



Faculty of Medicine and Health Sciences
Translational Neurosciences
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Pathophysiology and Treatment for Mal de Debarquement Syndrome

Pathofysiologie en behandeling voor Mal de Debarquement Syndroom

Thesis submitted for the degree of doctor in Medical Sciences at University of Antwerp to be defended by

Proefschrift voorgelegd tot het behalen van de graad van doctor in de medische wetenschappen aan de Universiteit Antwerpen te verdedigen door

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Antwerpen, 2018

De kandidate werd financieel gesteund door het Belgisch programma voor Wetenschapsbeleid Prodex en de Europese Ruimtevaartorganisatie (ESA).

The candidate was financially supported by the Belgian Science Policy programme Prodex and the European Space Agency (ESA).

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Figure 28: Example of the posturography recording from Healthy control and VID patients (female). The red line represents the recordings prior to the treatment and the blue line represents the recordings after the treatment. 248

List of Abbreviations:

AUC_ML	Area under the curve Medial-Lateral
AUC_AP	Area under curve Anterior-Posterior
3am 3 b	3a-hand-vestibular region and 3a-neck-vestibular region
BAI	Back Anxiety Inventory
BPPV	Benign Paroxysmal Positional Vertigo
Ca⁺⁺	Calcium
CaCO₃	Calcium Carbonate
CEA	Confidence Ellipse Area
CoP C	Centre of Pressure
CNS	Central Nervous System
CSD	Chronic Subjective Dizziness
CV	Cardiovascular
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalogram
E₂ or Est	Estrogen
EC	Entorhinal Cortex
FDG-PET	Fluorine- D-glucose integrated with computed tomography
fMRI	Functional Magnetic Resonance Imaging
HypoT	Hypothyroidism
HyperT	Hyperthyroidism
GABA	Gamma-aminobutyric acid
GIA	Gravito-Inertial acceleration
GP	General Practitioner
GPAQ	Global Physical Activity Questionnaire
HADS	Hospital Anxiety and Depression Scale
hCG	Human Chronic Gonadotropin
HPA	Hypothalamic Pituitary Adrenal Axis
Hz	Hertz Frequency
K⁺	Potassium
LH	Luteinizing Hormone
MdD	Mal de Debarquement
MdDS	Mal de Debarquement Syndrome
MISC	Misery Scale Score
MD	Ménière's Disease
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
MST	Medial superior temporal area
MT	Motion Triggered
MVS	Magnetic Vestibular Stimulation

OKN	Optokinetic nystagmus
OKR	Optokinetic Reflex
Prog	Progesterone
PCS	Post-concussion syndrome,
PCOS	Polycystic ovary syndrome
PCD	Posterior Canal Dehiscence
PDSS	Panic Disorder Severity Scale
PET	Positron emission tomography
PMS	Pre Menstrual Syndrome
PIVC	Parieto-insular vestibular cortex
Pre	Prior to
Post	After
PPPD	Persistent postural –perceptual dizziness
QoL	Quality of Life
rsfMRI	Resting-state functional magnetic resonance
rTMS	Repetitive transcranial magnetic stimulation
SD	Standard Deviation
SSCs	Semicircular Canals
SPSS	Statistical Package for Social Science
SO	Spontaneous Other Onset
SVV	Subjective visual vertical
T	Tesla
TMS	Transcranial magnetic stimulation
TSK	Tampa Scale for Kinesiophobia
TPJ	Temporo-parietal junction
V1	Primary Visual Cortex
V2	Secondary Visual Cortex
V5/MT	Middle Temporal visual area
VAS	Visual Analogue Scale
VVAS	Visual Vertigo Analogue Scale
VID	Visually Induced Dizziness
VIP	Ventral intraparietal area
VD	Vestibular dysfunction (unspecified)
VPS	Visual posterior sylvian area.
VCR	Vestibulocollic reflex
VM	Vestibular Migraine
VOR	Vestibular Ocular Reflex
VSR	Vestibulospinal reflex
VV	Visual Vertigo
VVM	Visual Vestibular Mismatch
VIII	Vestibulocochlear

Title:

Pathophysiology & Treatment for Mal de
Debarquement Syndrome

1. CHAPTER 1 INTRODUCTION:

- General introduction to the anatomy and physiology of the vestibular system
- Historical overview of dizziness

1.1 Anatomy and Physiology of the Vestibular system

1.1.1 The Vestibular System

Balance is a complex motor skill requiring fine central processing of vestibular, visual and somatosensory information to control and produce postural actions [1]. Without balance, humans normal functioning could not take place.

The primary system involved when considering balance is the sensory system. Its main purpose is to provide orientation in a three dimensional space through balance and muscle tone adaptation [2]. The vestibular system maintains the body's equilibrium in the gravitational field [3]. This system is responsible for coordinating motor responses, eye movements and posture during our everyday life activities.

The vestibular system is composed of three elements: a peripheral sensory apparatus, a central processor and a mechanism of motor output [4]. The balance system, in order to function correctly, integrates visual, proprioceptive and inner ear inputs [1]. With a precise integration of signals, this sophisticated system is able to discriminate between self and object motion, and maintains equilibrium [5].

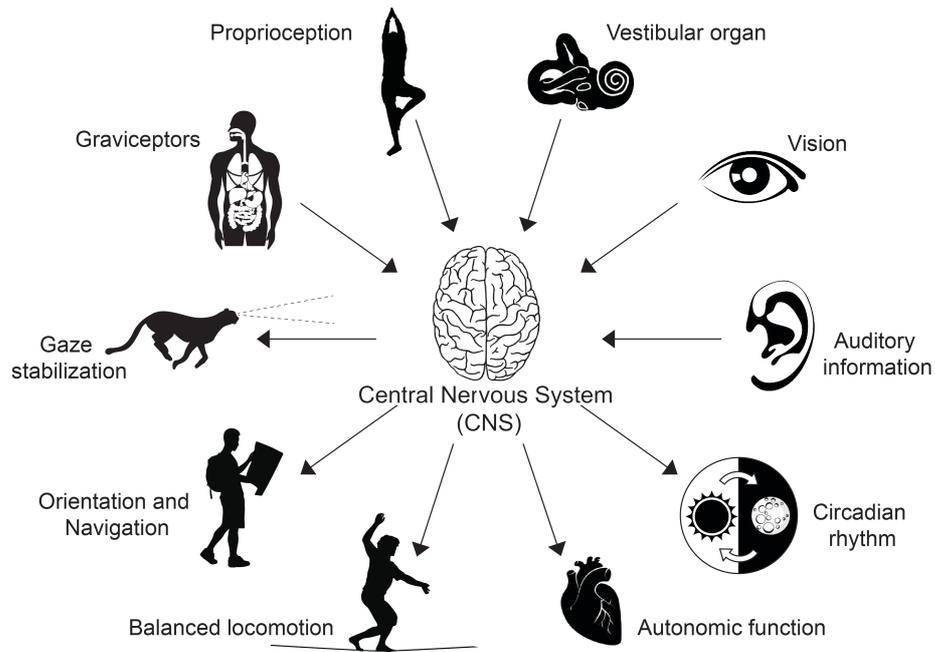


Figure 1: Schematic diagram of the integration of signals of the vestibular functions.

(Picture designed for thesis purpose)

1.1.2 Inner Ear Organs

The peripheral part of the vestibular system is located in the inner ear, it is made up of a bony and membranous labyrinth [6]. The bony labyrinth is filled with a fluid, which has a similar composition to cerebral spinal fluid named perilymph, and the membranous labyrinth contains a fluid called endolymph. The bony labyrinth consists of a spiral shaped cavity called the cochlea, an oval cavity called the vestibule and the semicircular canals (SSCs) (Figure 2). The cochlea contains the Organ of Corti, which contains mechano-electrical transduction of sound responsible for auditory processing. The receptors for detecting vestibular information are located in the vestibule and the semicircular canals, these two parts, along with the associated membranous labyrinth, make up the vestibular apparatus. The vestibular apparatus is composed of the vestibular organs, which are bilaterally present in the temporal bone, and they include three orthogonal semicircular canals (superior, posterior, and horizontal) and two otolith organs

(named the utricle and saccule) located within the vestibule [7] (Figure 2). These organs are able to provide continuous information to the brain about rotation and translational head motion as well as head orientation.

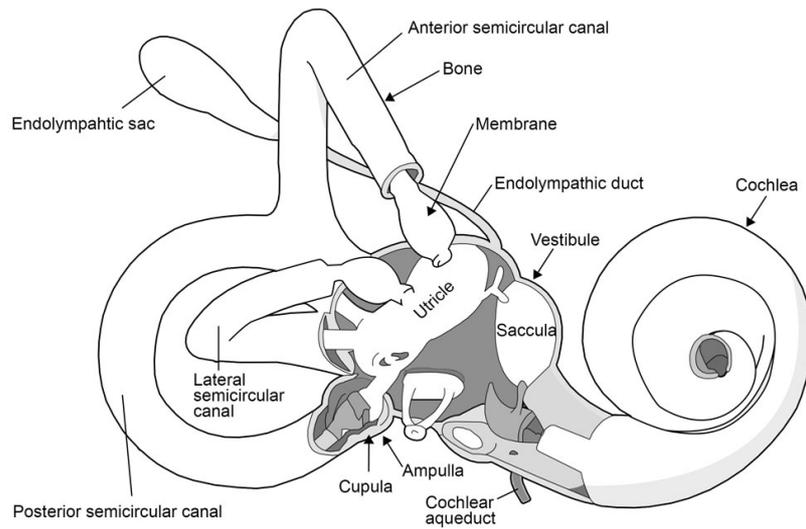


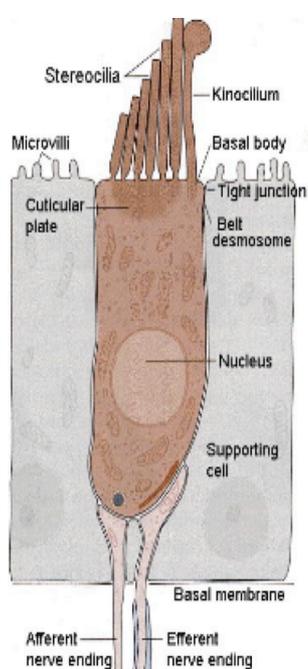
Figure 2: Anatomical representation of the inner ear. This figure shows the bony labyrinth partially removed to reveal parts of the membranous labyrinth.

(Picture designed for thesis purpose)

1.1.3 Sensory cells within the vestibular system

The vestibular system has two types of sensory neuroepithelium, the maculae and crista ampullaris. These contain sensory receptors, which detect the movement of endolymph moving through the membranous labyrinth (mechanoreceptors) named hair cells. These hair cells are embedded in a membrane of neuroepithelium.

The hair cells include a single large kinocilium and on the apical end 70 to 100 stereocilia. The latter are organised in rows from tallest, closest to the kinocilium and



they decrease in size as they get furthest from the kinocilium (Figure 3).

Figure 3: Representation of the stereocilia and kinocilium. (Picture from Hearing Journal, Canadian Audiologist, ENT News, Open Access).

The kinocilium resembles a true cilium, but it is not mobile. In contrast, the stereocilia are made up of actin rich parallel-connected filaments coated with various isoforms of myosin and they are connected to each other by the so-called "tip links". As a result, when the head moves towards the direction of the kinocilium, the stereocilia are forced to move toward the kinocilium via the movement of the endolymph. The shifting of the "tip links" causes mechanical opening of the transduction channels resulting in an influx of potassium (K⁺) ions.

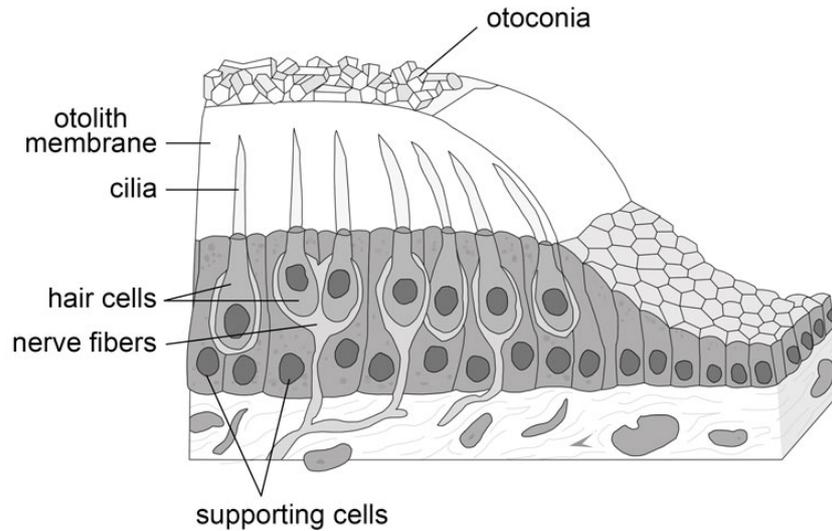


Figure 4: Schematic overview of the otolith membrane.

(Picture designed for thesis purpose)

This event induces a depolarization of the hair cell and opens calcium (Ca^{++}) channels, which triggers neurotransmitter stimulation and its release into the synapse of the vestibular nerve fibers. When moving the head in the opposite direction of the kinocilium (Figure 4), the bending of the stereocilia bends away from the kinocilium and leads to a decrease in the “tip link” tensions. This results in the mechanical closure of the channel, due to hyperpolarization of the hair cells and then there is a decrease of the neurotransmitter released [6].

1.1.4 Semicircular canals

The semicircular canals (SSCs) provide sensory input about head velocity. They sense angular acceleration or rotation of the head, and are oriented at right angles to one another. The superior and posterior ducts are aligned in a 45-degree angle to the sagittal plane, and the lateral canals are aligned in a 30-degree angle in the axial plane [6].

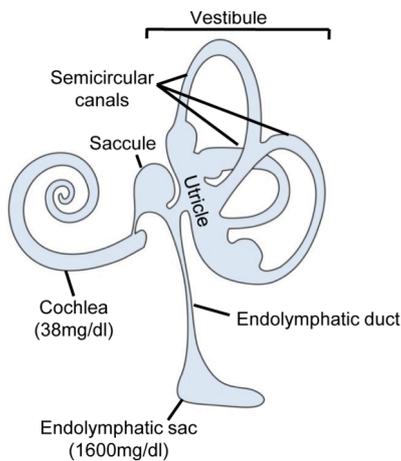


Figure 5: Representation of the semicircular canals (SSCs) within the inner ear organs [8].

In order to do so, the sensory region of the semicircular canals is located in the ampulla, an enlargement of the canal. The stereocilia of the hair cells are united in the cupula by a gelatinous mass overlying the cristae with the same density as the endolymph filling the SSCs (Figure 8). Whenever exposed to head rotation or angular acceleration, the inertia of the endolymph will result in a deflection of the cupula in the opposite direction. According to the movement either an excitatory or inhibitory action of the afferent nerve will take place. SSCs can detect rotation within a range of 0.1Hz and 10Hz but they are not able to detect rotations at constant velocity [9].

1.1.5 Otoliths

The utricle and saccule are structures of the static labyrinth (static head position, sensing linear accelerations,) that sense the orientation of the head in space and together they are part of the otolith system. Both respond to linear acceleration, gravitational forces, and tilting of the head. The sensory part of those structures is located in the sensory neuroepithelium, called the maculae. In the utricle, the macula senses motion in the horizontal plane, while the saccule, in the vertical plane [6].

Both of these organs contain a sensory epithelium, the macula, which consists of hair cells and associated supporting cells. Overlying the hair cells and their hair bundles is a gelatinous layer, and above this is a fibrous structure, the otolithic membrane, in which are embedded crystals of calcium carbonate (CaCO_3) called otoconia [10] (Figure 6).

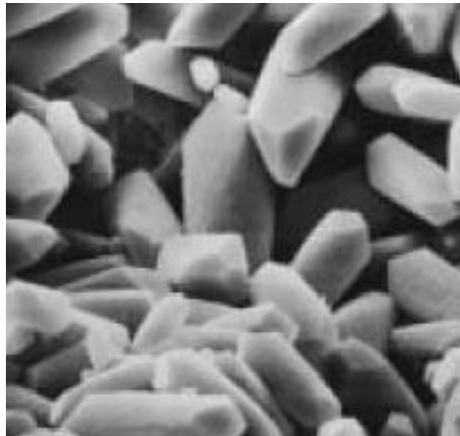


Figure 6: Representation of the scanning electron micrograph of calcium carbonate crystals (otoconia) in the utricular macula of the cat [10].

These crystals give the otolith organs their name (otolith is a Greek word for “ear stones”). The otoconia are also responsible for making the otolithic membrane more dense and heavier than the endolymph, allowing it to be sensitive to the shift of the sensory epithelium with regards to head tilts and gravity [10]. As a result, the

otoconia crystals are considered essential for the detection of linear acceleration as they shift with respect to the macula due to inertia of the endolymph. The otolith system however has a limitation, it is indeed able to only detect changes when a deflection of the hair cells occurs, as a result it cannot distinguish between acceleration and a backward tilt for example [10, 11].

1.1.6 Innervation of the peripheral vestibular organs

The Vestibulocochlear (VIIIth) nerve is the eighth cranial nerve and it is responsible for innervating the peripheral vestibular and auditory system. It contains afferent only fibres. This nerve can be divided into two parts: Nervous Acousticus (or Auditory Nerve) and Nervous Vestibularis (or Vestibular Nerve). The latter is also divided in two further parts: superior and inferior.

1.1.7 Vestibular Central Nervous System Integration

From the peripheral vestibular system, the information travelling through the VIIIth nerve are then regulated by the central nervous system (CNS) reaching the so called central vestibular system (vestibular nuclei and posterior cerebellum are the destination of vestibular primary afferents) [12]. First, they reach the vestibular neurons in the Ganglion of Scarpa, which then project to the secondary vestibular neurons. Those are located in the vestibular nuclei in the brainstem. The sensory information of balance are then projected to the cerebellum and other cortical areas, and modulated for fine-tuning [13].

The vestibular nuclei

The vestibular nuclei are considered the primary processor of vestibular input and consists of four major nuclei: medial, superior, lateral, and inferior (also named descending) [14] and at least seven “minor” nuclei. They are located below the floor of the fourth ventricle and extend from the rostral medulla to the caudal pons in two major columns. The medial vestibular nucleus is the largest and makes up the medial column. The lateral column consists of the superior, lateral, and inferior vestibular nuclei [14]. The medial vestibular nucleus receives afferents from the crista ampullaris of the lateral semicircular ducts.

The superior and medial vestibular nuclei are relays for the Vestibular Ocular Reflex (VOR). The medial vestibular nucleus are also involved in the Vestibular Spinal Reflex (VSP) and coordinate head and eyes movement[4] (more details about this specific reflex are reported in 1.1.8 section). In the vestibular nuclear complex the process of information occurs concurrently with the process of extra vestibular sensory information such as proprioceptive, visual, tactile and auditory [4].

Cerebellum

The vestibular nuclei are communicating with the vestibulo-cerebellum. The latter is the oldest part of the cerebellum [15]. The vestibular pathways previously described connect to neural centres essential to guarantee basic behavioural functions; for example, they connect with the spinal cord for body movements (vestibulo-cervical reflex and vestibule spinal reflex) and the oculomotor centres for eye movements (vestibular ocular reflex - VOR)[15].

From studies on patients with cerebellar lesions, it has now been understood that most parts of the cerebellar vermis (midline) respond to vestibular stimulation [15].

Patients with lesions of the anterior-superior vermis of cerebellum report issues with the VSR and they have profound gait ataxia with truncal instability [15].

The cerebellar projections to the vestibular nuclear complex have an inhibitory influence on the vestibular nuclear complex. The cerebellar flocculus adjusts and maintains the gain of the VOR (for more information about specific reflexes are reported in 1.1.8 section). As a result, lesions of the flocculus reduce or increase the gain of the VOR leading to greater instabilities in animal model [4]. The cerebellar nodulus adjusts the duration of VOR responses and is also involved with processing of otolith input. Patients with lesions of the cerebellar nodulus, such as those with medulloblastoma, show gait ataxia and often have nystagmus, which is strongly affected by the position of the head with respect to the gravitational axis [6].

Thus, more generally the cerebellum coordinates movements and balance and it is an essential key player to perfectly integrate the vestibular signals and producing accurate responses.

Higher levels - cortical areas

Unlike other sensory areas in the brain, like the auditory cortex or the visual cortex, there is no specific brain region allocated exclusively for the vestibular system. The vestibular cortex is spread around multiple areas [6].

A short overview of the vestibular cortical areas in humans are here reported and represented in Figure 7.

- Area 2v: responds to motion;
- Area 3a: involved in integrative motor control of the head and trunk;
- Parieto-insular vestibular cortex (PIVC): located in the posterior end of the insula [6], is relevant not only for vestibular information, but also for somatosensory and visual information, the latter generated when the

position of the body changes as well as subjected to optokinetic nystagmus (optokinetic stimuli) [16]. The PIVC plays a unique role in the vestibular cortex due to its robust response to vestibular stimuli and its dense connections with cortical and subcortical vestibular structures [17].

- Temporo-parietal junction (TPJ): this area together with the PIVC is multimodal area responding to visual motion, proprioceptive stimuli, somatosensory and motion-related inputs.
- The thalamo-cortical structures are involved and they allow the cognitive perception of motion, spatial orientation and navigation.
- Area 7: inferior parietal cortex, a major multisensory integration centre for spatial orientation and visuomotor functions [16].
- The medullary centres (e.g. formation reticularis, nuclei pontis dorsalis, nucleus tractus solitarius) facilitate the vestibule-autonomic control [18].
- Area 6 and Area 8: these are defined as the frontal eyes fields and they receive vestibular signals [13].
- Hippocampus/ entorhinal cortex: these regions contribute to spatial orientation, spatial memory and navigation [13].

