control, vestibulo-ocular reflex, motion sickness.

## Résumé

L'objectif de ce travail de thèse était d'évaluer le rôle du système vestibulaire dans l'homéostasie en relation avec l'orientation.

Nous avons évalué les réponses vestibulaires (1) dans une population normale pour évaluer le niveau d'implication des différents systèmes sensoriels dans la régulation cardiovasculaire et respiratoire et (2) dans des populations présentant des informations vestibulaires perturbées : soit des patients avec un déficit vestibulaire bilatéral soit des pilotes de voltiges aérienne.

Les résultats indiquent que les informations vestibulaires et celles des gravicepteurs du tronc s'associent pour réguler la réponse respiratoire lors de la rotation à axe incliné selon la gravité (RAIG). La contribution respective des récepteurs vestibulaires et des gravicepteurs dans cette réponse varie en fonction des individus. Une autre étude a testé l'hypothèse selon laquelle la modulation de la réponse cardio-vasculaire par le système vestibulaire peut être influencée par les informations visuelles pendant la RAIG. Les résultats préliminaires de cette étude ont montré que la stimulation RAIG a un effet sur les valeurs moyennes des paramètres cardio-vasculaires. L'effet modulateur de la RAIG sur la pression artérielle a également été démontré. Cette modulation de réponse, et plus particulièrement la phase, variait entre les individus, ce qui peut indiquer la nature neuronale de la modulation observée. Un effet de la stimulation visuelle sur la modulation semble être également présent, mais une analyse plus approfondie est nécessaire pour confirmer ce résultat. Dans une autre étude, il s'est avéré que des patients présentant une déficience vestibulaire bilatérale avaient la même réponse cardio-vasculaire aux changements de position de la tête pendant le protocole « *head down neck flexion* » que les sujets témoins. Ces résultats indiquent que cette reconstruction du réflexe vestibulo-sympathique semble provenir de sources sensorielles autres que labyrinthiques. Enfin, nous avons étudié les pilotes de voltige aérienne comme modèle de sujets subissant des stimulations vestibulaires intenses et inhabituelles. Nous n'avons pas observé l'habituation vestibulaire attendue lors d'explorations fonctionnelles vestibulaires (RAIG et échelon de vitesse) en comparaison avec des sujets témoins, en revanche les pilotes étaient moins sensibles au mal des transports. Nous suggérons que les pilotes ne développent pas d'habituation vestibulaire comme attendu car ils ont besoin des réponses vestibulaires préservées et non altérées pour maintenir une performance optimum lors des activités de voltige aérienne.

Nous concluons que pour générer des réponses en lien avec l'orientation, le système nerveux central intègre les signaux vestibulaires et non-vestibulaires et est sujet à un certain niveau de plasticité en conditions sensorielles altérées. Ce traitement multisensoriel est régulé individuellement, avec un poids variable des informations vestibulaires, en fonction de l'état sensoriel et des exigences liées à l'activité.

**Mots-clés :** Système vestibulaire, orientation, intégration multisensorielle, plasticité, système cardio-vasculaire, réflexe vestibulo-oculaire, mal des transports.