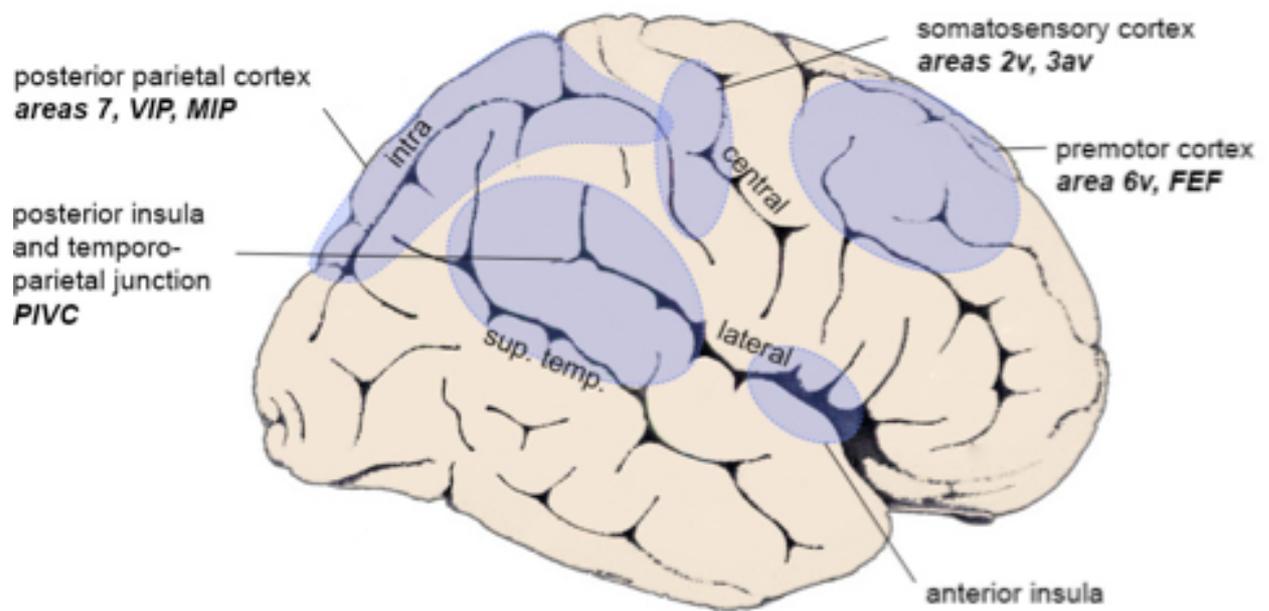


Figure 7: Schematic representation of the localization of vestibular cortical areas in humans.

Abbreviations: Areas 2v, 3a (3a-hand-vestibular region and 3a-neck-vestibular region), PIVC: parieto-insular vestibular cortex, VIP: ventral intraparietal area, MIP: medial intraparietal area, FEF: frontal eye fields. [19].

Knowledge about the vestibular cortex has greatly increased in the past years [16], however with regards to certain specific vestibular dysfunctions only recently has it been possible to comprehend the complexity of multiple interconnected areas (more relevant details with regards to this thesis are reported in section 1.1.10).

1.1.8 Vestibular Reflexes

From the central regions controlling the vestibular inputs, sophisticated reflexes are also modulated, such as the vestibular ocular reflex (VOR), the vestibulocolic reflex and vestibulospinal reflex.

The ascending axonal fibres travelling via the medial longitudinal fasciculus to the motor nuclei of the extra-ocular muscles are able to mediate the vestibular ocular reflex (VOR)[20]. The VOR generates eye movements that enable clear vision (gaze stabilization) while the head is in motion.

In addition to this reflex, the vestibulocollic reflex (VCR) and the vestibulospinal reflex (VSR) are also controlled by the central vestibular system [4, 21]. The VRC works to stabilize the head and neck and the VSR works to stabilize compensatory body movements in order to maintain head and postural stability and thereby prevent falls [4].

The integration of multisensory information from vestibular, visual, proprioceptive and somatosensory input leads to fine adjustment and the ability to adapt to different context.

1.1.9 Higher-Level Vestibular Processing – Velocity Storage Mechanism

A more sophisticated aspect of the central vestibular processing is presented here: the Velocity Storage Mechanism. This is not a reflex and requires much more processing, is generally much more accurate, and often is at least partially under conscious control [4]. Because it is a mechanism that is more modifiable than the vestibular reflexes, this is especially relevant to rehabilitation. The VOR ensures that the images in the retina are kept stable while the head is moving. When the head is rotating, the direction of the eyes has to be exactly opposite to that of head

movement. When this happens, the ratio of eye movement is named 'gain' and it is equal to -1. In addition, to maintain a stable image and guarantee normal vision, the retina motion must be less than 2°/sec. As a result the VOR has to be 98% accurate at all times to ensure vision [4]. However, the VOR is able to perform only with high frequency head motion but not with low frequencies. An example is seen when rotating and engaging the SSCs, the exponential decay of firing of the vestibular nerve has a time constant of around 7 seconds, which appears to not be long enough to be processed by the CNS. To continue the preservation of this input the Velocity Storage Mechanism is activated in the brainstem [4]. This mechanism processes multiple sensory inputs.

The Velocity Storage Mechanism is used as a repository of information about head velocity derived from any type of motion. For example, during rotation the vestibular nucleus is supplied with *retinal slip* information. Retinal slip is described as the difference between eye velocity and head velocity. The retinal slip can drive the Velocity Storage Mechanism and keep the vestibular related responses continuing. Somatosensory information can also influence and affect the Velocity Storage [22].

1.1.10 Main brain areas relevant for this thesis

The Entorhinal Cortex

The entorhinal cortex (EC), situated in the mesial temporal lobe anterior to the hippocampus [23], is one of the key areas in processing and transfer information [24]. The EC plays a role in vestibular memorization by receiving information from associated cortical areas and transmitting the information to the parahippocampal cortex, where they are then projected to the hippocampus. In 2005, in rats, it was discovered that the EC also contains a neural map of the space

environment. John O'Keefe, Maj-Britt Moser and Edvard Moser received the Nobel Prize in 2014 for this discovery.

More specifically, the medial entorhinal cortex receives highly processed spatial information from a broad swath of the neocortex, firstly from somatosensory association cortex, and perirhinal cortex, but with important connectivity to the medial prefrontal cortex and the amygdala [23]. This area is the principal gateway of neocortical information entering the hippocampus [23].

Within this area the so-called "Grid cells" respond to the subject location in the environment. With them also the "Border cells", which are expressing the person's proximity to geometric borders, the "Speed cells", reflecting the running speed of the subject, and the "Head direction cells", providing the orientation relative to landmarks in the environment are providing information about the self-position in space [25]. These cell classes are clearly distinguishable from one another, and cells never switch from one class to another [25]. These cells are responsible to provide to encode information about the current context of movement [25].

Vestibular system and the limbic system

Emotions are aroused state of mind, generating intense feelings, leading to autonomic and behavioural changes [26]. It is known that the vestibular system is able to influence emotions and it was been used therapeutically, such as the use of spinning chair to treat mania or elevated arousal in the nineteenth century [27].

While vestibular dysfunction are well known to affect mood, which results in a high number of vestibular patients being affected by depression or anxiety [28].

The vestibular nucleus are able to act as a relay station between the peripheral and central nervous system [26]. Experience and behavior are two major factors, which can influence emotions, and the cerebral cortex plays a critical role in

mediating these emotions [26]. Both superior and lateral vestibular nuclei have axons networking the ventral posterior nuclear complex of the thalamus, which projects to two cortical areas relevant to the vestibular sensation [26]. Thus, the pathways between the networking of the vestibular nuclei and the limbic regions involved with emotions are real and most likely connected with the networks of chemical (dopamine, serotonin, acetylcholine, and norepinephrine), acting as modulatory systems [26]. These links between the vestibular nuclei and the limbic regions is extremely relevant when assessing vestibular patients, given the high number of vestibular patients developing secondary mood disorders, as well as reporting cognitive impairment and emotional symptoms [28, 29].

The amygdala

The amygdala is another crucial area, which is involved with the emotional status of vestibular patients. The amygdala is the integrative centre for memory, emotions, emotional responses, emotional behaviour and motivation [25]. It is located in the deep and medially within the temporal lobes.

In addition to this, the amygdala plays a pivotal role in mediating the effects of stress on the consolidation and recall of memories, thus stress exposure can induce abnormal amygdala activations [30].

1.1.11 Relevant Eyes movements

Nystagmus

Nystagmus is defined as involuntary movement of the eyes. There are two fundamental types of nystagmus spontaneous (occurs without any provocation) and evoked (e.g. you have to do something to observe it) [31].

Optokinetic Nystagmus

The term optokinetic is used to indicate visual inputs able to induce a slow or fast phase optokinetic nystagmus response. Optokinetic nystagmus (OKN) is the eye movement elicited by the tracking of a moving field. It differs from smooth pursuit which is the eye movement elicited by tracking of a single distinct target, as the OKN involves multiple targets. As a result, usually the OKN performance (gain - ratio of eye tracking velocity to target velocity), exceeds that of smooth pursuit [32]. Nystagmus and optokinetic nystagmus are essential components of many diagnostic and treatment outcomes when dealing with vestibular disorders.

The vestibular system with its varied components ensure accurate processing of sensory input about rapid head and postural motion which are critical for functioning in a three dimensional reality and critical to survival.

Vection

When we are exposed to a visual motion field that simulates the retinal optical flow generated by our movement, we often perceive subjective movement of our own bodies. This phenomenon is called vection [33].

Vection refers to the perception of self-motion induced by visual stimuli. Several stimulus attributes are known to affect the subjective strength or direction of vection, i.e. stimulus size [33]. For example, the magnitude of vection increases with

an increase in stimulus size. Eccentricity has also been investigated as a determinant of vection. An example of naturally occurring vection is experienced while seated in a train and watching another train moving on an adjacent track. The stationary observer in these cases experiences a very compelling sensation of self-motion based solely on visual information [33].

1.1.12 Relevant Hormones presented in this thesis

Within certain vestibular disorders a female preponderance has been noted [34, 35]. As a result, within the scope of this thesis gonadal hormones were investigated. Consequently, this introductory section aims to provide a brief overview on the female principal steroid hormones regulating women reproductive life and provide the readers with more content outside of the vestibular system.

Female hormones are responsible for the physical changes of puberty, the menstrual cycle, the changes of pregnancy, and milk production for nursing. The end of their production results in a period of reduction of gonadal hormones named perimenopausal, until reaching the full cessation named menopause [36].

The principal hormones (ref for this section: [37]):

- *Oestrogen (Estrogen - E2)*: female reproductive hormone, produced primarily by the ovaries in the non-pregnant woman. It promotes the maturation and release of an ovum, (also known as an oocyte, female gamete, or egg), in every menstrual cycle. The placenta also produces it during pregnancy. Estrogen have been found to be relevant to modulate learning and memory of spatial navigation [38]. Estrogens have been also implicated in the pathophysiology of migraine [39].
- *Progesterone*: produced by the corpus luteum in the ovary; its function is to prepare the endometrium (lining of the uterus) for the reception and development of the fertilised ovum. It also suppresses the production of oestrogen after ovulation has occurred.
- *Gonadotropin-releasing hormone (GnRH)*: produced by the *hypothalamus*. When it circulates in the blood, it causes the release of gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) from the *pituitary gland*.

- *Follicle-stimulating hormone (FSH)*: produced by the pituitary gland during the first half of the menstrual cycle (follicular phase). It stimulates development of the maturing ovarian follicle and controls ovum production in the female, and sperm production in the male.
- *Leutenizing hormone (LH)*: similarly produced by the pituitary gland in the brain. It stimulates the ovaries to produce oestrogen and progesterone. It triggers ovulation, and it promotes the development of the corpus luteum.

The ovarian cycle

Every month women during their reproductive years are subjected to a series of events in the ovaries, associated with maturation and release of an ovum. The ovarian cycle consists of two consecutive phases, each of about 14 days. The first day of the menstrual cycle is intended as Day 1 of the menstrual period.

- *Follicular Phase (proliferative phase)*: this phase goes from Day 1 to 14 of the menstrual cycle. The GnRH is secreted in the hypothalamus, which stimulates the ovarian follicles to complete the ova maturation. During this period, a few ovarian follicles, containing immature ova, develop and mature under the stimulation of the FSH and LH. Two or three days before LH levels begin to increase, usually by day seven of the cycle, one or occasionally two of the recruited follicles emerges as dominant. In addition, the high estrogen levels characterising this phase, initiate the formation of a new layer of endometrium in the uterus. The vaginal secretions are then adapted to create a more hospitable environment for sperm. In addition, basal body temperature may lower slightly under the influence of high estrogen levels. Ovulation normally occurs 30 (\pm 2) hours after the beginning of the LH surge (when LH is first detectable in urine) [40].

- *Ovulation*: phase in which a mature ovarian follicle ruptures and discharges an ovum.
- *Luteal Phase*: this period goes from Day 15th to 28th of the menstrual cycle. If pregnancy doesn't occur after ovulation, the corpus luteum begins to secrete progesterone, as well as a small amount of estrogen. The hormones produced by the corpus luteum suppress production of the FSH and LH and the corpus luteum goes into atrophy. The death of the corpus luteum results in falling levels of progesterone and estrogen. This in turn causes increased levels of FSH, leading to recruitment of follicles for the next cycle. Continued drops in estrogen and progesterone levels trigger the end of the luteal phase, which culminate with menstruation, and the beginning of the next cycle [37].

1.2 Historical review on Dizziness

Vestibular symptoms in individuals have been recognised for thousands of years. Soranus of Ephesus (AD 98 – AD 138), one of the greatest physicians of classical times, was able to recognise acute and chronic vestibular conditions. A translation of his work named *Tardarum Passionum from Caelius Aurelianus* describes symptoms such as scotoma and triggers from moving stimuli [41].

“The disease is aggravated if the patient watches the flow of a river from a high point, or gazes at the potter's wheel or does anything when bending forward”.

Later in the 6th century, the famous physician Galen recognised that vertigo could be brought on by being “whirled around in a circle” and could be present also in absence of movement [42]. Already at the time, great subject inter-variability was noted as well as the many nuances of dizziness.

From antiquity to now, the understanding of vestibular disorders has increased and in the 17th century dizziness became accepted as a brain disorder. In 1825 the physiologist Flourens published his work [43]. At the time, accumulating body evidence led to the conclusion that vertigo could be generated from the ear and from the vestibulocochlear nerve. However the understanding of inner ear functions remained unclear until the work of Prosper Meniere, published in 1981 [43]. In the population assessed by Meniere, patients were not reporting signs of central deficits and the idea of the involvement of the semicircular canals in the pathophysiology of certain types of vertigo was raised. Barany, one of the founding scientists of the vestibular field, was able to prove that vertigo may be a result of inner ear dysfunctions.

Throughout the 20th century with the increase of vestibular testing and patient observation, multiple factors of complex vestibular disorders were understood. For example, the role of vision in balance started in 1935 with Koffka [42]. He stated after observing agoraphobic behaviours in vestibular patients: "lean on our eyes as we do with our feet" and "as we do without hands". This was the first time balance and multiple sensory integration were united.

2. CHAPTER 2 THESIS TOPIC INTRODUCTION:

- Introduction of Thesis Topics and Project Objectives

2.1 Thesis Topics

Abstract

This thesis focuses on a relatively unknown and poorly understood neurological disorder, named Mal de Debarquement Syndrome (MdDS). This condition is characterised by a constant sensation of motion, present also when the patient is not moving, which in most cases is triggered by a first exposure to passive motion [44]. Inexplicably, MdDS seems to be gender driven, with a great majority of female patients affected by this disorder. MdDS pathophysiology remains unclear despite a few hypotheses having been formulated, thus therapeutic interventions and patient management remains limited and poor.

The current research project focused on evaluating this disorder closely from an epidemiological and diagnostic perspective. Given the great gender imbalances, a close evaluation of potential hormonal components affecting MdDS is also undertaken here. In addition to this, one of the few treatment options for MdDS, based on optokinetic stimulation, is further examined. Lastly, an evaluation of MdDS patient's comorbidity with Visually Induced Dizziness is also reported and a series of further studies are suggested.

2.1.2 Mal de Debarquement Syndrome (MdDS)

Mal de Debarquement (MdD) is French for “*sickness of disembarking*”. This phenomenon has often been observed in or experienced by many healthy subjects [45], whenever disembarking from a vehicle. It is usually a temporal sensation of self-motion (e.g. phantom feeling of rocking or swaying side to side), which can last from a couple of hours up to a few days [44]. One of the earliest reports of MdD may be from Hippocrates when he wrote that sailing on the sea showed a motion disorder of the body. After him, Irwin, in 1881, was the first to note that after disembarking from a ship, an adaptation to ship motion would remain when returned to land [45]. In today's society, with the increased usage of different types of vehicles as transportation, we know that different exposures to passive motion are able to induce temporal MdD; for example after being on land, sea or air trips (e.g. car ride, cruise, flight or a combination of vehicles) [46, 47].

However, when symptoms are prolonged for more than a month from the onset time, MdD is defined as a pathological condition and it is then named as Mal de Debarquement Syndrome (MdDS) [21]. Although this definition can be considered incomplete, as it does not include the other form of MdDS, named non-motion triggered (non-MT) MdDS [48] or spontaneous MdDS [49], where symptoms are developing spontaneously or following a non-motion event.

MdDS was recognised as a clinical condition only in 1987 [45], therefore, it can be considered as a relatively new disorder. Despite the growing interest in this topic in the past decades, many questions remain to be addressed. MdDS patient characterization and consequently clear diagnostic criteria are not yet internationally validated and overall epidemiological data is limited. MdDS pathophysiology is not fully understood, consequently patient management and

available treatments are also limited and poor. What has been recognised about MdDS sufferers is that most of them developed the onset during the 5th decade of life, thus between 40 to 50 years [49, 50] of age. Additionally, an inexplicable female predominance has been reported in numerous studies [21, 50].

2.1.3 MdDS onsets groups

With the current increase in research, it is now clear that MdDS has multiple types of onset, despite a clear classification of onset types remains unclear and under discussion. MdDS seems to be primarily triggered by the exposure to passive motion, for example being on a boat, or after a flight or being on multiple vehicles. In those cases, MdDS is referred to as Motion Triggered (MT) MdDS. It is important to note, that symptoms, do not start immediately after disembarking but they occur in most cases after a night of sleep [49].

In addition to the MT MdDS, a less common and less acknowledged form of MdDS has now been recognised [49]. This form occurs without any clear motion event, this type of onset is referred to as Spontaneous MdDS or non-motion triggered onset [51]. Although there might be a better term than spontaneous MdDS or SO MdDS to describe the non-motion triggered [48] nature of MdDS, this term has been used in the following manuscript [21]. Within this category are also included the MdDS patients who report MdDS symptoms after non-motion (other) events such as, surgery, childbirth, etc., are also included. These patients can be referred to as Other onset MdDS. Together, the two groups are termed as Spontaneous/Other onset (SO) MdDS. In this thesis, the two main onset groups are going to be considered and referred to as:

- a) Motion Triggered (MT) MdDS;
- b) Spontaneous / Other (SO) MdDS;

At this stage, MT and SO appeared to share the same symptomatology features and only a few differences have been reported, such as a higher prevalence of migraine in the SO group [51] and a difference response to therapeutic intervention [51, 52]. However, a clear comparison between the two has never been attempted.

2.1.4 Symptomatology

The most distinguished symptoms characterising MdDS patients is a persistent sensation of internal motion (equally for MT and SO patients), also described as a self-motion feeling [53]. Patients can often described symptoms changes from mild to serious within 24 hours [47]. Despite symptoms are known for fluctuating from higher to lower levels throughout the day, they are considered to be constant [54], which clearly distinguishes MdDS from occasional episodes of vertigo. The self-perception of motion is often described as phantom motion, this does not always manifest in a tangible postural instability. The patient's sensations are described as a rocking (forward and backward), swaying (side to side) or bobbing (up and down) sensation. In some cases, the patients are able to describe one main direction of swaying or bobbing clearly and to report a clear associated physical postural instability [55]. This has been also named gravitational pull toward one side or another [52]. In other cases patients are reporting a more phantom perception of motion without being able to clearly indicate a main direction of movements [47].

However, aside from the perception of internal movements, MdDS patients also report a myriad of other symptoms such as: migraine, cognitive impairment, brain fog, secondary mood disorders [21]. Another typical distinguishing feature for MdDS sufferers is the temporary relief of symptoms when re-exposed to passive motion (e.g. as when passenger in a car) [21]. This unique feature characterise both onset groups (MT and SO) [21].

2.1.5 Epidemiology – Psychological and Social impact of MdDS

MdDS is currently considered a rare disorder [44], but perhaps this definition is inappropriate as currently the exact number suffering from this condition is not known, owing to the high number of misdiagnosed patients [56]. In the study of Clark [57] and in the review of Van Ombergen [58], many cases of MdDS had been reported to be misdiagnosed as other vestibular or psychiatric disorders, often because the relevant clinical history of the motion trigger has not explicitly been sought or due to the lack of awareness among physicians [56, 58]. The long period of duration also between onset and diagnosis can be considered as one of the important factors contributing to the debilitating effect and mental health consequences observed among MdDS patients [59, 60]. The lack of internationally recognised diagnostic criteria has delayed patient's diagnosis, and as a result, led to poor patient management. Thus, MdDS is considered a debilitating condition with a high level of intrusiveness and with associated psychological impact on a patient's mental health [55]. In a previous study by Macke [56], it was reported that on average an MdDS patient goes through 19 visits to different healthcare professionals before receiving an MdDS diagnosis. As a result, MdDS sufferers spend significant time, energy and money trying to be diagnosed and treated [49]. Consequently, MdDS is considered to have a relevant socio-economic burden [56].

In a retrospective study, 101 MdDS patients were examined and it was found that the condition negatively impacts their quality of life as well as imposing economic burdens for the patients and the healthcare systems, of roughly \$ 2997 (US Dollars) per patient [56].

Due to the delay in receiving a diagnosis and the poor recognition of the syndrome, high levels of depression as well as of anxiety are often observed in MdDS suffers [47, 49]. In the study of Clark [55] MdDS patients reported kinesiophobia (i.e. fear of movement [61]), high levels of fatigue and depression. Other vestibular patients are also known to be significantly affected by anxiety and secondary mood disorders [62]. Potentially anxiety traits may develop as the patients try to control themselves against the vertigo or imbalances [62]. As previously mentioned, some MdDS patients are also affected by tinnitus [47], which is known to negatively impact patients mental health [63].

2.2.1 Pathophysiology of MdDS

The pathophysiology of MdDS is currently considered unclear [44]. Two main theories have been developed based on neuroimaging and experimental observations. At this stage it remains ambiguous if these two theories may be interrelated.

2.2.2 Theory 1 - Abnormal Functional Connectivity

One theory has been developed following neuroimaging and neuromodulation studies on MdDS patients pathophysiology [64, 65] and the principal investigator of the majority of these studies is Dr. Cha. These findings led to one of the most recognised hypotheses for MdDS pathophysiology, where MdDS is described as a disorder of abnormal functional connectivity, driven by a central neural oscillator that becomes entrained during periodic motion exposure [54]. This central oscillator drives widespread cerebral connectivity and can toggle between high and low states [49]. These alterations are believed to be responsible for symptom fluctuations [49]. Over the last decade, neurological studies have included functional magnetic resonance imaging (fMRI), 18F-fludeoxyglucose positron-emission tomography (18F-FDG-PET) scans and electroencephalogram (EEG) in the attempt to unravel the underlying neural basis of MdDS [23, 64, 66, 67]. Resting-state fMRI (rsfMRI) studies have shown an increased functional connectivity between the left EC/amygdala and visual / vestibular processing areas, in the result of a decreased connectivity in multiple prefrontal areas [23].

Reported in Table 1 the key studies related to neuroimaging and neuromodulation assessed in MdDS subjects.

Key studies related to Theory 1	Subjects	M/F	Mean Age (SD) Years	Main Findings
Cha et al 2012 [23]	n= 20	5 M; 15 F	43.4 (2.5)	<i>Association between resting state metabolic activity and functional connectivity between the entorhinal cortex and amygdala.</i>
Cha et al 2013 [68]	n=8	0 M; 8 F	47.5 (15.2)	<i>Neuromodulation- rTMS on DLPFC tolerated in subjects with MdDS- short-term symptoms improvement.</i>
Ding et al 2014 [67]	n= 10	0M; 10F	47.6 (10.7)	<i>Quantify the neural changes after the DLPFC rTMS stimulation, through rsEEG.</i>
Pearce et al 2015 [69]	n= 66	4M; 62F	52.1 (12.2)	<i>Reproduce the study of Cha on MdDS subjects for 3 days instead of multiple days as proposed by Cha. DLPFC rTMS stimulation showed promising results with reduction of motion.</i>
Cha et al 2015 [64]	n=28	5M; 24F	43.0 (10.2)	<i>MdDS subjects reported changes in brain volume compared to healthy controls. Brain areas such as the vestibular visual processing areas were reporting abnormal functional connectivity.</i>

Table 1: Summary of the key studies related to neuroimaging and nuerostimulation, Theory 1.

Abbreviations: n= number of subjects, M=Male, F= Female, SD= Standard Deviation, MdDS= Mal de Debarquement Syndrome, rTMS= repetitive Transcranial Magnetic Stimulation, DLPFC = dorsolateral prefrontal cortex, rsEEG= resting state electroencephalogram.

In the study conducted by Cha in 2012, with FDG-PET a baseline changes in brain glucose metabolism was assessed and MdDS patients were compared with age- and sex-matched controls. For the first time, MdDS patients were found to report a hypermetabolism in the left entorhinal cortex (EC) and amygdala [23].

The EC area is known to play a key role in mapping one's spatial environment [70] while the amygdala, together with the hypothalamus, serves to reorient attention to functionally relevant internal and external stimuli [23]. Within the same study, it was also reported the involvement of the amygdala activity, which was in line with the EC influence over the amygdala activity. In another study from the same team of researcher, using structural MRI, it was found that in the left middle frontal gyrus,

a region of the dorsolateral prefrontal cortex (DLPFC), brain volume decreased [23, 65]. The DLPFC is an important pathway in cognitive control over spatial information processing and spatial working memory [44], thus this indicates that both cognitive and emotional networks were affected in MdDS subjects [65]. From these observations the DLPFC area was also chosen to be a target area in a pilot study for a treatment based on repetitive transcranial magnetic stimulation (rTMS) [68] (more details are reported in the treatment section 2.4.2.).

In another study, through voxel base morphometry analysis [64], it was possible to observe that MdDS patients exhibit alterations in grey matter volume in visual-vestibular processing areas, such as area V5 of the visual cortex, a critical area for the perception of visual motion [71] and Middle Temporal (MT), an area considered the hub of visual motion processing [64, 71] also in default mode network (e.g. cingulate cortex), in the somatosensory network (e.g. postcentral gyrus), involved with pre-motor cortex [49] and in the central executive network DLPFC. The enhanced functional connectivity between V5/MT and the EC suggested that there may be enhanced transfer of motion information to the EC from V5/MT or that motion information from V5/MT can more efficiently drive EC activity with time in MdDS patients [64]. As a result from these studies, MdDS pathophysiology is considered as a disorder of functional connectivity, where the EC area has been suggested to have a pivotal role [49].

2.2.3 Theory 2 - Vestibulo-ocular Reflex Maladaptation

The second main theory regarding MdDS pathophysiology is based on the Vestibular Ocular Reflex (VOR) and velocity storage adaptation. This theory has been formulated [53] by Dai and colleagues and it primarily derives from animal research in subhuman primates [72].

The relevant work about this theory is presented in Table 2, where the key papers are briefly described.

Key Studies related to Theory 2	Subjects	M/F	Mean Age (SD) Years	Main Findings
Dai et al 2014 [53]	n=24	3M; 21 F	42.0 (8.8)	<i>OKN stimulation reduced MdDS symptoms in 70% of the participants</i>
Dai et al 2017 [52]	n=141	22M; 119F	49 (13)	<i>1-year follow up after patients being exposed to the same protocol performed in 2014, reduction of success rate from 70% to 42%.</i>
Cohen et al 2018 [73]	X	X	X	<i>Theory and review of the potential mechanism involved in the optokinetic treatment</i>

Table 2: Summary of the key studies related to VOR maladaptation Theory 2.

Abbreviations: n= number of subjects, M=Male, F= Female, SD= Standard Deviation, MdDS= Mal de Debarquement Syndrome, OKN= Optokinetic.

This theory suggests that MdDS results from mal-adaptive coupling of multiplanar information of the (VOR). The VOR ensures gaze stabilization during rotation of the head around three axes (i.e. yaw, pitch and roll). Each of these VOR components is subject to contextually dependent adaptation. VOR adaptation can occur across different axes [74] and it is controlled by the velocity storage. This contextual VOR adaptation may be long lasting [75] and is the basis for suggesting VOR maladaptation as an underlying mechanism in MdDS [52]. This theory hypothesises that MdDS patients are failing to readjust to a new stable context due to the information retained by the velocity storage mechanism [22, 76], while subjected to passive motion. This could suggest that cross-axis-coupled stimuli have the ability to alter the velocity storage mechanism of the VOR. From previous animal studies [77, 78], it is now possible to understand that the velocity storage is not only critical for spatial orientation with regard to gravity, but it can be modulated during habituated repeated rotations. Thus, the velocity storage also serves as an input to

the sympathetic nervous system and can be modulated by shortening the VOR (velocity storage) time constant. Those studies, have been for example implemented when reducing patients' subjective motion sickness stimuli [77]. Within this theory and observations, it has been hypothesised that the changes in velocity storage may be responsible for the postural instability, induced primarily by prolonged travel on water [53]. Interestingly, of particular significance, is the fact that MdDS patients have been reported to physically move (rocking or swaying) at a frequency of 0.2 Hz, showing that the velocity storage integrator not only is associated with spatial orientation, eye movements and activation of the sympathetic system, but also with descending vestibulo-spinal projections that are associated with strong postural instability as reported in some cases for MdDS patients [77].

Are theory 1 and theory 2 interrelated?

The two theories presented may not be mutually exclusive. The VOR coupling may be a brain manifestation of the brain-step, with resulting cortical changes altering functional connectivity. However, this remains to be empirically shown. In addition to this, the two-onset type may underlie pathophysiological differences that remain to be explored and addressed.

2.3.1 Extra factors to consider

2.3.2 MdDS and Migraine

MdDS patients have a high prevalence of migraine compared to the general population [44]. In addition, SO patients have been reported to have a higher history of migraine compared to the MT patients [59].

Similarly MdDS and migraine both have a high number of female patients [79, 80]. Before puberty, migraine is known to affect males and females equally, however a 20% increase of migraine attacks is reported in females after menarche [79], indicating a clear relation between female hormones and migraine.

To date, it is still unclear if a similar hormonal influence may be present for MdDS patients. Migraine in both MdDS onset groups seems to increase after MdDS onset, as a result it has been previously suggested that migraine and MdDS might have a pathophysiological overlap [49, 51]. Because of this potential overlap between migraine and MdDS, migraine medications have been trialled as an intervention for MdDS [49], of which more is discussed in the treatment section (Section number 2.4.5).

2.3.3 Motion Sickness and MdDS

Several studies have investigated if MdDS patients were more prone to suffer from motion sickness prior to their MdDS onset [21]. A previous study assumed that the relationship between entities is based on the underlying problem of both conditions to adapt to their contextual environment [81]. Motion sickness, similarly to migraine, appeared also to be subject to hormonal influences in female patients [82], however up to now, it is still unclear if a similar influence affects MdDS patients. Additionally, it is

still not clear how many MdDS patients with spontaneous onset may be suffering from motion sickness and what relation between these two phenomena there could be.

2.3.4 Visually Induced Dizziness in MdDS patients

MdDS patients seem to report heightened visual motion sensitivity [49, 52]. In those cases, it is assumed that they are experiencing Visual Induced Dizziness (VID), which literally means that visual stimulation such as computer screens, optic flow and visual motion in general can trigger dizziness [83].

As in numerous vestibular disorders when the integration or compensation at the central level is not appropriate, patients become extremely reliant on visual inputs, developing high visual field dependency [84]. In most cases this visual dependency develops in patients with a distinct peripheral vestibular disorder, however it is now clear that it can also develop in patients with central vestibular pathologies such as vestibular migraine, or MdDS [85].

Despite a clear indication of the presence of VID symptoms in MdDS patients, no study has ever been done to further explore therapeutic intervention, which addresses MdDS patient's visual sensitivity.

2.4.1 Treatment Currently Available

At this stage there is no clearly established treatment option for MdDS sufferers of either onset group. However experimental treatment options have been investigated in recent years. A summary of some treatment interventions are reported below.

2.4.2 Treatment Based on Theory 1

Neuroimaging studies have led to the implementation of non-invasive brain stimulation as a therapeutic strategy for MdDS [66]. Specifically, repetitive transcranial magnetic stimulation (rTMS) over the left prefrontal cortex (DLPFC) [65]. Transcranial magnetic stimulation (TMS) has proven to be an important neural stimulation tool in investigating the pathophysiological bases of neurological and psychiatric conditions [65]. In several cases MdDS is used to modulate cortical excitability, using facilitator high- frequency stimulation (to excite) (≥ 5 Hz) or inhibitory low-frequencies (≤ 1 Hz) [66]. TMS effects results in not only affecting the specific areas stimulated, but also in inducing anatomically and or functional connected site changes [66]. The effects of TMS in remote cortical structures are of therapeutic interest, since deep brain and certain neocortical structures that exhibit more individual variations are difficult to accurately and efficiently target with surface stimulation. In addition to this, repetitive TMS (rTMS) seems to be able to induce long-lasting effects [66]. Thus this technique was chosen as a potential treatment tool for MdDS patients. Particularly rTMS were performed on the DLPFC area. The DLPFC area is not only relevant for MdDS patients, but has been widely used to enhance baseline functional connectivity in other disorders, such as depression [67, 69, 86].

It was thought that rTMS directed at the DLPFC could influence multiple interconnected networks related to mood as well as cognition and visual-spatial processing [49, 65]. Promising results were reported among 4 of the 8 total participants for a sham controlled study. They reported mild to great improvement of symptoms and little sham effect [49].

However, this treatment is currently being trialled by a relatively small number of patients worldwide (unpublished Canceri et al 2018). As a result it remains unconfirmed if this could offer a substantial therapeutic intervention for MdDS patients.

2.4.2 Treatment Based on Theory 2

Based on theory 2 another treatment method was created. In theory 2 MdDS was believed to be the result of a maladaptation for the VOR and velocity storage. As a result a “*recalibration*” of the VOR by passive exposure to optokinetic stimuli was hypothesised to be effective in restoring the VOR and reducing MdDS symptoms [53]. Optokinetic stimuli are known to have an effect on the VOR, by inducing an optokinetic response, which indirectly modulates the VOR [52]. This treatment not only involves the exposure to optokinetic stimuli, in the form of vertical stripes rotating right or left or horizontal stripes moving up and downwards, but also includes head motion of the patients while watching the moving stripes [53]. The subjects' heads is rolled $\pm 20^\circ$ at their rocking frequency by the researcher [53]. The combination of head roll and optokinetic stimuli is believed to be responsible for inducing the changes in the VOR and velocity storage mechanism. This approach is based on personalised stimuli. The optokinetic stimuli and the head roll are adjusted to the patient's internal oscillation perception which is measured by posturography and Fukuda Step Testing [53]. The treatment was first assessed in 24

patients in 2014, where 70% of patients reported an improvement of symptoms, which lasted up to roughly 11 months after the exposure [53]. In 2017 the same group published the follow up data, where a larger sample of patients were assessed [52]. Overall they included 120 MT and 21 SO patients and evaluated how their subjective feelings may have changed a year after the exposure to the treatment. A significant reduction in their success rate was then reported in the follow up study, which dropped from 70% to 42% [52]. The same researchers also reported a higher success rate among the patients from the MT group, when compared with the SO onset subtype. This indicates that the two onset groups should be closely evaluated and further studies should explore more in depth potential differences with regards to treatment response.

2.4.3 Pharmaceutical therapies for MdDS

These experimental treatments involving neuromodulation or recalibration of the VOR are not easily implemented in a clinical practice. As a result, additional treatments involving medication have been trialled by medical professionals to ease MdDS patients' symptoms. A series of studies and data indicating the most trialled medications used for MdDS patients are summarised below.

2.4.4 Antidepressant Drugs

From the literature the use of pharmaceutical agents is described in several studies. In particular, benzodiazepine and selective serotonin re-uptake inhibitors have been described as able to alleviate MdDS symptoms [44, 59, 80].

It has been reported that there is general consensus that benzodiazepines provide the best symptomatic relief, with clonazepam being favoured for its longer half-life

[47, 80] and a dose between 0.25 mg twice daily to 0.5 mg twice daily has been reported to be the mostly widely used by practitioners [47]. It has also been indicated that higher doses are not more effective.

Hain performed a survey analysis of 27 patients with MdDS and noted that benzodiazepines were of most benefit in symptom reduction [60]. However, MdDS symptoms are never completely relieved with benzodiazepines, but overall patients have reported an overall increase in balance function [47]. The main associated risks to such pharmaceutical intervention are the quick dependency and sedation, which are often reported [50]. Selective serotonin reuptake inhibitors (SSRIs) have also been reported to be helpful in treating MdDS patients [47, 51].

2.4.5 Treating MdDS as Vestibular Migraine

Given the high prevalence of migraine, migraine medications have been trialled to ease MdDS complaints. In the study by Ghavami [80] it has been noticed that management of MdDS as vestibular migraine could improve the patients' symptoms and increase quality of life (QoL). In Ghavami's study, nearly all the patients suffering from MdDS had a personal or family history of migraine headaches or had signs or symptoms suggesting an atypical form of migraine [80]. Thus, this study described that apply migraine medications and implement life style changes involving social and psychological aspects, could help MdDS subjects, as often observed for migraine subjects [80]. However the sample size assessed by Ghavami and colleagues was relatively small and a larger study cohort is needed to reconfirm these results.

Pharmacological treatment of the patients also involved prophylactic medical therapies that have been found to be highly effective in the management of migraine such as tricyclic antidepressants (e.g. nortriptyline), anticonvulsants (e.g.

topiramate), and calcium channel blockers (e.g. verapamil) [80]. It is still unclear if some of these drugs as for example calcium channel blockers are really beneficial for MdDS symptoms or rather help to ease stress in these patients, ultimately resulting in an improvement of the subjects' wellbeing. In addition to this, Hain [50] also reported that gabapentin, amitriptyline, and venlafaxine alleviate MdDS symptoms, those are all medications often used in migraine patients.

2.4.6 Vestibular Rehabilitation in MdDS

As for many vestibular disorders, it seemed reasonable to encourage MdDS patients to attend vestibular rehabilitation therapy (VR) [47], however it has been reported that "only rarely MdDS patients seem to be cured or to benefit from vestibular therapy" [47]. A case study reported that sensory reweighting was successful in reducing MdDS symptoms [61]. However, at this stage it is still unclear which type of VR and if MT and also SO may be responding differently to such an intervention. Further research on VR and MdDS is needed.

2.5. MdDS Thesis Objective

Despite the growing knowledge of past years, many questions remain to be addressed. As a result this thesis focuses on covering some knowledge gaps and overall to increase the current understanding of MdDS.

As discussed in the epidemiology section (2.1.5), patient information on MdDS is relatively recent, additionally MdDS patients are often misdiagnosed and overall the awareness among physicians is limited. Thus, one of the primary aims of this research was to evaluate the percentage of misdiagnosed patients and to evaluate which other vestibular or neurological disorders are most often confused with MdDS. As noted in the onset section, a clear comparison among onsets has never been attempted; as a result, gaining more information about MdDS onset groups and typical features was another key component of this study. From the information gathered, we aimed to propose new potential guidelines to diagnose MdDS patients from both onset types.

It was hypothesised that this study would obtain similar findings from previous investigations, with a high number of patients misdiagnosed and similar clinical features between MT and SO patients [44, 48]. Another hypothesis formulated was that from the data collected a high level of intrusiveness of MdDS would be reported. This would indicate that MdDS is having a great negative impact on patients' lifestyle [56, 87].

The inexplicable female predominance can be considered one of the key aspects of MdDS, yet no studies have ever attempted to investigate gonadal hormones and gender influences over MdDS patients. For the first time, this research aimed to gather preliminary information on how steroid hormones may influence MdDS

patients and when possible to compare onset differences. This was done after establishing a worldwide collaboration, which allowed us to collect the largest patients data set on MdDS ever created.

For this study, it was hypothesised that hormonal fluctuations may influence MdDS and that MdDS patients may be subjected to estrogen withdrawal theory, often described for migraine patients [39]; indicating that when estrogen are lower (during menses) symptoms can aggravate. Moreover it was hypothesised that peculiar hormonal phases (i.e. menopause, perimenopausal, travelling during menses) or hormonal conditions may be a predisposing factor for developing MdDS.

Another aspect of this investigation involved the assessment of optokinetic treatment for MdDS subjects. Treatment options are still limited and optokinetic stimulation is one of the few currently available. Thus, our study aimed to reproduce for the first time the same protocol proposed in Mount Sinai Hospital, New York US, where the study was designed in 2014 and test for a placebo effect. The focus of this research was to further explore the use of optokinetic stimuli and head roll for easing MdDS symptoms in both onset groups. Additionally we aimed to standardise the protocol procedure in order to facilitate its implementation in clinical settings.

It was hypothesised that the OKN treatment would not induce a placebo effect and that patients would benefit from this intervention as similarly observed in Dai's studies [52, 53].

From the patients examined during the OKN treatment protocol and from recent retrospective online surveys [52], it was noted that MdDS patients even after improving their self-motion perception, reported a heightened visual motion

sensitivity. This specific symptom has been often described in other vestibular disorders and it is termed Visually Induced Dizziness. Similarly to MdDS, treatment options for desensitize patients from visual dependency and sensitivity are limited. However, optokinetic exposure (in the form of a rotating disk), has reported to be beneficial in reducing visual motion sensitivity in general vestibular patients. As a result we proposed a rehabilitation protocol including optokinetic exposure as well as vestibular rehabilitation exercises customized for each patient and behaviour instructions to different kinds of vestibular patients. Thus our objective was to examine how effective this protocol was in easing VID symptoms to further evaluate if a similar protocol could be used for MdDS, who retained VID symptoms. It was hypothesised that OKN stimuli for VID patients would reduce visual sensitivity in VID patients as previously observed in recent studies [32, 88].

Lastly, with this dissertation we aimed to report some of the main limitations and challenges faced in the study of MdDS. A series of questions remain, prompting future studies, with a particular emphasis on neuroimaging studies, which were not performed in the current research.

Summary of the aims and hypothesis of this dissertation

- Aim: Gain more information about epidemiology, misdiagnosis, main clinical features and characteristic of MdDS SO and MT subtypes. Aim to improve the current diagnostic criteria for MdDS;

Hypothesis: It was hypothesised that a large number of MdDS patients were misdiagnosed, in line with previous studies [49]. Regarding epidemiological data and features or characteristics the study were explorative and that most patients would fall in the age range 40 to 50 years a previously observed [44]. Additionally It was expected that most respondents were female [44].

- Aim: Examine a potential influence of gonadal hormones on MdDS pathophysiology, when possible compare SO and MT patient groups;

Hypothesis: The hypothesis was that due to the great gender imbalance in relation to MdDS, gonadal hormones would be involved in MdDS symptomatology. It was hypothesised that gonadal hormone may be intricate in developing and influencing MdDS symptoms, more in details that most female patients were in menopause or perimenopausal when onset occurred; suggesting that hormonal changes may be a predisposing factor for developing MdDS. Also it was hypothesised that hormonal fluctuations recorded during the menstrual cycle are influencing MdDS symptoms. Lastly that, in relation to onset for the MT MdDS group, it was hypothesised that they were travelling during menses, when onset occurred.

- Aim: Reproduce the OKN treatment for MdDS patients, evaluate if patients are subjected to a placebo effect, aim to standardised the treatment protocol;

Hypothesis:

It was hypothesised that MdDS subjects would benefit from the OKN treatment, as previously reported from Dai's study [52], despite using a standardised procedure (fixed head frequency in our protocol and fixed time of exposure for the first three days of treatment). It was hypothesised that no placebo effect would be recorded in our setting.

- Aim: Aim to evaluate if vestibular patients reporting VID symptoms can ease their visual dependency with a combination of optokinetic stimuli, vestibular rehabilitation and behavioural guidance, as a similar protocol could be used for MdDS subjects.

Hypothesis:

The main hypothesis was that VID patients would reduce their symptoms after being exposed to OKN stimuli and to have implemented life style changes.

- Aim: Provide an overview on the limitations of the current studies and difficulties in researching MdDS. Present future studies that should be implemented.

3. CHAPTER 3 - DIAGNOSTIC:

- Mal de Debarquement Syndrome: a survey on subtypes, misdiagnoses, onset and associated psychological features

This chapter was published in Journal of Neurology.

Mal de Debarquement Syndrome: a survey on subtypes, misdiagnoses, onset and associated psychological features.

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3.1 Mal de Debarquement Syndrome: a survey on subtypes, misdiagnoses, onset and associated psychological features

Abstract

Introduction: Mal de Debarquement Syndrome (MdDS) is a neurological condition typically characterised by a sensation of motion, that persists longer than a month following exposure to passive motion (e.g. cruise, flight, etc.). The most common form of MdDS is motion triggered (MT). However, recently it has been acknowledged that some patients develop typical MdDS symptoms without an apparent motion trigger. These cases are identified here as spontaneous or other onset (SO) MdDS. This study aimed to address similarities and differences between the MdDS subtypes. Diagnostic procedures were compared and extensive diagnostic guidelines were proposed. Secondly, potential triggers and associated psychological components of MdDS were revealed.

Methods: This was a retrospective online survey study for MT and SO MdDS patients. Participants were required to respond to a set of comprehensive questions regarding epidemiological details, as well as the diagnostic procedures and onset triggers.

Results: There were 370 patients who participated in the surveys. It is indicated that MdDS is often misdiagnosed; more so for the SO group. In addition to the apparent self-motion, both groups reported associated levels of stress, anxiety and depression.

Discussion: It appears at present that both MdDS subtypes are still poorly recognised. This was the first attempt to evaluate the diagnostic differences between MdDS subtypes and to propose a set of comprehensive diagnostic guidelines for both MdDS subtypes. In addition, the current research addressed that associated symptoms such as stress, anxiety and depression should also be considered when treating patients. We hope this study will help the medical community to broaden their awareness and diagnostic knowledge of this condition.

Introduction

Mal de Debarquement Syndrome (MdDS) is a neurological disorder, typically characterized by the perception of self-motion that persists for more than one month from an onset, which in most cases occurs after disembarkation from a vehicle (e.g. boat, cruise, train, plane). The phenomenon was first described by Erasmus Darwin in 1796 [89] and anchored by Brown and Baloh in 1987 as Mal de Debarquement [45]. Those cases with a symptomatic remission in one month from the onset are considered transient and hence named Mal de Debarquement (MdD) [44]. The main features of MdDS are a constant sensation of rocking, swaying, bobbing and bouncing when walking, as well as continuing when lying down [47, 58]. These sensations are persistent while patients are awake and are independent on body position or movements. They are also accompanied by a myriad of symptoms such as heightened sensory sensitivity (e.g. photophobia), head pressure, nausea, agoraphobia, brain fog, associated migraine and fatigue, as well as depression and anxiety [47]. Interestingly, these symptoms often subside temporarily when patients are re-exposed to passive motion (e.g. driving or being a passenger in a car) [47]. This temporary alleviation of symptoms is unique to MdDS patients and usually used for confirming a diagnosis of the condition [90].

In the past decade, there has been a growing interest in MdDS from the scientific community, as well as from patients. Despite some MdDS information that is available from the MdDS community, many patients still find it difficult to receive a clear diagnosis from a healthcare professional for timely treatment [87]. In general, MdDS is still considered a rare neurological disorder [47], and the prevalence of this condition has only been assessed in one study to date [49], where it was estimated to have an occurrence rate of 1.3% in a neuro-otological clinic. Currently, it is still unclear how many MdDS patients are misdiagnosed or undiagnosed. It is known that on average,

MdDS patients undergo around 19 appointments with healthcare professionals before receiving a correct diagnosis [56], and that this diagnostic process can take as long as several years [91]. This is primarily due to unawareness and limited knowledge of MdDS amongst physicians or healthcare professionals, but also due to the lack of clear diagnostic guidelines [90]. There was only one publication by Van Ombergen et al, that set forth preliminary diagnostic guidelines based on a literature review [44]. Due to the lack of understanding of the condition when they developed the guidelines, specific aspects of MdDS such as onset types were not distinguished [58]. MdDS is often unremarkable in peripheral vestibular function [44] and brain imaging studies. This makes diagnosis even more challenging. According to recent publications, MdDS, regardless of the cause of onset, has been typically misdiagnosed as vestibular migraine [49], 'atypical' Ménière's disease, general space and motion disorder, panic disorders and generalised anxiety disorders [87].

The past few decades has seen rapid growth in interest and knowledge regarding MdDS. As more patients have been evaluated, it has become clear that typical MdDS symptoms can occur from events other than motion or spontaneously. It is apparent that MdDS can be categorized into two subtypes according to the patient's onset cause. From the literature, a less common and less acknowledged form of MdDS is non-motion or spontaneous/other (SO) onset MdDS. This type of MdDS can occur either in the complete absence of an event or trigger, uncharacterised by a specific motion-related event (spontaneous), or can be associated with stressful events such as surgery, trauma, childbirth and others. Although there might be a better term than spontaneous MdDS or SO MdDS to describe the non-motion triggered nature of MdDS, this term has been accepted differentially from MT MdDS. The literature about spontaneous MdDS is very limited and there is a need to develop clear diagnostic guidelines for both MdDS subtypes. Aside from the differences in onset cause, MT and SO MdDS appear to be

symptomatically identical [49] and to respond similarly to at least one of the proposed treatments for MdDS [52]. However, a clear comparison between the two subtypes has yet to be done, in particular taking into account epidemiology, diagnostic procedures and potential triggers responsible for the onset.

It has been reported that MdDS patients have a high level of depression, poor quality of life and high illness intrusiveness [87], regardless of their onset type. Illness intrusiveness is considered an underlying determinant of the psychosocial impact of chronic diseases and illness, and it has been found to be correlated with poor quality of life [87]. Psychological and mood disorders (e.g. anxiety, depression) secondary to MdDS have been previously described in patients [44, 52]. It has been proposed that secondary mood disorders develop as a consequence of the continuous perception of motion, which may lead to mental strain [49], as well as the frustration with the endless search for a correct diagnosis and the changes in lifestyle required to cope with the condition. MdDS is believed to be extremely debilitating, both physically and mentally [47, 49, 56]. The lack of awareness and recognition of MdDS from healthcare professionals further aggravates patient predisposition to the development of psychological disorders (e.g. anxiety and / or depression) [90]. Despite psychological symptoms being common, and considered part of the MdDS pathophysiology, it remains unclear if they are a pure consequence of MdDS inducement; or rather exist as vulnerability factors for developing the condition. Similarly, stress has also been known for negatively impacting MdDS patients [90]. It has long been known that stress has many physiological effects on the body [92] and it may be involved in influencing central vestibular and automatic functions in healthy individuals as well as in patients [93]. However, despite the potential role of stress in MdDS [90], the relevance of stress has never been closely evaluated. As a result, it remains unclear if it is a key trigger during MdDS onset, or if stress responses are triggered once the condition is established.

Observing the commonality of specific triggers across MdDS patients could help researchers understand why MdDS develops at a specific time. For example, it is possible that MT patients might have been exposed to similar passive motion before but yet they did not develop MdDS. As a result, the current study aimed to examine such factors as stress, depression and emotional status that may be equally important for eliciting MdDS. We also assess the prevalence of psychological comorbidities before and after MdDS onset. Based on previous studies [49, 55], it is reasonable to believe that psychological symptoms originate from MdDS. However, in this study we also investigated if psychological disorders (e.g. being previously diagnosed with depression / being previously diagnosed with anxiety) were pre-existing conditions in MdDS patients. If true, this may help us to understand why there is a particular group of the population who seem more susceptible to develop MdDS.

To assess differences and similarities between MT and SO MdDS, specifically regarding diagnosis, onset and the major associated symptoms, two online surveys were made available to MT and SO MdDS patients. To date, some surveys have been popularized: the first by Gordon on transient MdD [94], followed by Hain et al. in 1999 [60] on MdDS. Epidemiological questionnaires and surveys on MdDS pathophysiology were also performed more recently [56, 58]. However, in this study we aimed to provide a broad overview of MdDS and comprehensive diagnostic guidelines for both MdDS subtypes. The current study analysed diagnostic procedures, onset and additional features associated with MdDS such as depression, anxiety and the role of stress. The vestibular system has been shown to have connections to the hypothalamic–pituitary–adrenal axis (HPA axis), the central stress response responsible for neuroendocrine adaptation to stressors [93]. Investigate stress may be of great relevance for MdDS subjects.

Methodology

Ethical approval / study population and recruitment

Ethical approval was provided by the Ethics Committee of the University Hospital Antwerp Belgium (IRB number 15/44/454) and by the Western Sydney University Human Ethics Committee (H11962). Each respondent gave informed consent. All investigations have been conducted according to the principles expressed in the Declaration of Helsinki.

Patients diagnosed by specialists or believing to suffer from MdDS (also referred to as self-diagnosed patients) were recruited for the study. Patients were recruited across the USA, Europe, and Australia, however respondents from Asia and South America were also able to access the study. MdDS patients were recruited through the Department of Otorhinolaryngology at the University Hospital of Antwerp, Belgium. Patients were also recruited globally through the main MdDS support groups: MdDS Australia Facebook Support Group, MdDS UK Facebook Support Group, website of MdDS Research Group at Mount Sinai Hospital, Western Sydney University MdDS Research Group Facebook page, website and Facebook of Vestibular Disorders Association (VEDA), and website and Facebook of Whirled Foundation and the REACT Community Facebook. A total of 370 respondents completed the surveys. Within these, 266 responded to the MT questionnaire and 104 to the SO questionnaire.

Inclusion and exclusion criteria

Inclusion criteria: Patients reporting sensations of self-motion (rocking, rocking, swaying and bobbing) for longer than one month, where the symptoms could not be explained by another diagnosis. Only patients >18years old were included. Patients reporting MdDS symptoms after the exposure to passive motion, most frequently a boat trip, or travel over air or land were denoted as the *motion-triggered group (MT group)*. Patients

reporting similar symptoms without a clear motion event or any obvious cause were allocated to the *spontaneous onset MdDS group*. Patients reporting the initial symptoms after a strong emotional or stressful event (e.g. child birth, concussion, physical trauma, surgery, etc.) were defined as the *other onset MdDS group*. Both 'Spontaneous' and 'Other' onset MdDS patients were unified in one group, termed the *SO group*.

Self-diagnosed respondents were also included in the survey as numerous questions assessed their symptoms; we were able to screen them while also gaining information about their onsets.

Exclusion criteria: Patients <18yr. old. Patients reporting symptoms which do not fit with the MdDS guidelines [44].

Questionnaires

The questionnaires were distributed online using Survey Monkey (MT group) and Qualtrics (SO group). The MT MdDS survey consisted of 51 questions and the SO MdDS survey consisted of 85 questions. More questions were made available to the SO group, as the respondents were re-directed to one of two specific categories: 1) spontaneous, and 2) other, according to their onset. Additionally, more extensive questions about hormonal profiles were distributed in the SO MdDS questionnaire. However, only the same questions were examined for both onset groups. The questions were divided into separate categories for both surveys: *epidemiology* (demographic details), *diagnosis* (i.e. who made the initial diagnosis, time frame before receiving the diagnosis, number of appointments), *onset triggers* (potential triggers related to the onset: events, hormonal fluctuations, medications, stress), *symptom triggers* (i.e. symptom fluctuation, assessments of potential triggers, susceptibility to visual inputs), *hormonal influences* and *symptom management and treatment*. This manuscript focuses on the *diagnostic*,

psychological components of MdDS (stress; secondary mood disorders) and onset trigger data (Questions available in Supplementary Material Annex 1).

Statistical analysis

Statistical analysis was performed with SPSS version 24 (IBM Corp). Chi Square was used for comparison between MT MdDS and SO MdDS groups.

Results

Epidemiology

The mean age was similar for both groups, i.e. 48.9 (SD = 11.4) years for the MT group and 48.9 (SD =13.6) years for the SO group. A total of 370 surveys were collected, with 266 (71.9%) being the MT group, and 104 (28.1%) being the SO group. A female predominance was observed in both groups, with 242 female respondents (93.1%) in the MT group and 92 (88.5%) in the SO group. Half of all the respondents from both surveys were from North America (50.9% MT – 51% SO), while 25% of the MT group and 24% of the SO were from Europe, 21.9% and 22.1% from Australia. A small number of respondents completed the surveys from Asia (0.8% MT - 1% SO) and from South America (0.8% MT -1.9% SO). Respondents did not complete all questions. As a result, the number of answers received per question and the respective percentage, is indicated for each question.

Diagnosis

Initial diagnosis

Respondents from both groups were asked who initially diagnosed them with MdDS, and when comparing the two onset groups (MT versus SO), there was a significant difference between the two groups with respect to which health professionals initially diagnosed their MdDS ($p<0.003$). See Table 3.

Initial Diagnosis	MT n (%)	SO n (%)
Self-diagnosed	125 (47%)	33 (35.9)
ENT	61 (22.9%)	19 (20.7%)
Neurologist	42 (15.8%)	25 (27.2%)
Health care professionals (physiotherapists, chiropractors, physical therapists, nurses, etc.)	23 (8.6%)	15 (16.3%)
General physician / Primary care physician	15 (5.6%)	0 (0%)
Total number of respondents that answered this question (%)	266 (100%)	92 (88.5%)

Table 3: Initial diagnosis of MT and SO respondents expressed as the number of respondents (n) and percentage of respondents for both groups. Self-diagnosis was the most common initial diagnosis in both groups, followed by ENT doctors, then neurologists for the MT group, and neurologists, then ENT doctors for the SO group.

Diagnosis Confirmation

After initial diagnosis, respondents were asked who confirmed their diagnosis. Only around one in five respondents (59 MT respondents (22.2%) and 17 SO respondents (18.5%)) received the MdDS diagnosis as their initial diagnosis. The remaining respondents subsequently consulted multiple healthcare professionals. ENT doctors and neurologists were among the majority of doctors who confirmed the diagnosis for the MT group (ENT = 69 (25.9%), neurologists = 68 (25.6%)). For the SO group, a smaller number of ENT doctors (14 -15.2%) confirmed the diagnosis, compared to neurologists (26 -28.3%).

Medical Appointments

In response to the following question: 'provide an estimate of how many medical appointments you attended before your MdDS diagnosis', the majority of the MT and

SO group received their diagnosis from a healthcare provider within 2 to 5 appointments. However, the percentage of respondents between the two groups was statistically different ($p < 0.024$), especially for a single appointment (Table 4).

Number of Appointments	MT n (%)	SO n (%)
1	26 (17%)	5 (6.7%)
2 - 5	68 (44.4%)	24 (32%)
6 - 10	33 (21.6%)	23 (30.7%)
10 - 20	17 (11.1%)	12 (16%)
20 - 40	8 (5.2%)	10 (13.3%)
40+	1 (0.7%)	1 (1.3%)
Total number of respondents that answered this question (%)	153 (57.1%)	75 (72.1%)

Table 4: Number of appointments attended in the search for a MdDS diagnosis expressed as the number of respondents (n) and percentage of respondents for both groups. Respondents within the MT group had a higher chance of being diagnosed in fewer amount of appointments than those within the SO group.

Number of appointments attended by self – diagnosed respondents

The number of self-diagnosed respondents was significantly different between the MT and SO subtype, with 112 (42.1%) respondents from the MT MdDS subtype and 40 (23.5%) respondents from the SO MdDS group ($p = 0.002$).

The majority of self-diagnosed MT respondents (59 responses - 52.7%) attended 2-5 appointments, compared to a smaller number of the SO respondents (9 responses - 22.5%). 10-20 appointments were reported among self-diagnosed MdDS respondents, with similar prevalence between MT group (11 responses - 9.8%) and SO group (13 responses - 32.5%).

Time frame before being diagnosed

The time before receiving a diagnosis after onset differed significantly between the MT and SO groups ($p < 0.001$) (Table 5) and in general, the results show that SO respondents wait a longer period of time to receive the correct diagnosis.

Time before receiving MdDS diagnosis	MT n (%)	SO n (%)
1-2 months	76 (34.1%)	10 (12.8%)
3-6 months	73 (32.7%)	21 (26.9%)
7-12 months	22 (9.9%)	12 (15.4%)
1-2 years	12 (5.4%)	9 (11.5%)
2+ years	17 (7.6%)	15 (19.2%)
5+ years	23 (10.3%)	11 (14.1%)
Total number of respondents that answered this question (%)	223 (83.8%)	78 (75%)

Table 5: Time before receiving MdDS diagnosis expressed as the number of respondents (n) and percentage of respondents for both groups. Respondents within the MT group had a higher chance of being diagnosed earlier than those within the SO group. With two thirds of respondents within the MT group being diagnosed within 1-6 months from onset, and one third of respondents within the SO group being diagnosed within 2 – 5+ years of onset.

Other Diagnoses

Various diagnoses were given to respondents within the MT and SO groups (see Figure 8). The two groups received similar misdiagnoses. 263 (98.9%) responses were collected from the MT group and 104 (100%) from the SO group. All respondents received at least one misdiagnosis, with several reporting multiple misdiagnoses. On average, the respondents within the MT group received 2.1 different diagnoses and those within the SO group received 3 misdiagnoses. In summary, in both MT and SO the term vertigo was used as a diagnoses and this was one of the most common misdiagnoses reported by

participants, followed by anxiety and vestibular dysfunction (unspecified). After vertigo, anxiety and vestibular dysfunction, the next most common misdiagnoses for the MT group was labyrinthitis, inner ear infections, BPPV, vestibular migraine (VM) and depression. For the SO group, the following most common misdiagnoses BPPV, VM, labyrinthitis, inner ear infections and depression. No statistical differences were noted between the two groups.

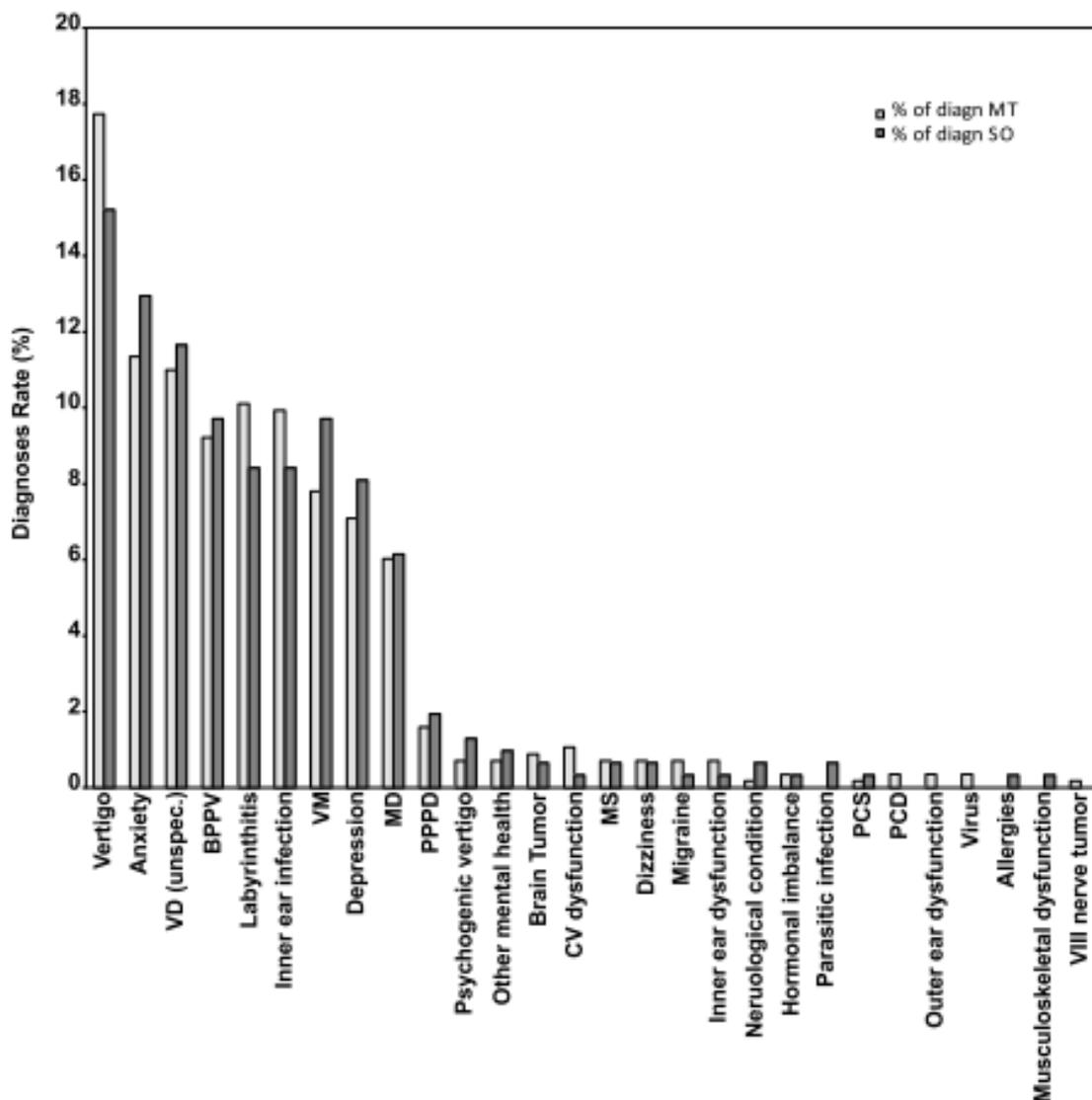


Figure 8: Various misdiagnoses received by respondents of the MT (light grey bars) and SO (dark grey bars) groups prior to MdDS diagnosis expressed as a rate (%) of received diagnoses. In both groups, vertigo was the most common misdiagnoses, followed by anxiety and then vestibular dysfunction.

Abbreviations / Legend: VD = vestibular dysfunction (unspecified), BPPV = Benign paroxysmal positional vertigo, VM = vestibular migraine, MD = Ménière's Disease, PPPD = Persistent postural-perceptual dizziness, CV = cardiovascular, MS = multiple sclerosis,

PCS = post-concussion syndrome, PCD = Posterior Canal Dehiscence, VIII = vestibulocochlear.

Open Ended Comments – Diagnostic Experience

Patients from both onsets subtypes were also given the opportunity to comment on their diagnostic experiences. 31 respondents within the SO group participated in this question, 71% of the comments described negative experiences, 16% described positive experiences and 13% of the responses were neutral regarding their quest for a diagnosis. 91 respondents within the MT also participated in this question, 58% of the comments described negative experiences, 20% described positive experiences and 22% of the responses were neutral.

Onset

In Table 6, an overview of the respondents' onset trigger (passive motion: car, bus, tram, flight, cruise), and of a potential trigger for the SO onset is represented as a percentage of respondents.

Triggers Associated with MT Onset	MT n (%)
Cruise	162 (60.9%)
Flight	50 (18.8%)
Combination of Vehicles (e.g. flight and car; boat and car etc.)	33 (12.4%)
Train	6 (2.3%)
Car	8 (3%)
Bus	2 (0.8%)
Simulator (virtual reality)	5 (1.9%)
Total number of respondents	266 (100%)

Possible Triggers Associated with SO Onset	SO n (%)
Stress (psychological, physical)	10 (32.3%)
Strong emotion	5 (16.1%)
As a result of a previous vestibular disorder	3 (9.7%)
Physical trauma (e.g. concussion)	7 (22.5%)
Virus	2 (6.5%)
Child birth / Pregnancy + Hormonal imbalances	3 (9.7%)
Spontaneously (unable to recall a specific event)	1 (3.2%)
Total number of respondents (%)	31 (29.80%)

Table 6: Onset triggers reported by respondents within the MT and SO groups expressed as the number of respondents (n) and percentage of respondents for both groups. Cruising was the most common onset trigger for respondents within the MT group, followed by flights. Stress and physical trauma were the most common onset triggers for respondents within the SO group.

Additional features

Re-exposure to passive motion

Respondents were asked if there was an absence or a significant reduction of symptoms upon re-exposure to passive motion (e.g. driving or being a passenger in a car). 264 respondents from the MT group and 24 respondents of the SO group completed this question. Among those, 94.7% of the MT respondents and 91.7% of the SO respondents confirmed that they had a reduction of symptoms or full alleviation of symptoms when travelling in a moving car. Despite the small number of SO respondents, the majority of those who responded reported an alleviation of symptoms when exposed to passive motion, similar to the MT group. Combining the two groups together, the number of positive responses was significantly higher when compared to the respondents who did not report an improvement ($p < 0.001$).

Depression and Anxiety

Respondents were asked if they had been diagnosed with depression and secondly, they were asked if they had been diagnosed with anxiety before or after developing MdDS in two distinct questions (Table 7). Respondents with depression were equally distributed and there was no significant difference between the two groups. However the two groups differed significantly ($p < 0.001$) regarding the number of respondents diagnosed with anxiety before MdDS (20% MT - 9% SO).

Depression	MT n (%)	SO n (%)
Before MdDS	51 (19.3%)	9 (28.1%)
After MdDS	26 (9.8%)	4 (1.4%)
Never diagnosed with depression	187 (70.1%)	19 (59.2%)
Anxiety	MT n (%)	SO n (%)
Before MdDS	53 (20.1%)	3 (9.4%)
After MdDS	35 (13.3%)	12 (37.5%)
Never diagnosed with anxiety	176 (66.7%)	17 (53.1%)
Total number of respondents	264 (99.2%)	32 (30.7%)

Table 7: Respondents' diagnosis of depression and anxiety within the MT and SO groups expressed as the number of respondents (n) and percentage of respondents for both groups. The majority of the MT and SO groups reported to have not been diagnosed with depression or anxiety.

Psychological consequences of MdDS

Respondents who answered positively to depression and anxiety were asked whether they considered that their anxiety or depression were consequences of the syndrome per se. 107 (59.5%) of the MT respondents and 19 (70.4%) of the SO respondents replied that they believe MdDS was the cause of their psychological symptoms (e.g. depression, anxiety). No statistical difference was reported between the two groups. When considering the two groups together, a total of 291 answers were collected and

176 respondents answered that they believed MdDS was the cause of their psychological symptoms/conditions ($p < 0.001$).

Lifestyle Changes

In response to the question regarding MdDS affecting respondents' lifestyle, the following question was asked: *'Do you feel that you have made lifestyle changes to avoid your triggers?'* (Symptom triggers such as exposure to bright, flickering light, excessive noise, going to the supermarket, etc.). This question was answered by 166 MT respondents (62.4%) and 36 SO respondents (34.6%). Both groups reported to have significant lifestyle changes to avoid triggers (166 (63.1%) MT respondents – 36 (69.2%) SO respondents. Considering the two groups together, a total of 215 respondents reported to have had to change their lifestyle ($p < 0.001$), 202 of which reported *'a significantly changed lifestyle'*. No statistical differences were found between the two groups (*'somewhat changed lifestyle'*: 28.1% MT – 26.9% SO; *'little changes to lifestyle'*: 1.5% MT – 0 % SO; *'no changes to lifestyle'*: 7.2% MT – 3.8%SO).

General Open-ended Comments

Throughout both questionnaires, the respondents had the opportunity to add open-ended comments regarding anything they were willing to share about their MdDS experience. A great proportion of respondents expressed a high level of frustration and helplessness related not only to misdiagnoses and unawareness of MdDS in the medical community but also the debilitating nature of this condition and how much their lives had changed, *"I regard myself as handicapped now"* – SO respondent, *"My whole life has significantly changed. I cannot go anywhere without my husband to hold on to. I am unable to travel on public transport on my own. I cannot go shopping on my own without a shopping trolley to hold on to. My whole life has changed."* – MT respondent.

Patients also indicated that they were unable to work full time and live a normal life, others expressed their concerns about ageing with the condition, “My life barely resembles what it used to... I no longer travel, cannot see friends or have energy to do anything but work and come home to my family. I don't go out, can't physically exert myself, get seriously ill if I do exert myself, and can no longer do most of my hobbies or goals” – MT respondent, “It has changed my life. I am not able to do all the things I once enjoyed.” – SO respondent, “The biggest change to my lifestyle is a reluctance to go out unaccompanied due to the way I feel when I am walking. I feel much more secure with company and somebody to hold to alleviate the feeling of unsteadiness” - SO respondent.

Stress

As shown in Fig. 9, stress is a significant symptom trigger for MT respondents ($p < 0.001$).

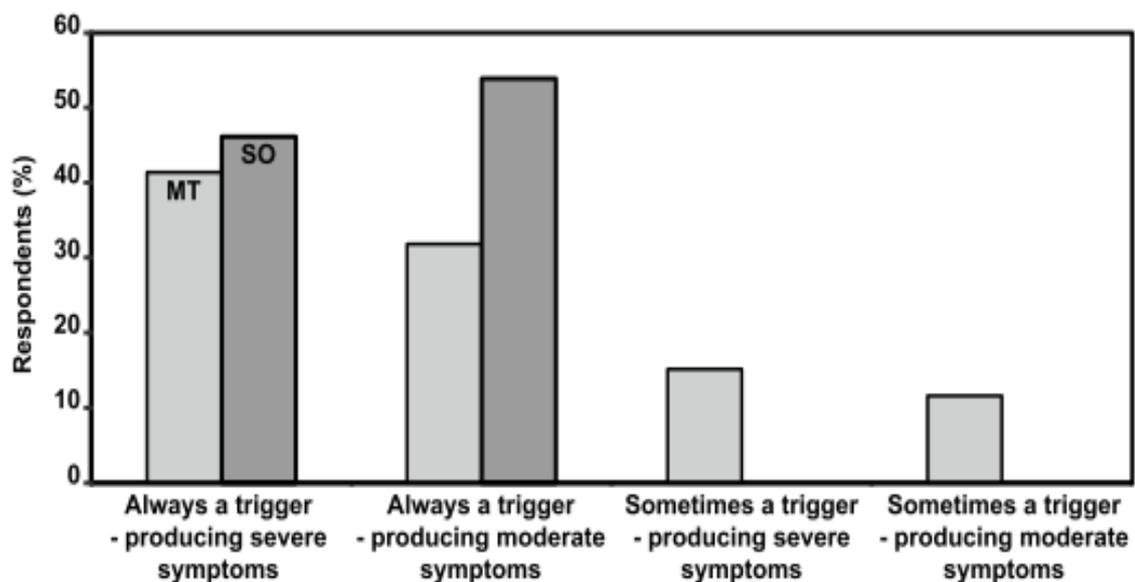


Figure 9: Stress as a trigger for increased symptoms (with various levels of aggravation) reported by respondents of the MT (light grey bars) and SO (dark grey bars) groups expressed as percentage of respondents who answered the question. In both groups, stress is viewed as a trigger that can produce a moderate to severe aggravation of symptoms.

The SO group was asked if they were under stress during the potential onset. The question asked was: 'Were you under stress during what you believe being the MdDS onset?' The number of respondents answering positive was 21 (65%) ($p < 0.001$) and this question was answered by 31 SO respondents (20.2%) (Figure 9).

Discussion

In light of the difficulties involved in recruitment for a study concerning a rare condition, a multi-institutional collaboration was setup to collect data from MdDS respondents around the world. In total, 370 respondents completed either the MT or SO questionnaire. The current study is the largest in terms of MdDS respondents recruited to date, and is the only survey comparing MT versus SO subtypes. Furthermore, this study is the first to assess MdDS patients in a multicentred design and international setting. When considering the two onset subtypes, we have ascertained that the two categories clearly meet the clinical features of MT and SO MdDS. In line with published research [53], most MT respondents reported that their MdDS symptoms developed after a cruise, despite being on a cruise may be less frequent than being in a car, train or on a plane, time normally spent on a cruise is longer and during such type of travel, passengers are exposed to complex oscillation frequencies capable of disrupting the vestibular system and potentially the vestibular ocular reflex, following Dai's theory [53]. Specifically, cruise ships are normally rock from side to side at ≈ 0.2 Hz [52], which is known to induce motion sickness. We hypothesise that the exposure to such a strong stimulation and longer exposure times (typically), may be the reason why more people develop MdDS after disembarking a cruise ship. While 32 % of the SO respondents developed MdDS after a period of psychological or physical stress or strong emotional experience, without the involvement of a motion event. It is possible that SO patients associate the onset of their disorder with a biographical event, and may appear

ambiguous, nevertheless for this early stage of investigation, we believe it is important to collect as much information as possible about patients' onset to identify any correlations between individuals within the subtype and to better objectify the differences between MT and SO subtypes.

We are aware that terms such as 'psychological stress' and 'emotional experience' are subjective terms with potentially broad interpretations. However, as these are the only events that these subsets of patients associate with their onset, they are of likely significance. A more extensive number of SO respondents is needed, as the SO survey was completed by a smaller number than the MT. A larger sample group could allow us to further define the psychological related aspects that SO patients attribute to MdDS onset.

Respondents from the MT and SO groups showed similar epidemiological results. The average age was 49 years old for both groups, with a strong female predominance. These results are comparable to a mean age of 45 years reported by other studies [44, 59, 60]. MdDS is a poorly understood disorder, and the lack of recognition and poor symptom management ultimately impact upon the patient's mental state and lifestyle [49].

Patients learn to coexist with the syndrome. As reported by respondents from both groups, significant lifestyle changes were necessary, which in some cases it had affected their employability, social life and ability to live, what they consider, a normal life. A large number of MT patients reported to have made significant adjustments to their lifestyle in order to avoid major triggers (such as exposure to bright, flickering light, excessive noise, going to the supermarket, etc.). The percentage of SO respondents implementing significant lifestyle changes was high (69.2%), similar to the MT group (63.1%). However, the number of total respondents in the SO group that responded to this question was much less than the MT group. Indeed, the open-ended comments

received from both patient groups reveals the devastation that many MdDS experience after their onset. The majority of comments made by respondents in both groups referred to their high level of frustration and helplessness due to the great impairment that this condition has on their lives.

The lack of awareness among healthcare professionals contributes severely to misdiagnoses, and as a result some MdDS patients are unable to receive the correct diagnosis for long periods of time. In this survey, as previously stated, a high number of MT (47%) and SO (35.9%) respondents were self-diagnosed, meaning that they did not receive the MdDS diagnosis from any healthcare professional, despite their symptoms coinciding with the criteria for MdDS. Despite the potential risk of inclusion of non-MdDS sufferers, this category was maintained, based on previous research indicating that patients living with undiagnosed or highly debilitating conditions often resort to self-education through internet literature searches [49] and support group discussions [95]. As a result, the self-diagnosed MdDS patients in this study were patients who are still hoping to receive a confirmation of diagnosis but believe themselves to be suffering from MdDS. Results of this study found self-diagnosed SO respondents attended a higher number of medical appointments than the MT self-diagnosed group, indicating perhaps that the SO respondents have been continually seeking answers as they have not yet been officially diagnosed. On average, the SO respondents received a higher number of misdiagnoses with 3 different diagnoses, compared to 2.1 for the MT respondents. Similarly, both groups reported the same most prevalent misdiagnoses, which were vertigo and anxiety. Though these are not diagnostic terms, but rather symptoms, preliminary discussions with multiple patients revealed that many healthcare professionals often reported these terms as diagnoses, as a result we decided to include them in the questionnaire as diagnoses. The high number of patients misdiagnosed with vertigo and anxiety indicates that a great majority of healthcare

professionals are not aware of vestibular disorders and more specifically MdDS, and are diagnosing patients with broad terms which focus on symptoms rather than an actual condition. Following vertigo and anxiety, the most common misdiagnoses reported in the MT group was vestibular dysfunction, labyrinthitis, inner ear infection and BPPV. While the SO group reported diagnoses of vestibular dysfunction, VM, BPPV, labyrinthitis, inner ear infection, and lastly with depression. Related to the numerous misdiagnoses, more than 50% from both groups reported to have had negative experiences with health care providers. Most of the MT respondents were diagnosed by ENT doctors, followed by neurologists, whilst the opposite was true for SO respondents. This difference in diagnostic predominance between the ENT doctors and neurologists is probably due to the peculiarity of the SO group. The atypical onset is likely to have led to incorrect diagnoses. In addition, the MT respondents were found to have received the correct diagnosis earlier than the SO group. This data is understandable given the absence of clear diagnostic criteria for SO MdDS.

Thus, from the data obtained it is clear that diagnostic guidelines are needed to reduce misdiagnoses and improve patient's management, and which include also the spontaneous or other forms of MdDS.

Hereto, we propose (Table 8 and 9) new diagnostic guidelines for MT MdDS and SO MdDS respectively. In order to be diagnosed with MT or SO MdDS, a patient should fulfil all the below mentioned criteria.

1. Chronic perception of motion (e.g. rocking dizziness, bobbing, swaying movements), that started after passive motion such as water, air and land travel, and that it is not affected by a patient's position or movements
2. Symptoms lasting at least one month
3. Temporary relief of symptoms when re-exposed to motion (e.g. riding in a car), not necessarily the same motion that induced the onset, any passive motion.
4. Normal inner ear function or non-related abnormalities as tested by electronystagmography (ENG)/ videonystagmography (VNG) and audiogram should be present. However, if minor dysfunctions (e.g. minor hearing loss) are present, which do not implicate other vestibular pathologies, the patients can be included.
5. Normal brain imaging study with standard MRI methods
6. Symptoms not better accounted for by other diagnoses made by a physician or health care professional

Table 8: New proposed MdDS diagnostic guidelines for patients with MT onset, adding new elements to Van Ombergen's 2016 guidelines [44].

1. Chronic perception of self-motion (e.g. rocking dizziness, bobbing, swaying movements), and that it is not affected by a patient's position or movements.
2. Symptoms lasting at least one month
3. Temporary relief of symptoms when re-exposed to motion (e.g. driving or being a passenger in a car).
4. Normal inner ear function or non-related abnormalities as tested by electronystagmography (ENG)/ videonystagmography (VNG) and audiogram should be present. However, if minor dysfunctions (e.g. minor hearing loss) are present, which do not implicate other vestibular pathologies, the patients can be included.
5. Normal brain imaging study with standard MRI methods
6. Symptoms not better accounted for by other diagnoses made by a physician or healthcare professional
7. Onset being spontaneous and not involving any exposure to passive motion

Table 9: New proposed MdDS diagnostic guidelines for patients with SO onset.

Distinguish feature for MdDS

Symptomatic relief during passive motion was similarly reported for the MT and SO groups as presented in the results. This specific feature can clearly help distinguish MdDS patients from Persistent Postural Perceptual Dizziness (PPPD) (previously described as Chronic Subjective Dizziness) [9, 18], Visually Induced Dizziness (VID), phobic postural vertigo and motion sickness.

We are aware of the recent updates of the PPPD classification, which includes the previously named, Chronic Subjective Dizziness, Visual Vertigo as well as Phobic Postural Vertigo. Hereto, the most recent PPPD classification [96].

A. One or more symptoms of dizziness, unsteadiness, or non-spinning vertigo are present on most days for 3 months or more.

A1. Symptoms are persistent, but wax and wane.

A2. Symptoms tend to increase as the day progresses, but may not be active throughout the entire day.

A3. Momentary flares may occur spontaneously or with sudden movements.

B. Symptoms are present without specific provocation, but are exacerbated by:

B1. Upright posture,

B2. Active or passive motion without regard to direction or position, and

B3. Exposure to moving visual stimuli or complex visual patterns, although these three factors may not be equally provocative.

C. The disorder usually begins shortly after an event that causes acute vestibular symptoms or problems with balance, though less commonly, it develops slowly.

C1. Precipitating events include acute, episodic, or chronic vestibular syndromes, other neurologic or medical illnesses, and psychological distress.

C1a: When triggered by an acute or episodic precipitant, symptoms typically settle into the pattern of criterion A as the precipitant resolves, but may occur intermittently at first, and then consolidate

into a persistent course.

C1b: When triggered by a chronic precipitant, symptoms may develop slowly and worsen gradually.

D. Symptoms cause significant distress or functional impairment.

E. Symptoms are not better attributed to another disease or disorder.

Despite the fact that MdDS shares similar features with these conditions now included and named as PPPD, (i.e. being triggered by visual stimuli, psychological stress and the development of anxiety and depression) [97], MdDS patients, regardless of their onset, are the only category of patients who experience an alleviation of symptoms when exposed to passive motion. Normally, PPPD patient's symptoms are worse in motion [49], while VID patients are more prone to dizziness when observing their surroundings whilst moving (e.g. being in a car) due to busy or complex visual fields [98]. Lastly, sufferers of phobic postural vertigo do not report any improvement of symptoms when exposed to passive motion. Yet, they do experience a reduction of symptoms once the mechanism of their complaints are explained to them and the patient feels reassured [99]. A potential theory regarding why MdDS patients report a reduction of symptoms when exposed to passive motion, may rely in the theory of adaptation to previous stimuli. As previously observed from functional Magnetic Resonance Imaging (fMRI) and electroencephalography (EEG) studies [49], MdDS patients have been shown to have increased functional connectivity between multiple areas involved in spatial awareness (e.g. posterior sensory processing areas and the left entorhinal cortex (EC) [64], as well as within the amygdala). We hypothesize, as previously stated by Cha [64], that the exposure to passive motion generates vestibular and somatosensory signals, which produce frequencies of various amplitudes that are able to override or momentarily suspend any underlying oscillating rhythm perceived by the patients. It is apparent that more research is needed to understand the exact mechanism of this paradoxical relief of symptoms during re-exposure to motion. Novel neuroimaging research should be

performed to address the phantom perception of motion experienced by all MdDS patients.

It was identified for most of the SO respondents that psychological stress, or physical or emotional trauma, was present at the time of their believed MdDS onset. The relation of the emotional event to the symptomatic onset is also observed in phobic postural vertigo patients [99]. In order to distinguish those two entities, we suggest using the criterion point number 3 (n3 = relief by passive motion).

Stress and anxiety in MdDS

In general, more attention should be given to stress and its impact on MdDS development and symptomatology. The MT group reported to be significantly affected by moderate and severe stress, resulting in an aggravation of symptoms. In addition, the SO group reported to be under severe stress during the period when the potential onset occurred. This strongly indicates that stress can be involved in aggravating symptoms and therefore be considered as a trigger, or it may be involved during onset in MT or SO group. Stress remains an extremely challenging factor in patients with vestibular disorders due to its physiological component and individuality aspect (e.g. age, gender, genetic factors, and early life experiences), as well as the variability of an individual's perception over time [93]. Recently, the effects of stress on vestibular function and compensation have proven significant and are being increasingly recognized [93]. Several studies have observed stress in vestibular disorders such as chronic subjective dizziness (currently named PPPD) [97], Ménière's disease [100] and vestibular migraine [101]. Other studies have reported that a chronic stress response was present in patients with a persistent vestibular dysfunction [102]. Balaban and Thayer in 2001 described the pathophysiologic mechanism of this problem [103]. The interaction between vestibular disorders and the psychiatric sphere is mediated through neurological pathways that are common to the control of the vestibular and autonomic systems, as well as emotional responses and anxiety [104].

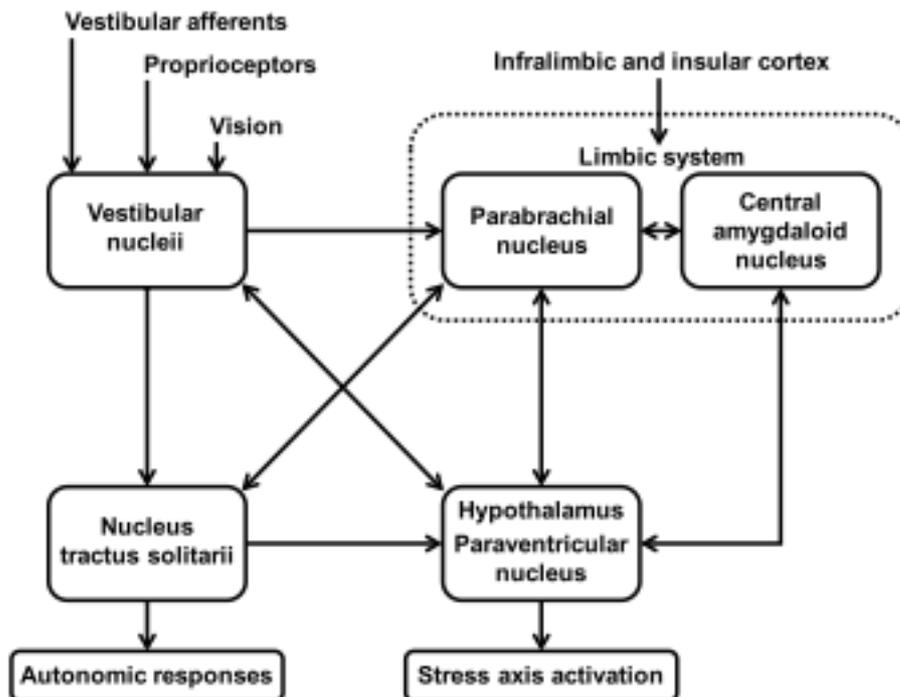


Figure 10: Schematic of the stress axis activation and its interrelation with the vestibular system. Adapted from [93].

As presented in Fig. 10, the connections from the vestibular nuclei to the parabrachial nucleus [105] are a direct link between the vestibular system and neural networks involved in expressing anxiety and emotion [106]. Stress may not only be affecting the patient's symptoms, but also their physiological vestibular compensation mechanisms [107]. In the study of Tschan and colleagues, stress, resilience and anxiety were considered among different vestibular patients as potential factors preventing vestibular compensation and rehabilitation [108]. Chronic stress is able to inhibit normal brain plasticity, leading to detrimental changes in the brain (e.g. hippocampus and prefrontal cortex) [109]. Potentially, chronic stress, as a result of MdDS, may be implicated in the pathophysiology of the disorder per se. Future studies should focus on assessing if MdDS patients report aberrant stress responses and consequently abnormal autonomic responses, ideally before and after a successful intervention.

A disrupted HPA-axis and autonomic response to stress could potentially be responsible for affecting an individual's central compensation. Specifically, it could be responsible for the prolongation of MdD symptoms as well as having stress influencing symptoms and being involved in its onset.

Additional features characterising MdDS

Anxiety and/or depression are recognised as the most common psychological symptoms associated with MdDS [44, 56]. MdDS patients have been previously described as being prone to developing psychological symptoms and disorders such as anxiety and/or depression due to the impact the condition has on a patient's quality of life and lifestyle [56]. However, our study aimed not only to evaluate the prevalence of psychological disorders (specifically depression and anxiety) in MdDS patients, but also to evaluate whether predisposition factors were present before the syndrome onset. From our results, a smaller group of the SO respondents (3 respondents) reported to have been diagnosed with anxiety before MdDS compared to the MT group (53 respondents).

The development of anxiety after MdDS onset, was relatively high in the SO respondents (37.5%). This reinforces our previous diagnostic argument, where the SO group's levels of anxiety may be the consequences of a poorly understood and managed disorder as reported in previous research [3, 4]. However, given the limited number of responses, more data is required. For the MT group, on the other hand, anxiety for certain individuals can also be considered as a predisposing factor for developing MdDS. However, this should be further evaluated. Theoretically, generalised anxiety may contribute to develop an aberrant stress response [110], directly linked to changes in the sympathetic nervous system.

Depression was equally present in the MT and SO respondents prior to MdDS onset. Although the number of SO responses was limited, further studies with larger sample

sizes are necessary to ascertain the relationship between depression and MdDS for this subtype.

Some anecdotal studies have previously asserted that depression was a predicting factor in vestibular disorders, but this was never proved [111]. However, if not considered as a predisposing factor, it is well known that depression is associated in many patients affected by central vertigo/vestibular disorders (e.g. migraineous vertigo) [62]. A great number of MT respondents were diagnosed with depression after MdDS, confirming previous research [49]. Depression in MdDS patients may also be particularly important if considering its effect on cognitive functions [112]. Cognitive problems such as brain fog, and difficulties in focusing and concentrating, have been previously observed in MdDS [80], however there has not been an established link between depression and the psychological component of MdDS with cognitive dysfunctions. We encourage future studies to examine closely the association between the two.

It is also very likely that the presence of psychological disorders may contribute to altering sensory information and interpretations in the brain regions (amygdala, insular cortex, cingulate cortex and prefrontal cortex) [113].

Previous studies focussing on brain functions in MdDS patients have reported hypometabolism in the left prefrontal cortex, left temporal cortex, right amygdala, and right insula [64]. The severity of MdDS bodily sensations and of vestibular dysfunction suggests that there may be a critical dependence of the brain and body upon vestibular input. It is known that there is a higher presence of depersonalization and derealisation symptoms in patients with vestibular dysfunctions, suggesting that the vestibular inputs are greatly contributing to the definition of self, in terms of the sense of where the body is in relation to the external environment [28]. The association of psychological disorders with MdDS may contribute to the neuroimaging differences

previously observed.

Lastly, our study suggests that MdDS is the cause for developing psychological disorders in both its subtypes, which is supported by the fact that antidepressants as well as sedative medications (e.g. benzodiazepines) are found to be helpful in MdDS patients and therefore often prescribed by healthcare professionals [80]. The use of such medication may also have an impact on stress levels, which from our study seems to be responsible for aggravating MdDS symptoms. A further and more detailed examination of the psychological component, psychological symptoms associated to MdDS and of stress on MdDS patients should be undertaken.

Study Limitations and future perspective

Access to patients was limited to those active on social media and those who may have visited webpages that promoted our studies. The study was primarily limited by the inability of all respondents to recall or their lack of knowledge regarding specific details, particularly those connecting previous diagnoses and onsets. A great limitation was that we did not ask for the clear age of onset. We are aware that the number of SO respondents was limited and less than the MT group, and that more SO subjects were self-diagnosed. In addition to this, the definition between 'other onsets' and 'spontaneous' onsets could have been better clarified to the respondents of the SO survey, who for the first time had to self-define if they had 'spontaneous' or 'other onset' MdDS. Some respondents in this study were self-diagnosed, however we assumed that many were able to diagnose themselves through resources available on the Internet. Ideally, a larger patient pool where all respondents have received an official MdDS diagnosis would be preferable in future studies. Lastly, regarding the psychological features of MdDS, we recognise that more detailed questions should have been asked. The current questionnaires only addressed the presence of two main psychological entities - anxiety and depression, before or after MdDS onset. In relation to psychological features also cognitive performances and socio-economical status should have been further explored to provide a full picture of the patient characterization. For future studies we encourage the distribution of validated questionnaires used for assessing both psychological features, psychosomatic symptoms and match them with cognitive and socio-economical data in MdDS subjects.

Conclusion

This was the first online survey comparing two subtypes of MdDS. No major significant epidemiological differences were reported between MT and SO groups; both reported a female prevalence and the same mean age. MT patients are easier to diagnose than SO patients in terms of diagnostic procedures. Almost all the MT and SO respondents equally reported to have a reduction or absence of symptoms when re-exposed to passive motion. We encourage further EEG or fMRI studies to address this paradoxical perception of motion in MdDS patients. With this taken into account, we propose an updated version of the diagnostic criteria previously proposed by Van Ombergen and colleagues [44], to which we include a symptom alleviation when exposed to motion, and also including the SO subtype.

Lastly, these surveys allowed us to gain valuable information about other potential triggers and psychological features associated with MdDS. Stress was identified as a result of MdDS, a symptom aggravation factor, as well as a trigger for the onset especially in SO patients. Further studies should focus on measuring stress responses and autonomic reactions in MdDS. Depression and anxiety were identified as a clear consequence of MdDS and as a result they should be taken into account for treatment options and patient management.

Overall, this study showed to be clinically relevant, providing more accurate diagnostic guidelines that can help establish an earlier and more accurate diagnosis in MdDS patients and provide more information about MT and SO MdDS subtypes.

4.CHAPTER 4 – HORMONAL COMPONENT IN MdDS:

- Gonadal Hormones & MdDS

Part of this chapter (section 4.1) has been published as:

Mal de Debarquement Syndrome: A Retrospective Online Questionnaire on the Influences of Gonadal Hormones in Relation to Onset and Symptom Fluctuation

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Section 4.2 of this chapter has been submitted and it is currently under review:

Pilot Study on Mal de Debarquement Syndrome Patients during Pregnancy

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This chapter covers multiple aspects and investigations between potential relations among sex steroids (gonadal hormones) and MdDS patients, the sections are going to be divided into 4.1; 4.2; 4.3.

4.1. The study presented in section 4.1 was created in the form of retrospective questionnaires and it was related to MT and SO patients, with the aim to compare the two onset groups.

4.2 The research project presented in the section 4.2 is a specific study designed for pregnant women affected by MdDS. The study was performed in the form of a retrospective online survey.

4.3 In section 4.3 study limitations, ongoing and future projects are discussed.

All these projects (4.1/2/3) shares the similar goal of increasing the current understanding of a potential gonadal influence on MdDS pathophysiology and symptoms fluctuations.

4.1 Mal de Debarquement Syndrome: A Retrospective Online Questionnaire on the Influences of Gonadal Hormones in Relation to Onset and Symptom Fluctuation

Introduction: Mal de Debarquement Syndrome (MdDS) is a condition characterized by a persistent perception of self-motion, in most cases triggered from exposure to passive motion (e.g. boat travel, a car ride, flights). Patients whose onset was triggered in this way are categorized as Motion-Triggered (MT) subtype or onset group. However, the same syndrome can occur spontaneously or after non-motion events, such as childbirth, high stress, surgery, etc. Patients who were triggered in this way are categorized as being of the Spontaneous/Other (SO) subtype or onset group. The underlying pathophysiology of MdDS is unknown and there has been some speculation that the two onset groups are separate entities. However, despite the differences in onset between the subtypes, symptoms are parallel and a significant female predominance has been shown. To date, the role of gonadal hormones in MdDS pathophysiology has not been investigated. This study aimed to evaluate the hormonal profile of MdDS patients, the presence of hormonal conditions, the influence of hormones on symptomatology and to assess possible hormonal differences between onset groups. In addition, the prevalence of migraine and motion sickness and their relation to MdDS were assessed.

Method: Retrospective online surveys were performed in 370 MdDS patients from both onset groups. Data was analyzed using Fisher's exact test or Fisher-Freeman-Hanlon exact test. When possible, data was compared with normative statistical data from the wider literature.

Results: From the data collected, it was evident that naturally cycling female respondents from the MT group were significantly more likely to report an aggravation

of MdDS symptoms during menses and mid-cycle ($p < 0.001$). A few preliminary differences between the onset groups were highlighted such as in regular menstrual cycling ($p = 0.028$), reporting menses during onset ($p < 0.016$), and migraine susceptibility after onset ($p = 0.044$).

Conclusion: These results demonstrate a potential relation between hormone fluctuations and symptom aggravation in the MT group. This study is an important first step to suggest a hormonal involvement in the pathophysiology of MdDS and provides a base for further hormonal investigation. Future prospective studies should expand upon these results and explore the implications for treatment.

Introduction

From the epidemiological survey presented in Chapter 3, it is clear that a female predominance was confirmed also in our survey. Most of the previous studies on MdDS have similarly describe a female predominance (ratio 9:1). As such, this can be considered a typical feature for the disorder [21, 44, 45, 47, 58–60]. During one of the first clinical assessments on MdDS, Hain and colleagues reported that 80% of the MdDS patients included in their study were female [50] and, since the age range was limited, most patients were post-menopausal [60]. Sex steroids are known to be potent modulators of neural plasticity under normal and pathological conditions. Thus, considering that MdDS has been defined as a neuroplasticity disorder [23] and the clear gender disproportion within MdDS patients, it seems logical to argue the presence of a potential involvement of gonadal hormones in affecting MdDS pathophysiology or symptoms. Despite numerous studies have identified MdDS gender disparity, up to now, no study has ever explored the potential role that hormones could play in developing or influencing MdDS.

In general, it is known that women are susceptible to hormonal changes throughout their menstrual cycle, reporting mood and behavioural changes in parallel with the fluctuation of hormones, e.g. progesterone, estrogen and luteinizing hormone [114]. Hormonal fluctuations have been found to play an important role in other vestibular disorders, such as vestibular migraine and Ménière's disease (MD) [36]. Furthermore, hormonal fluctuations are linked to variations in symptoms of several inner ear disorders, e.g. vertigo, instability, tinnitus, hearing loss and intra-aural pressure [115, 116]. In female vestibular patients, it is therefore suggested that gonadal hormones may have the ability to influence vestibular symptoms. Additionally a greater number of vestibular patients report their onset to be in the perimenopausal phase [117]. The vestibular

apparatus communicates with the central nervous system (CNS), which is very sensitive to the influence of pathological or physiological factors that can disturb homeostasis (from the Greek: “homoios” – similar – like and “stasis” – fixed, immobile) [117] or to better named it homeodynamics, reflecting more accurately the plastic structural and functional modification that the organism undergo. The central controls for the vestibular apparatus may therefore be sensitive to homeodynamic changes, where hormones may act as master regulators of brain plasticity changes induced, for example by external factors, sensory inputs or a peculiar pathological condition [118].

Another aspect to consider within MdDS patients is migraine. Several vestibular pathologies have been shown to be epidemiologically associated with migraine [101], such as MD, benign paroxysmal positional vertigo, psychogenic vertigo and many others. Similarly, MdDS has a strong interrelation with migraine also, with a high number of MdDS patients reporting migrainous symptoms [49, 51]. When considering migraine, it is essential to think about hormones. Estrogen as well as ovarian steroid hormones have been implicated in migraine symptom fluctuation and pathophysiology [39, 119]. From a recent publication [49], it has been reported that both MdDS subtypes similarly report to be affected by migraine after MdDS onset. In migrainous patients the drop in estrogen, the so called *estrogen withdrawal*, observed during menses, has been described as the principal cause for migraine vulnerability in women [39]. Migrainous female patients also experience symptom variability in response to fluctuating hormonal levels, for example observed during pregnancy, menopause, hormone replacement therapy (HRT) and the use of hormonal contraceptives [120]. Considering hormonal changes throughout different ages, along with migraine headache, dizziness is one of the common symptoms in perimenopause [121]. With ageing the neuroprotective effect of sex steroids that depend on the activation of their nuclear

receptors may be impaired in aged nervous system, where ageing can affect the expression of steroid receptor and steroid receptor co-activators [122]. Estrogen is known for stimulating neural excitability while progesterone exhibits inhibitory actions in the central nervous system. Therefore imbalances between these hormones may give rise to physiological conditions that predispose patients to develop MdDS, similarly to what observed for migraine patients [122].

Another condition affected by hormonal fluctuations is motion sickness. Females are known to be generally more prone to motion sickness than males, especially during menses if not on any form of hormonal [123–125]. Interestingly, two-thirds of general migraine sufferers also report to be prone to developing motion sickness [123, 126].

In this study, we hypothesize that hormones may be implicated in affecting MdDS patients, with a similar mechanism as is involved in migraine, motion sickness and MD.

Given the clear predominance of female patients affected by MdDS [44], and acknowledging the strong role of female gonadal hormones on the CNS [127] as well in the implication of other disorders like migraine [39], we hypothesised that hormones may be implicated in MdDS pathophysiology. With this study we aimed to survey the two onset groups (MT and SO) with regards to their hormonal profile, hormonal associated conditions and potential symptoms fluctuations with regards to different hormonal status (e.g. menopause, etc.). The aim of this study was also to gain primary explorative data on the hormonal profile of male respondents. When possible a comparison between the two onset groups was performed, in order to assess if the two onset groups differ from an hormonal perspective. Lastly both genders and onset group were asked if they have experienced migraine and motion sickness, prior to and after MdDS onset.

Specifically our main hypothesis was that MdDS female patients would be vulnerable to hormonal changes, particularly to the fluctuations of estrogen. Thus, that withdrawal of estrogen (as is the case in the peri-menopausal - menopausal transition, and menstruation [39]) might lead to an aggravation of symptoms in female MdDS patients, similarly to what is observed in MD and migraine sufferers [128]. This may also cause a state of vulnerability for potential MdDS onset. The hormonally regulated mechanism considered for migraine is here hypothesized as a potential contributor to MdDS pathogenesis in female subjects.

Materials and Methods

Study Population and Recruitment

Patients diagnosed by specialists or believing to suffer from MdDS (also referred to as self-diagnosed patients) were recruited for the study. Inclusion criteria for this study are summarized in Table 10 and are based upon guidelines that were published earlier [21]. Patients were recruited across the USA, Europe, and Australia, however respondents from Asia and South America were also able to access the study. MdDS patients were recruited through the Department of Otorhinolaryngology and Head and Neck Surgery, a tertiary referral centre, at the University Hospital of Antwerp, Belgium. Patients were also recruited globally through the main MdDS support groups: MdDS Australia Facebook Support Group, MdDS UK Facebook Support Group, website of MdDS Research Group at Mount Sinai Hospital, Western Sydney University MdDS Research Group Facebook page, website and Facebook of Vestibular Disorders Association (VEDA), and website and Facebook of Whirled Foundation and the REACT Community Facebook. Ethical approval was provided by the Ethics Committee of the University Hospital Antwerp Belgium (IRB number 15/44/454) and by the Western Sydney University Human Ethics Committee (H11962). Each respondent provided informed consent. All

investigations have been conducted according to the principles expressed in the Declaration of Helsinki.

1)	≥18years old
2)	Patient reporting sensations of self-motion (rocking, rocking, swaying and bobbing) for longer than one month, where the symptoms could not be explained by another diagnosis
3)	Patients reporting MdDS symptoms after the exposure to passive motion (<i>MT group</i>)
4)	Patients reporting similar symptoms without a clear motion event or any obvious cause (<i>spontaneous</i>). Patients reporting the initial symptoms after a strong emotional or stressful event (e.g. childbirth, physical or emotional trauma, surgery, etc.) (<i>Other</i>) (<i>Combined = SO group</i>)

Table 10: Inclusion criteria used for the study. See guidelines [21, 44].

Abbreviations: MdDS = Mal de Debarquement Syndrome, MT = Motion-Triggered and SO = Spontaneous/Other.

Questionnaires

The questionnaires were distributed online using two survey platforms; Survey Monkey (MT survey) and Qualtrics (SO survey). The MT survey consisted of 51 questions and the SO survey consisted of 85 questions. More questions were made available to the SO group, as the respondents were re-directed to one of two specific categories: 1) Spontaneous, and 2) Other, according to their onset. Additionally, more extensive questions about hormonal profiles were distributed in the SO MdDS survey (Questions available as Supplementary Material Annex 2).

The questions were divided into separate categories for both surveys, from diagnostic to hormonal questions to onset triggers. For more details on the diagnostic and onset features please refer to Mucci et al 2018 [21]. With regards to the current manuscript, the sections included are: epidemiology, sensitivity to triggers, hormonal section including: *hormonal fluctuations, imbalances, hormonal clinical conditions and medications* as well as *migraine and motion sickness* prevalence reported by MdDS respondents prior and after MdDS onset. Female respondents were required to answer questions about their hormonal status. They were asked if they have reached menopause, defining menopause as 12 months' absence of the menstrual cycle

according to its medical definition [129]. The MT and SO surveys were created in two phases. The SO survey was conducted a few months after the MT survey allowing some improvements to be incorporated. However, the questions were presented to the groups were the same, but in some cases the format changed. For example, in the SO group the questions relating to menses and mid-cycle/ ovulation were distinguished as two separate questions, while in the MT survey those questions were merged in one. In addition to this, at the end of the hormonal question section, respondents from both groups and genders were given the opportunity to comment or add information in an open-ended comment section that they believed was relevant to the hormonal section of the survey.

Normative Data Comparison

As this study lacked a control group, whenever possible, the results from the surveys were compared with normative data, collected from previous publications. The importance of normative data has been previously described [130], so as a result, the most appropriate data that matched age and condition was carefully selected. To increase the quality of the normative data, we considered data from the USA population, firstly because the majority of respondents were US based, secondly because a larger number of studies were available within the US population only.

Statistical analysis

There was little control over sample size and no formal sample size calculations were undertaken prior to data collection. The sample size of 370 was sufficient to provide 95% confidence intervals on proportions with a maximum margin of error of $\pm 5.1\%$ (calculated using: <http://www.polarismr.com/help-center/stat-calculator-sample-size/>). The per group sample sizes of 266 and 104 provide at least 80% power to detect a

difference of 16 percentage points or more between groups (e.g. 50% versus 66%) statistically significant at the 5% significance level (calculated using G*Power Software: <http://www.gpower.hhu.de/en.html>).

Sample data was summarized using means for age and percentages for the categorical variables. Population results were extrapolated from the sample using 95% confidence intervals. Independent samples t-test were used to investigate possible differences between the MT and SO populations. Associations between categorical variables are investigated using Fisher's exact test (for 2x2 tables) or Fisher-Freeman-Hanlon exact test, which are robust to small strata. Due to likely biases in the pattern of missing data, we have included missing observations as a separate category. Warnings about the potential for biases arising from both the volunteer sample and missing responses are included in the discussion. Binomial tests were used to check for any evidence of preference towards a 'yes' or 'no' answer on questions of the association between menstrual cycle and MdDS symptoms. Statistical analysis was performed with SPSS version 24 (IBM Corp) and an online calculator for the confidence intervals on proportions was used (online calculator: <http://www.sample-size.net/confidence-interval-proportion/>).

Responses to open-ended questions were processed by a single coder. When respondents reported extra comments, for example reflecting their beliefs as to the causes or contributors to their MdDS or to symptom fluctuations, those were tabulated into categories of opinion. Illustrative examples and relative frequencies of particular opinions are provided in the results.

Epidemiology – sample description

A total of 370 surveys were collected, with 266 (72% of the whole group) being of the MT subtype, and 104 (28% of the whole group) being of the SO subtype. The MT group consisted of 242 females (93% of the MT group), 18 males (6.7%), and 6 respondents did not specify their gender (2.3%). The SO group consisted of 92 females (88.4% of the SO group), 7 males (6.7%) and 5 subjects with unspecified (4.8%) gender. The mean age was similar for both groups, i.e. 48.9 years (SD = 11.4) for the MT group and 48.9 years (SD = 13.5) for the SO group. Half of all the respondents from both surveys were from North America (50.9%) and about a quarter each from Europe (25.2%) and Australia (22%). The data indicates that officially diagnosed females, from North America in the fifth decade of their lives represented the majority of respondents. The main characteristics of respondents are summarized in Table 11, where an account of missing data is also provided.

	Total n=370	MT n=266	SO n=104	Difference (pvalue)
Age				
Mean (95% CI)	48.9 (47.7 , 50.1)	48.9 (47.5 to 50.3)	48.9 (46.2 to 51.6)	0.998 ^a
SD	12.03	11.4	13.5	
Missing*	1.4% (5)	0.4% (1)	3.8% (4)	
Gender with a missing value category				
Female %	90.3% (334)	91.0% (242)	88.5% (92)	0.476 ^b
Male %	6.8% (25)	6.8% (18)	6.7% (7)	
Missing	3.0% (11)	2.3% (6)	4.8% (5)	
Gender excluding missing responses				
Female % (95% CI)	93.0% (89.9 , 95.4)	93.1% (89.3 , 95.8)	92.9 % (86.0 , 97.1)	1.000 ^b
Location				
North America	50.9% (188)	50.9% (135)	51.0% (53)	0.858 ^b
Europe	25.2% (93)	25.7% (68)	24.0% (25)	
Australia	22.0% (81)	21.9% (58)	22.1% (23)	
Asia	0.8% (3)	0.8% (2)	1.0% (1)	
South America	1.1% (4)	0.8% (2)	1.9% (2)	
Missing*	0.3% (1)	0.4% (1)	0	
Officially diagnosed by a health professional a with missing value category				
Yes	82.4% (305)	86.5% (230)	72.1% (75)	<0.001 ^b
No	14.3% (53)	13.5% (36)	16.3% (17)	
Missing	3.2% (12)	0% (0)	11.5% (12)	
Officially diagnosed by a health professional excluding missing responses				
Yes (95% CI)	85.2% (81.1%, 88.7%)	86.5% (81.8%, 90.3%)	81.5% (72.1%, 88.9%)	0.306 ^b

Table 11: Demographics and diagnostic confirmation of all respondents, and within the Motion-Triggered (MT) and Spontaneous/Other (SO) onset groups.

Abbreviations: SD = Standard Deviation and CI = Confidence Interval.

*Omitted from the hypothesis tested. a. Independent samples t-test / b. Fisher's exact or Fisher-Freeman-Hanlon exact test.

Female Hormonal Survey Section

Unfortunately, only around half of the respondents from the SO group completed the hormone-related questions, as some respondents exited the survey before it ended. Data were analysed including and excluding a missing category. Including the missing category produced statistically significant differences between MT and SO, which

confirms the potential for response bias in the analyses, which exclude the missing data. Results from these questions are summarized in Table 12,13,14.

Hormonal phases, associated medications and hormonal conditions

Female respondents from both MT and SO groups were asked if they had reached menopause or were still in an active reproductive phase, more details are reported in Table 3. 41.2% of female respondents (both MT and SO) had experienced menopause, with no statistically significant evidence of any difference between the MT and SO groups ($p=0.195$), and 58.8% were still in an active reproductive phase. Respondents who answered 'yes' to menopause were asked if they had been using HRT, assuming they were in perimenopause or menopause, if they were taking a combined HRT medication (i.e. combined containing both estrogen and progesterone) or an estrogen-only medication. A total of 21% of menopausal respondents were using HRT (combined or estrogen only HRT). The number of respondents from the SO group was small and no statistical significance difference was reached between the two onset groups ($p=0.197$ Fisher's exact test). 8.7% of MT subjects and 20% of SO respondents reported to use combined HRT and 11.5% MT and 6.7% SO to use oestrogen only HRT respectively, thus their difference was rather small ($p=0.197$).

A total of 170 females who reported to be in their active reproductive years (naturally cycling), from both onset groups, were asked whether they had a regular menstrual cycle. The SO group had a much higher rate of missing data than the MT group. After excluding missing data, the MT group had a statistically significantly higher proportion of females with regular cycles compared to the SO group (72.1% versus 47.8% - Fisher's exact test $p=0.028$), suggesting higher menses irregularity within the SO group. About 7.1% of respondents had been diagnosed with Polycystic Ovarian Syndrome (PCOS),

with no statistically significant differences between groups when excluding the respondents who did not answer this question or that were unsure. Excluding the less than 3% missing data, 23.6% of the naturally cycling respondents reported to use hormonal contraceptives, with no statistically significant difference between groups (Fisher-Freeman-Hanlon exact test $p=0.362$).

Respondents from both groups were asked if they have been diagnosed with any hormonal imbalances or conditions. Definitive answers were provided by 205 respondents, with 85% of the female MT respondents but only 14.6 % of the female SO respondents engaged in this question. Excluding the uncertain answers, the majority of both groups reported no hormonal imbalances or conditions. 24.0% of MT and 26.7% of SO reported to have a hormonal condition respectively with no statistically significance difference between them ($p=0.818$). The most reported condition was hypothyroidism in both groups (30 out of 42 (73%) in the MT and 7 out of 8 (87.5%) in the SO group).

Females	Total n=334	MT n=242	SO n=92	Difference Fisher's exact test or Fisher-Freeman-Hanlon exact test (pvalue)
Menopause including a missing category				
Yes %	35.6% (119)	43.0% (104)	16.3% (15)	<0.001
No	50.9% (170)	57.0% (138)	4.8% (32)	
Missing	13.5% (45)	0.0% (0)	48.9% (45)	
Menopause excluding missing responses				
Yes % (95% CI)	41.2% (119)	43.0% (104)	31.9% (15)	0.195
HRT	Total n=119	MT n=104	SO n=15	
Combined HRT	10.1% (12)	8.7% (9)	20.0% (3)	0.197
Est-only HRT	10.9% (13)	11.5% (12)	6.7% (1)	
No	79.0% (94)	79.8% (83)	73.3 (11)	
Regular Menses including a missing category	Total n=170	MT n=138	SO n=32	
Yes	61.2% (109)	71.0% (98)	34.4% (11)	<0.001
No	29.4% (50)	27.5% (38)	37.5% (12)	
missing	6.5% (11)	1.4% (2)	28.1% (9)	
Regular Menses excluding missing responses	Total n=170	MT n=138	SO n=32	
Yes	68.6% (109)	72.1% (98)	47.8% (11)	0.028
PCOS including a not sure & missing category	Total n=170	MT n=138	SO n=32	
Yes	7.1% (12)	7.2% (10)	6.5% (2)	<0.001
No	75.1% (127)	86.2% (119)	25.8% (8)	
Not sure or missing	17.8% (30)	6.5% (9)	67.7% (21)	
PCOS excluding missing responses				
Yes	8.6% (12)	7.8% (10)	20.0% (2)	0.208

Hormonal Contraceptive Use including a missing category	Total n=170	MT n=138	SO n=32	
Combined (Est & Prog)	17.1% (29)	16.7% (23)	18.8% (6)	0.061
Prog only	5.9% (10)	7.2% (10)	0% (0)	
No	74.1% (126)	74.6% (103)	71.9% (23)	
Missing	2.9% (5)	1.4% (2)	9.4% (3)	
Hormonal Contraceptive Use excluding missing responses	Total n=170	MT n=138	SO n=32	
Combined (Est & Prog)	17.6% (29)	16.9% (23)	20.7% (6)	0.362
Prog only	6.1% (10)	7.4% (10)	0% (0)	
No	76.4% (126)	75.7% (103)	79.3% (23)	
Hormonal Condition including a not sure & missing category	Total n=334	MT n=242	SO n=92	
Yes (e.g. high Test, high Est, HypoT, HyperT, etc.)	15.0% (50)	17.4% (42) / (73% who replied Yes had HypoT)	8.7% (8) / (87.5% who replied Yes had HypoT)	<0.001
No	46.4 (155)	55.0% (133)	23.9% (22)	
Not sure & missing	38.6% (129)	27.7% (67)	67.4% (62)	
Hormonal Condition excluding not sure and missing responses	Total n=334	MT n=242	SO n=92	
Yes	24.4% (50)	24.0% (42)	26.7% (8)	0.818

Table 12: Hormonal related data from female respondents in relation to MdDS onset (e.g. menopausal), use of hormonal replacement, therapy, use of contraceptive, hormonal imbalance conditions), presented as a percentage of the group and raw number.

Abbreviations: MT = Motion-Triggered, SO = Spontaneous/Other, NA= Not Applicable, CI = Confidence Interval, HRT = Hormone Replacement Therapy, PCOS = Polycystic Ovarian Syndrome, Test = Testosterone, Est = Estrogen, Prog = Progesterone, HypoT = Hypothyroidism and HyperT = Hyperthyroidism.

Menstrual cycle phase during onset

Respondents were asked 'to the best of your knowledge:

1) were you menstruating during the motion event that you believe initiated your MdDS? For the SO group only

2) were you ovulating (~ 2 weeks prior to period) during the time your MdDS symptoms started?

3) were you on any form of hormonal contraception during the time your MdDS symptoms started?'

Results are reported in Table 13. Aside from differences in response rates, no further statistically significant differences were observed between MT and SO groups with regards to MdDS onset starting during menstruation ($p=0.543$) or starting while using hormonal contraceptive ($p=0.378$).

SO/MT: Onset started during menses including a not sure & missing category	Total n=170	MT n=138	SO n=32	Difference Fisher's exact test or Fisher-Freeman-Hanlon exact test (pvalue)
Yes	21.2% (36)	23.9% (33)	9.4% (3)	0.016
No	44.1% (75)	46.4% (64)	34.4% (11)	
Missing & Not sure	34.7% (59)	29.7% (41)	56.3% (18)	
SO/MT: Onset started during menses excluding the not sure & missing responses	Total n=170	MT n=138	SO n=32	
Yes	32.4% (36)	34.0% (33)	21.4% (3)	0.543
SO/MT: Onset started while using a hormonal contraceptive including a not sure & missing category	Total n=170	MT n=138	SO n=32	
Yes	25.9% (44)	29.7% (41)	9.4% (3)	<0.001
No	56.5% (96)	93 (67.4%)	9.4% (3)	
Not sure and missing	17.6% (30)	2.9% (4)	81.3% (26)	
SO/MT: Onset started while using a hormonal contraceptive excluding the not sure missing responses	Total n=170	MT n=138	SO n=32	
Yes	31.4% (44)	30.6% (41)	50.0% (3)	0.378
SO: Onset started during ovulation or mid-cycle	Total SO n=32	Difference (pvalue)		
Yes	9.4% (3)			
No	21.9% (7)	NA		
Not sure	62.5% (20)			
missing	6.3% (2)			

Table 13: Number of female subjects in different menstrual phases or conditions during the believed onset, presented as a percentage of the group and raw number.

Abbreviations: MT = Motion-Triggered and SO = Spontaneous/Other.

Menstrual cycle phases and symptom aggravation

Naturally cycling respondents from both onset groups were asked if their symptoms were normally higher during menses or mid-cycle around ovulation. For the SO group, the two hormonal phases were asked about in two separate questions. We could not compare results between the MT and SO groups. Instead we tested the hypothesis that respondents were more likely to answer this question with a yes rather than no. From Table 14 and Figure 11 it is evident that the MT group were 2.5 times more likely to answer 'yes' to an aggravation of symptoms during menses or mid-cycle/ ovulation (Binomial test excluding "not sure" $p < 0.001$), with no corresponding differences in the SO group.

Symptom aggravation during menses and ovulation including not sure	MT n=149	MT excluding Not sure	Binomial test^a (pvalue)
Yes	49.7% (74)	71.8% (74)	<0.001
No	19.5% (29)	28.2% (29)	
Not sure	30.9% (46)		
Symptom aggravation during menses including not sure and missing	SO n=28	MT excluding Not sure	
Yes	39.3% (11)	57.9% (11)	0.648
No	28.6% (8)	42.1% (8)	
Not sure	32.1% (9)		
Symptom aggravation during ovulation including not sure and missing	SO n=28		
Yes	28.6% (8)	52.9% (8)	1.000
No	32.1% (9)	47.1% (9)	
Not sure & missing	39.3% (11)		

Table 14: Reported aggravation of symptoms during menses and ovulation, presented as a percentage of the group and raw number. Testing for evidence of a difference in the proportions of yeses and nos.

Abbreviations: MT = Motion-Triggered, SO = Spontaneous/Other, and NA= Not Applicable

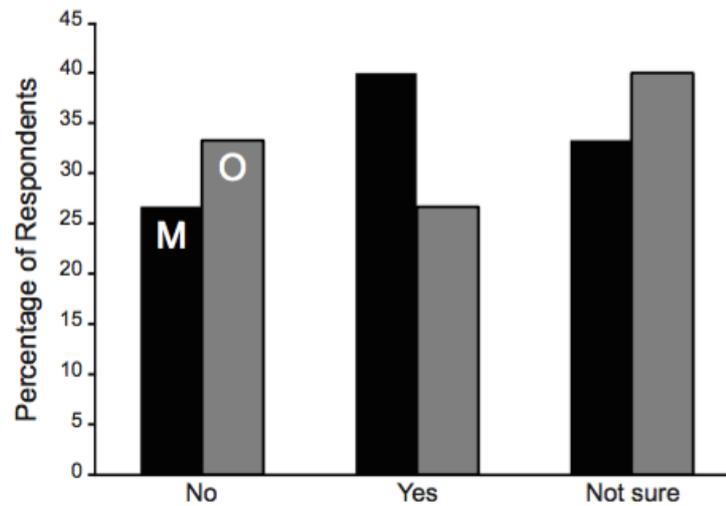


Figure 11: Symptom aggravation during menses (black bars; M) and mid-cycle around ovulation (grey bars; O) in SO group expressed as the percentage of respondents. No statistically significant difference was observed among the SO group reporting an aggravation of symptoms during menses or ovulation.

From the table and figure above it seems clear that the MT group were 2.5 times more likely to answer 'yes' to aggravation of symptoms during menses or mid-cycle/ ovulation ($p < 0.001$), with no corresponding differences in the SO group.

Menstrual cycle phases and sensitivity to triggers

Respondents were asked a series of questions regarding triggers, including:

'Do you feel that you are more sensitive to your triggers during menses / or during mid-cycle (around ovulation)?' (The SO group had two distinguished questions provided for menstruation and mid-cycle around ovulation).

From Table 15 it is evident that the MT group were more statistically more likely to say 'no' than 'yes' to being more sensitive to triggers during menses or mid-cycle around ovulation ($p < 0.001$), while no statistically significant departures from chance variation were found for the SO group.

More sensitive to triggers during ovulation and menses	MT n=148	MT Excluding Not sure	Binomial test^a (pvalue)
Yes	17.5% (26)	28.3% (26)	p<0.001
No	44.5% (66)	71.7% (66)	
Not sure	37.8% (56)		
More sensitive to triggers during menses	SO n=30	SO excluding not sure	
Yes	40% (12)	63.2% (12)	
No	23.2% (7)	36.8% (7)	0.359
Not sure	36.7% (11)		
More sensitive to triggers during ovulation	SO n=30	SO excluding not sure	
Yes	26.7% (8)	47.1% (8)	
No	30% (9)	52.9% (9)	1.000
Not Sure	43.3% (13)		

Table 15: Reported sensitivity to triggers during different phases of the menstrual cycle, presented as a percentage of the group and raw number.

Testing for evidence of a difference in the proportions of yeses and nos.

Abbreviations: MT = Motion-Triggered and SO = Spontaneous/Other.

Pregnancy and MdDS

Respondents were questioned about pregnancy during MdDS, with only 6% reporting to have had MdDS while being pregnant. Given that pregnancy is one of the common triggers for SO MdDS, it is not surprising to find that twice the percentage of the SO group were pregnant than the MT group (MT 12/242, 5.0% versus SO 5/45, 11.1%) during onset. However, these numbers were too small to provide evidence of difference from the wider population (p=0.108 one sided Fisher's exact test)

Hormonal Imbalances and Conditions in Males

There were 25 male respondents; 18 (72.0%) in MT and 7 (28.0%) in SO. Both groups were asked if they had been diagnosed with a hormonal imbalance or condition (e.g. low or high testosterone, hypothyroidism). Three out of 18 (16.7%) reported having been diagnosed with low testosterone levels, 2 SO respondents and 1 MT respondent, while 1

SO respondent reported high testosterone. Due to the very low sample size, no significant difference among MT and SO group was reported ($p=0.088$).

Overlap of MdDS with Migraine and Motion Sickness

All respondents (male and female) were asked if they experienced migraine and motion sickness before and/or after their MdDS symptoms appeared. A statistical significant difference between the MT and SO groups was observed with regards to migraine, with a higher percentage of SO respondents affected ($p=0.044$), (Fisher-Freeman-Hanlon exact test $p=0.063$ considering before, after or similarly before and after onset), for details see Table 16. Similarly, despite small a higher percentage SO respondents (64.0%) reported to be affected by motion sickness after MdDS onset compared to the MT group (45.5%) (Fisher exact test $p=0.094$). Onset of motion sickness is statistically significantly more likely to occur after MdDS for the SO group ($p=0.032$) although SO results may be affected by response bias.

Do you experience migraines or frequent headaches/head pressure?	Total n=296	MT n=264	SO n=32	Fisher-Freeman-Hanlon exact test (pvalue)
Yes	201 (67.9%)	174 (65.9%)	27 (84.4%)	0.044
No	95 (32.1%)	90 (34.1%)	5 (15.6%)	
When did you experience migraines or frequent headaches/head pressure?	Total n=296	MT n=264	SO n=32	
Before and after MdDS onset	95 (47.3%)	83 (47.7%)	12 (44.4%)	0.063
Before MdDS only	10 (5.0%)	6 (3.4%)	4 (14.8%)	
After MdDS onset only	96 (47.8%)	85 (48.9%)	11 (40.7%)	
Are you prone to having motion sickness?	Total n=289	MT n=264	SO n=25	
Yes	136 (47.1%)	120 (45.5%)	16 (64.0%)	0.094
No	153 (52.9%)	144 (54.5%)	9 (36.0%)	
When were you prone to having motion sickness?	Total n=289	MT n=264	SO n=25	
Before and after MdDS onset	74 (54.4%)	69 (57.5%)	5 (31.3%)	0.032
Before MdDS only	25 (18.4%)	23 (19.2%)	2 (12.5%)	
After MdDS onset only	37 (27.2%)	28 (23.3%)	9 (56.3%)	

Table 16: Reported migraine and motion sickness experience with relation to MdDS onset presented as a percentage of the group and raw number.

Abbreviations: MdDS = Mal de Debarquement Syndrome, MT = Motion-Triggered and SO = Spontaneous/Other.

Normative Data

Normative data from the literature on hormonal aspects [131–138] taken from the US population, are reported in Table 17. Normative data with regards to motion sickness and menopause have been excluded, as the interest of this study was to evaluate how many menopausal women suffer from MdDS and; secondly how motion sickness may be affecting MdDS patients differently, according to their onset (prior to or after onset) or to their onset type.

Regular menses in naturally cycling females:	<i>Distribution of the regularity and length of menstrual cycles among 4900 females aged 34-45 - 12% had irregular menses [131]</i>
Polycystic Ovarian Syndrome in naturally cycling females:	<i>In a study conducted in 1990, considering Caucasian females, 5.5% of the general female population was estimated to suffer from Polycystic Ovarian Syndrome [136].</i>
Use of hormonal contraceptives in naturally cycling females:	<i>25% of females aged 30-35 / 19.9% of females aged 35-39 (average 22.5%) [133].</i>
Use of hormonal replacement therapy:	<i>A study on perimenopausal and menopausal females showed that 20.2% were on some form of hormone replacement therapy medication [138].</i>
Hypothyroidism:	<i>9.4% suffer from Hypothyroidism (clinical and subclinical), and this rate increases with age [137].</i>
Migraine:	<i>18.9% of females reported severe migraine, twice higher than males [135].</i>

Table 17: Normative Data from previous studies of the US population, which correspond to the focal points of this study.

Normative data from the literature regarding hormonal characteristics, conditions and medications, and migraine [131–138], taken from the US population, are reported in Table 17. When comparing the data collected from the MdDS respondents with normative data, the number of female MdDS respondents with irregular menses was more than twice as high than the normal population when considering the MT group (27.5% vs. 12%), and was more than 4-fold higher in the SO group (52.2% vs. 12%). The number of respondents with PCOS was slightly higher (7.1% excluding missing responses) when compared to the normal population (5.5%), considering a 1990 NIH report on White Caucasians [132]. Additional normative data reported that 25% of females aged 30-35 years and 19.9% aged 35-39 years reported hormonal contraceptive use (average of 22.5%) [132], which was marginally lower than what was reported in this study (23%). 21% of the female respondents who had experienced menopause indicated to be taking either a combined or estrogen-only HRT medication, this is very slightly higher than the general population which reports a usage rate of 20.2% in perimenopausal and menopausal females [138], 17.3% (50 of 289) of respondents reported to have some form of hormonal condition, and 38 of these 50 respondents indicated having hypothyroidism (MT and SO together). Considering the whole group of respondents that answered this question, the rate of hypothyroidism was 13.1%, which was higher than the prevalence in the US population, 9.4% [137]. The percentage of MdDS respondents who were prone to experiencing was 81.6% considering an average among suffering from migraine before and after onset and only after MdDS onset. This was higher than the normal population at 18.1% [135].

Open-Ended Comments

Female Respondents

A total of 100 open-ended comments were collected. 74 comments were made by the MT group and 26 from the SO group. Among those, a high number from both onset groups, reported to believe that perimenopause (often expressed by the respondents as “going into menopause”) or menopause contributed to their MdDS onset (55 out of 100 comments). Similarly, both groups reported to believe that hormones and hormonal imbalances were related to their MdDS symptoms (72 out of 100 comments). A few respondents (13 out of 100 comments), equally from MT and SO groups, reported to have undergone surgeries related to female reproductive organs (e.g. uterine polyp removal, endometrial ablation, hysterectomy or bilateral oophorectomies) in the past and believed that it influenced their MdDS symptoms or pathophysiology. The SO group reported that they believed these surgeries were involved in their initial MdDS onset. Furthermore, for both onset groups, menstruating just before, during or just after being exposed to a motion event or when the spontaneous onset occurred was believed to have influenced or triggered their onset (46% of comments), also ceasing hormonal contraceptive medications was believed to be a trigger for onset in both groups for some respondents (2 out of 100 comments - MT and 2 of out of 100 comments - SO). Additionally, a great proportion of the SO group comments, reported to have higher MdDS symptoms during the week break from their hormonal contraceptive medication. 13 MT and 7 SO respondents reported to have higher symptoms during menstruation, strengthening the previously questions that was asked about aggravation of symptoms.

Considering the MT and SO comments together, in total 12 respondents reported to have developed hypothyroidism specifically after MdDS onset. While some respondents specified that while being pregnant (7 out of 24 who indicated that they were pregnant while having MdDS) reported to have had a full remission of MdDS symptoms or a great improvement in symptoms during pregnancy.

Male Respondents

A total of 7 open-ended comments were collected, 5 from the MT group and 2 from the SO group. 2 respondents from the MT group and 2 from the SO group reported to have been taking, using, or experimenting with drugs that influence hormonal levels (e.g. testosterone replacement therapy, anabolic steroids). One respondent believed that his symptoms started during puberty due to the hormonal changes, while another believed his onset was triggered by the combination of steroidal drugs and the use of other recreational drugs.

Discussion

Given the predominance of female MdDS patients and the lack of investigation into hormonal associations in this condition, a multi-institutional collaboration was setup to collect data from male and female MdDS respondents on a global scale. In total, 370 MdDS patients completed either the MT or SO questionnaire. The current study is the largest, in terms of MdDS respondents recruited to date with regards to hormonal enquiries, and is the only study that compares MT and SO subtypes. Furthermore, this study was the first attempt to link hormonal profiles and clinical hormonal conditions with MdDS onset, symptom fluctuations and other associated features. As the current investigation was based on a retrospective study, we encourage the reader to consider this data as preliminary. The analysed data suggests a potential relationship does exist between gonadal hormones and the fluctuation and aggravation of MdDS symptoms, however further examinations should be continued to assess if physiological changes are also present. From the results collected, a great female predominance was reported as well as an average age within the 5th decade of life (40 to 50 years old), as expected based upon reports in previous studies [50, 59].

Hormonal fluctuations and aggravation of MdDS symptoms

The survey results appear to support our main hypothesis, that estrogen withdrawal is linked to the aggravation of symptoms for female MdDS patients; a majority of which reported an aggravation of symptoms in response to hormonal fluctuations during the menstrual cycle phases. In particular, this aggravation is potentially caused by estrogen level changes, specifically, by the drop in estrogen. In parallel, this has also been observed in migraine patients during the pre-menstrual phase and menstruation [120]. When estrogen is at its lowest, symptoms are heightened [39]. The MT group clearly reported an aggravation of symptoms during menstruation and during mid-cycle,

around ovulation; if considering only the respondents who answered this question and therefore excluding the missing values. As reported in Figure 12, estrogen rises between Day 12 and 14 of the menstrual cycle and then gradually decreases following the luteinizing hormone surge, which is responsible for triggering ovulation [139]. Estrogen levels are known to fall around ovulation (mid-cycle), specifically estradiol levels, immediately prior to the luteinizing hormone peak (surge), although is not always observed in all females [40]. These significant drops in estrogen may explain the reported aggravation of symptoms around these points in the menstrual cycle.

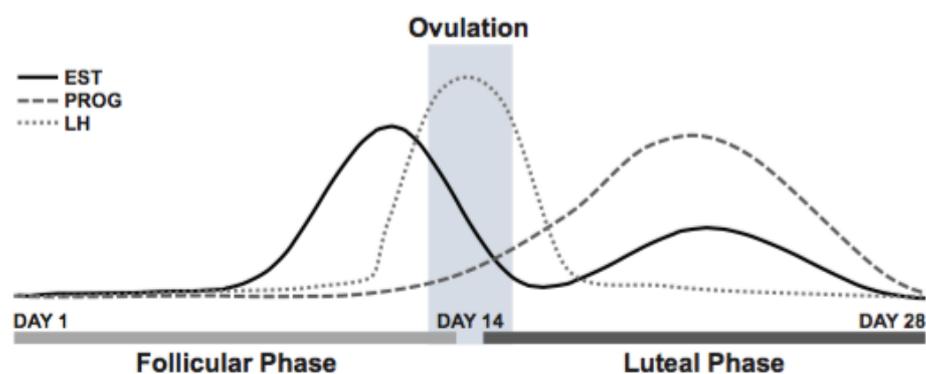


Figure 12: Fluctuations of Estrogen, Progesterone and Luteinizing Hormone (LH) during a typical 28-day menstrual cycle. Ovulation is here reported occurring around 36hours after the LH surge.

Abbreviations: EST = Estrogen, PROG = Progesterone and LH = Luteinizing Hormone.

Similar to the MT results, many respondents from the SO group also reported an aggravation of symptoms linked to hormonal changes. Unlike the MT group, these respondents were asked to distinguish their experience during menses and during mid-cycle around ovulation separately. A large number of SO respondents were unsure as to when their ovulation occurred each month. This posed a great limitation to this question. Consequently, for the SO group, the number of respondents was limited and thus no statistical significance was reached. However, the open-ended comments

collected from SO respondents clearly indicated higher MdDS symptoms during menses. Further evaluation of both subtypes with inquiry into defined menstrual cycle phases is encouraged, by perhaps aiding patients through use of commercial urine strips to detect with precision when ovulation is occurring.

In migraine patients, the estrogen withdrawal mechanism is known to be associated with an increase in migraine symptoms and migraine occurrence [79]. This has been supported for more than 30 years, since it was proven that the supplementation of estrogen was able to reduce the incidence of migraine attacks until the level of estradiol fell again [39] however, no reduction in migraine attacks was reported with progesterone [39]. A similar improvement of symptoms may be possible for MdDS patients, and thus more research is encouraged to assess if therapeutic hormonal intervention is able to reduce MdDS symptoms.

A specific limitation of these surveys was that subjects were not asked about Pre-Menstrual Syndrome (PMS). PMS is a common condition, which affects 30-40% of healthy females in the days prior to menstruation [140]. In this case PMS could be responsible for the symptom aggravation reported by the MdDS patients. PMS is characterized by a mix of physical and psychological symptoms [140]. In a previous study, it was shown that PMS affects postural stability, where significant increases in postural sway was observed in healthy individuals in the days surrounding menstruation compared to controls [141]. As a result, given that healthy females experience changes in postural stability during PMS around menses, it is possible that MdDS patients, who normally experience an increased postural sway, may perceive themselves as even more unstable in the days surrounding menstruation and during menses itself. This phenomenon may be compounded by a natural increase of postural sway during PMS,

resulting in an aggravation of symptoms during these times. Future studies should extend upon this by focusing on the potential relationship between MdDS and PMS.

A potential theory on why estrogen fluctuations could be related to MdDS

pathophysiology

The influence of the fluctuation of estrogen in MdDS may also lie within the estrogenic ability to affect the central nervous system function. Steroid hormones (which includes corticosteroid and sex steroid hormones) are able to modulate the physiological and neuroplastic properties of the central nervous system, and affect the existence of specific intracellular steroid receptors in the cerebral cortex, the limbic system, cerebellum and preoptic part of hypothalamus and brainstem [117]. For example, changes in estrogen levels may be indirectly related to changes in the optokinetic function [142], as well as inducing changes in the brain functions related to cognitive capacity, memory and mood [143]. Another example is provided by assessments on the development of depression, which have been linked to female hormonal fluctuations [144].

Estrogen operates via two nuclear receptors, estrogen-receptor α and β [145]. These receptors operate as transcription factors via genomic mechanisms, regulated by an altered expression of target genes [146], as well as by excitatory action within the central nervous system [147]. These receptors have been found in brainstem vestibular nuclei concerned with optokinetic, vestibular-ocular and vestibule-spinal reflex [142]. This is significant if considering the VOR maladaptation theory for MdDS [53]. Potentially, low levels of estrogen, as during the luteal phase, may alter the brain's adaptability to new environments, by influencing the subject's central neural control for the velocity storage mechanism that has been implicated in the maladaptation of the VOR [52]. The velocity storage integrative network is constituted of GABA_b sensitive neuron

receptors. Gamma-Aminobutyric Acid (GABA) is the main inhibitory neurotransmitter in the human brain, and is often the focus of much clinical and neurological research [148]. For example, previous studies have shown that low GABA plasma is associated with depression [149] and that low GABA plasma is a characteristic in Pre-Menstrual Syndrome (PMS) sufferers in the luteal phase [148]. In addition, GABA-mediated neurons are known to have a prominent inhibitory role in spatial navigation. Consequently their deregulation, by altering hormonal levels, could hold some significance in the aggravation of MdDS symptoms [150]. If GABA are implicated in MdDS pathophysiology, this could also explain why drugs acting on the release of GABA such as clonazepam may be effective for MdDS patients [47]. Evaluating GABA plasma levels in MdDS patients may provide fruitful insights about MdDS pathophysiology. Regarding the second theory (theory 2 pathophysiology of MdDS), where MdDS is described as a neuroplasticity disorder [49], it might be hypothesized that the hormonal receptors activated by female hormones may also affect the hippocampal and EC interneurons. This suggests that these projections could influence firing patterns within the EC-hippocampal circuit, resulting in symptom changes for MdDS patients. However, more research is needed, as we recognise that for the MT group the question (combining menses and ovulation) was expressed vaguely and a more accurate evaluation should be performed.

Perimenopause and menopause in MdDS patients

Another interesting aspect to consider was the average age of MdDS respondents in both groups (mean age = 48.9 years old SD = 12.03), which matches the fifth decade of life, as previously described [60]. This is particularly important in females as it usually indicates a perimenopausal phase (period up to 8 years prior to menopause, characterized with endocrinological, biological and physiological changes), or the

menopausal phase [151]. This supports one of our hypotheses that the majority of female respondents would be within an age range when menopausal transition typically occurs. With regards to menopause, 43% of the females within the MT group reported to be menopausal compared to 16.3% of the SO group, as a result menopausal females were not the major group of respondents engaged in this study. However, great number of respondents from both groups commented that they believed that perimenopause and menopause was involved in triggering their MdDS onset. Fundamentally, this could provide an explanation for the great predominance of female respondents within the same age group, in line with previous research [44, 47, 59, 60]. During perimenopause, irregular menstrual cycle length, changes in period pain, or PMS, affect most females [140]. Thus, the significant hormonal changes during this phase may lead to an increased period of susceptibility for females; this could be investigated further in prospective surveys and clinical studies. More research of this nature could further elucidate why MdDS is more prevalent in this time frame in women's lives. In parallel, this is also observed for migraine and dizziness [152], with an equally high incidence in perimenopausal females. In line with our hypothesis, the high number of perimenopausal females may also be linked to estrogen decline, which normally occurs in this phase [39], resulting in potentially altered neurotransmitters and brain regions implicated in MdDS pathophysiology.

Menstrual cycle (Mid-Cycle) phases during onset

Naturally cycling respondents were asked if they were in a particular phase of their menstrual cycle (e.g. menstruation, ovulation) when their MdDS symptoms appeared. The majority of respondents were not sure if they were menstruating or in the middle of their cycle (when ovulation usually occurs) during the time of onset. However, a statistically significant difference was noted between the MT and SO groups when

considering the missing variable, with a higher number of MT respondents reporting to have been menstruating during onset. This however could simply indicate a difference in the number of respondents engaging in this question, thus those results should only be considered preliminary. However, to support this data, for both onset groups, a few respondents indicated in the open-ended comment section that they were menstruating just prior, during or soon after the believed onset. From previous investigations, the influence of subtle estrogen fluctuations on brain structural connectivity has been shown in healthy females, in particular regarding the capacity of the human brain to adapt to the environment [153], which has potential relevance for MT patients. This supports our theory that low estrogen levels may be implicated in developing MdDS.

Furthermore, respondents were asked to recall if they were using hormonal contraceptives during the believed onset. A higher number of MT respondents reported to be using hormonal contraceptives compared to the SO group when including the missing data, however similarly this data should be considered as preliminary. A deeper analysis is needed in order to establish if gonadal hormonal fluctuations are involved in contributing to MdDS onset specifically.

Triggers and hormonal fluctuations

Interestingly, the increase in MdDS symptoms was not directly linked to an increased sensitivity to typical triggers for MdDS (e.g. bright lights, being under stress) during menses. The SO group reported to be more sensitive to triggers during menses compared to the MT group. This could suggest that an increased sensitivity to triggers is not responsible for aggravating MT MdDS symptoms during menses or mid-cycle around ovulation, but rather that the hormonal changes per se are responsible for higher MdDS symptoms overall.

Hormonal profiles of female MdDS respondents (PCOS, Regular Menstruation, Pregnancy, Hypothyroidism)

Overall, a difference among the MT and SO groups was reported regarding the regularity of their menstrual cycles. Despite the number of SO respondents being much smaller compared to the MT group, a statistical difference between the two groups was reported, with the SO group reporting to have a higher number of respondents with irregular menses. This could suggest that SO patients may have hormonal imbalances or condition, which makes them more likely to have irregular menstrual cycles and potentially more vulnerable to developing MdDS spontaneously. In addition, both MT and SO groups had a higher incidence rate of irregular menses compared to the general population, which further supports the argument that MdDS patients may have underlying hormonal issues that make them more susceptible to developing MdDS overall. Another aspect to consider is stress, as high levels of stress are known to affect the regularity of the menstrual cycle, and therefore menses, despite the mechanism remaining unclear [154]. Chronic stress induced by persistent MdDS symptoms [21] could be one of the causes for this irregularity. However, this peculiar difference between onset groups should be further examined.

On the contrary, equally, the majority of the MT and SO groups had not been diagnosed with PCOS and, in general, the number of respondents who reported PCOS was double than that of the normative data (reported rate of PCOS was 5.5% of a female Caucasian population, indicating that this condition can be quite common [132, 136]). However, a large number of respondents were not sure if they suffered from PCOS (missing and unsure= 6.5% MT; 67.7% SO). Thus our results should be only considered preliminary. Overall, considering the respondents who confirmed to be suffering from PCOS, it could suggest that MdDS patients have hormonally associated

conditions or abnormal hormonal profiles at a higher rate than the general population. Also of interest, a similar number of female respondents from both groups (14.6% MT – 12.5% SO) indicated in the open-ended comments that they had undergone hysterectomies or some sort of surgery removing reproductive organs (e.g. uterine polyp removal, endometrial ablation or bilateral oophorectomies). These interventions should be closely evaluated, as it is known they may impact hormonal homeostasis, for example, a recent study reported that after bilateral oophorectomies (surgical removal of the ovaries only), a pronounced and sustained reduction in testosterone levels was recorded in patients [155, 156]. Further data is required to confirm a clear relation between hormonal conditions and MdDS.

Respondents were asked whether they had experienced MdDS symptoms whilst being pregnant, and only a very small number responded positively. This can perhaps best be understood as a reflection of the perimenopausal and menopausal hormonal stages that most respondents were in [60]. In addition, some of the respondents who reported to be pregnant while having MdDS symptoms, reported a reduction of symptoms during pregnancy, often a full remission of symptoms, which returned shortly after birth. This may reflect the consistently increasing level of estrogen which starts in the first trimester and reaches its peak in the third trimester of pregnancy as well as the absence of cyclic hormonal fluctuations [157, 158]. Although anecdotal, it could suggest that MdDS patients might benefit from stable hormonal levels for potential alleviation of MdDS symptoms. This ought to be an important area of future research to further investigate its therapeutic potential. It is also important to note that there is no estrogen withdrawal during pregnancy (and an absence of cyclic fluctuations), but a subsequent withdrawal does occur after delivery, (more details are reported in the section Chapter 4.2). This could suggest a possible mechanism for why some SO

patients report childbirth as cause of their onset. An accurate analysis of hormonal changes in respect to MdDS symptoms is needed for pregnant females.

No hormonal clinical dysfunctions were reported overall. However, among the respondents who reported to have an hormone-related condition, hypothyroidism was the most prevalent disorder in both groups. Hypothyroidism, which is characterized by a myriad of symptoms including many that are typically considered as associated symptoms in MdDS as well, such as depression, memory loss, muscle weakness, has been reported to affect 9.4% of the US population (Canaris 2000). The decreased activity of the thyroid leads to many hormonal imbalances and of particular importance to this study, it leads to a decrease in estrogen in females and testosterone in male and female patients [159]. Our results indicate a larger number of MdDS sufferers with hypothyroidism (15%) in comparison with the general population. In addition to this, a few respondents reported to have developed hypothyroidism after MdDS onset, in the open-end comments. Further assessment could be performed in order to evaluate if MdDS patients are unaware of potential thyroid, adrenal or gonadal dysfunctions. Similarly, the incidence of hypothyroidism in respondents affected by Ménière's Disease is high, however in numerous patients affected by Ménière's Disease, no thyroid enlargement was reported or clinical examination was performed, indicating that patients with less severe thyroid dysfunction may not be diagnosed and therefore improperly managed [160].

Hormonal contraceptives, hormone replacement therapy and MdDS

The number of respondents (from both onset groups) that were taking hormonal contraceptives was small and not significant, although a great majority of 50 respondents who contributed to the open-ended comment section, reported to have

increased symptoms during the suspension week of contraceptive. This was not the case for the MT group, which in line with a previous epidemiological study no substantial correlation between vestibular symptoms and hormonal contraceptive was found [111]. Certain hormonal contraceptives have the ability to restrain the estrogen fluctuation (therefore eliminating estrogen withdrawal), which perhaps holds potential to reduce the symptomatology of some MdDS patients, similar to what has been observed in migraine patients [161]. Such treatment include the continuous use of a combination hormonal contraception, or the use of estrogen alone during the perimenstrual period [161]. A further assessment of the SO group is required to confirm why such aggravations occur, as well as if hormonal therapy can influence or improve MdDS symptoms. Furthermore, from the open-ended comment section, 4 respondents commented that they believed their MdDS onset was triggered after ceasing a hormonal contraceptive medication. Regarding HRT, the number of respondents affected by MdDS and using such medications was small and not relevant for both onset groups. Future studies should assess if hormonal therapies may be relevant (perhaps in a protective role) for MdDS patients.

Male MdDS respondents

When considering male respondents, the sample size was relatively small and therefore these results should be considered preliminary. A comparison between the MT and SO group was performed using Fisher's exact test due to the limited number of SO respondents. A difference among MT and SO group was reported ($p=0.088$), although given the small number of respondents, this is not conclusive.

Overall, considering the two onset groups together 16.7% reported having been diagnosed with low testosterone levels. Additionally, in the open-ended comments section, it was reported that 4 out of 7 of the male respondents from both groups had

reported hormonal imbalances in the past and to be taking a hormonal-related medication (e.g. specifically, some respondents mentioned the use of steroids and recreational drugs). Steroids are known to lead to hypogonadism [162], which causes a wide range of symptoms including loss of libido, erectile dysfunction, diminishing cognitive functions, depression, lethargy, osteoporosis and loss of muscles mass and strength [163]. Additionally, published studies conclude that testosterone is an anxiolytic, having a crucial implication in anxiety, exhibiting an anti-depressant role as well as improving spatial abilities [156]. As a result, testosterone levels could also be explored in male MdDS patients. The results acquired from the male data does not support one of our hypotheses that male respondents would have a higher rate of hormonal conditions compared to the general population, however, given the low response rate from males, this still should be further investigated.

Migraine and motion sickness

When considering migraine and MdDS, migraine proneness featured in both onset groups. Due to the small number of SO (only 32 compared to the 296 respondents from the MT group), Fisher-Freeman-Hanlon exact test was used and a statistical significant difference was present. These results, though preliminary, indicate a slightly higher number of SO group reporting migraine overall, compared to the MT group. Considering both subtypes, from our results it is also clear that an increase in migraine occurrence is associated with having MdDS, and that it is not a predisposing factor, as only a small number of respondents suffered from migraine before onset (3.4%MT; 14.8% SO). The association with migraine has been observed in previous studies [49, 51] especially so for the SO group [51], however a potential onset difference remains to be elucidated. It has been previously suggested that perhaps MT and SO patients share abnormal brain functioning and physiology, perhaps via different pathways or

mechanisms [51], and that the mechanism(s) involved in SO MdDS could be closely related with migraine and vestibular migraine. The pathophysiology of vestibular migraine is less understood [164]; however, there are several obvious links between central vestibular pathways and proposed mechanisms involved in migraine, which could correlate with MdDS. If considering migraine and dizziness and their potential interaction with ovarian hormones in females, different theories have been proposed. One possible theory applying to both disorders and potentially influencing both onset group relies within the estrogen withdrawal [152].

When considering motion sickness, the number of SO respondents that engaged in this question was much lower than the MT group, (120MT versus 25SO), as a result also for this variable we applied the Fisher-Freeman-Hanlon exact test. A difference was reported with a higher number of SO respondents being more susceptible after MdDS onset, however as reported in the result section, the SO results may be affected by response bias. Overall, there was no evidence to suggest that motion sickness could be a predisposing factor for developing MdDS, given that the majority of MdDS respondents did not report to be particularly prone to motion sickness prior to onset. As previously argued [49], if motion sickness is due to a failure of adaptation to passive motion, it would be logical to speculate that people who do not adapt to passive motion would have fewer issues readapting to land. Hain and colleagues also failed to find a correlation between motion sickness and MdDS, and this may hold some significance for understanding the mechanism(s) involved in each condition [50].

Study strengths and limitations

This is the largest survey performed on people with MdDS and has quite a comprehensive coverage of Western countries. This study is novel in its approach by enquiring about the hormonal aspects of MdDS patients and collating their opinions. It was fully anonymous, allowing respondents to be open. However, we do acknowledge the surveys suffer from non-response and we have no satisfactory method for estimating response rates or response biased in this survey. The best we could do was to clearly present the missing data per enquire and to compare our sample against normative data from the literature, which suggested no major biases in the limited number of variables we examined. The results where a statistically significant difference between the groups was present only when the missing values were included imply that there is a significant difference in response rates between the two groups. This means there is potential for bias in the following analysis where the missing data is excluded, thus these data should be interpreted carefully.

The survey questions sometimes requested information about events which occurred many years prior and we included no specific strategies for reducing recall bias. The questions were designed for the needs of the current study only and could not be fully validated or tested for reliability prior to use. Further, as this was a volunteer sample rather than a probabilistic sample, the validity of the statistical inference is undermined. All confidence intervals and p-values should be interpreted with caution. Access to patients was limited to those active on social media, those who visited webpages related to our studies, or those being assessed at Antwerp University Hospital. As in all retrospective survey studies, our study is also limited by the inability of all respondents to recall or their lack of knowledge regarding specific details, particularly those connecting symptoms patterns to cycle phases of the menstrual cycle (e.g. ovulation). This, as seen in many other surveys [165], made it difficult to assert specific relationships.

Also, participant numbers for the SO group were limited. Lastly, a small number of respondents were self-diagnosed, although most patients received a diagnosis from a healthcare professional.

Future research

Further research is needed to fully elucidate hormonal involvement and to confirm the hypothesis of estrogen withdrawal being involved in the aggravation of MdDS symptoms. Future studies should consider the implication of estrogen within the vestibular system, for example focusing on estrogen receptors found in brainstem vestibular nuclei, and brain areas concerned with optokinetic, vestibulo-ocular and the vestibulospinal reflex [142], as well as influencing central neurotransmitters (i.e. GABA). Neuroimaging studies, coupled with estrogen testing, could prove useful in assessing the effect of estrogen on hippocampal and entorhinal cortex interneurons, which have been theorized to be involved in MdDS pathophysiology [54]. We also encourage future research to conduct a detailed analysis of the perimenopausal phase and PMS in MdDS sufferers; in order to elucidate what other potential causes may be implicated with MdDS symptom fluctuations and onset. The difference in irregular and regular menses for MT and SO subtypes should be further evaluated. Additionally, testosterone testing could prove beneficial for male and female MdDS patients alike to provide detail concerning its effect on cognitive functions and memory [156, 166], which are also described as impaired following MdDS onset. Overall, a clinical assessment of female and male hormonal profiles and underlying hormonal conditions should be performed to elucidate possible mechanisms behind the development of MdDS, and provide direction for potential MdDS hormonal treatment strategies.

Conclusion

This was the first global survey, with the highest number of MdDS respondents that attempted to identify a link between MdDS and gonadal hormones. From these results, it is evident that hormonal fluctuations are able to influence the symptomology of female MdDS patients (with MT onset), which we hypothesized being due to estrogen withdrawal. Additionally, we have suggested that the hormonal fluctuations occurring in the perimenopausal phase may create a period of vulnerability in females, given the average age of onset of our respondents. We have also suggested that the MdDS population is more likely to have hormonal imbalances or dysfunctions, as supported by our findings of higher rates of PCOS and irregular menstrual cycles, especially in the SO group, when compared to the general population, which may indicate an underlying lack of hormonal homeostasis in our respondents, which potentially contributed to their MdDS onset. Additionally, this study also reported a high prevalence of migraine associated with MdDS, and failed to support any significant relationship between motion sickness and MdDS.

This suggests that the mechanism(s) involved in hormonally regulated migraine may be present, or relevant, for female MdDS patients. A theory regarding estrogen influences in MdDS pathophysiology has been proposed, suggesting that more attention should be given to perimenopause and PMS. Although we did not observe a higher rate of hormonal conditions in male respondents when compared to the general population, future studies should consider examining hypogonadism.

Overall the data revealed that the rate of hypothyroidism in the female MdDS respondents was higher than the general population. Additionally, a few differences between the MT and SO were reported, such as the differences in symptom fluctuation regarding menstrual cycle phases, irregular menses, migraine susceptibility, and motion sickness susceptibility.

In conclusion, this study has provided novel insights into the potential hormonal influences within MdDS pathophysiology and peculiar differences related to onset types. These results require future studies to further elucidate the role of hormones in MdDS, and in particular, call for more detailed clinical investigations to help elucidate the role they play in MdDS symptomatology, onset, and lastly if hormonal intervention can have a therapeutic potential.

4.2 Pilot Study on Mal de Debarquement Syndrome Patients during Pregnancy

Abstract

Background: Pregnancy leads to various maternal physiological changes to adapt to growing the embryo and foetus, some of these changes are known to affect brain and inner ear function. It has been previously shown that pregnancy positively influences symptoms of patients who have migraines and other conditions, and we have hypothesised that a similar influence or alleviation may be observed in patients affected by Mal de Debarquement Syndrome (MdDS). MdDS is a rare neurological disorder characterised by a constant sensation of motion (e.g. rocking, swaying or bobbing), which has two onset subtypes; Motion Triggered (MT) and Spontaneous/Other (SO). To date there have been no investigations into the symptomology of MdDS patients throughout pregnancy. As a result, this study aimed to conduct a preliminary pilot questionnaire to evaluate if pregnant MdDS patients reported differences in symptom levels or type during pregnancy.

Methods: This was a retrospective online questionnaire study for MT and SO MdDS patients. Respondents were required to answer a set of comprehensive questions regarding hormonal profiles, diagnosis as well as differences in symptom levels or type during pregnancy.

Results: Twenty respondents participated in the questionnaire and 66.7% of respondents reported that their symptoms were lower during pregnancy compared to before pregnancy. Respondents reported a differing perception of motion and less dizziness while being pregnant.

Conclusions: Pregnant MdDS respondents reported an improvement of symptoms, potentially attributable to the rise in estrogen and progesterone during pregnancy. We

hope this pilot study will help the medical community to broaden their awareness and hormonal knowledge of this condition, and that the results of this study will lead to further research.

Introduction

Hormonal changes during pregnancy can cause vestibular and cochlear disorders [167]. In females, any change in the metabolism of steroid hormones (estrogen and progesterone), can cause complications within the vestibular sphere [167]. Conversely, pregnancy and hormonal changes lead to symptoms improvement in patients' affected by migraine, as well as for clinical pain conditions (e.g. arthritis) [168]. Thus, whilst pregnancy is recognised to induce certain pathological conditions, whilst alleviating the symptoms of others, no information is currently available when considering a particular group of vestibular patients affected by Mal de Debarquement Syndrome (MdDS).

MdDS has a significantly higher number of female patients (80% versus 20% of male) which is well documented [21, 44, 47, 50]. In the literature, given the female predominance it has been suggested that hormonal fluctuations may be responsible for influencing MdDS symptoms and onset [80]. To date, there have been no investigations into the role of hormones in MdDS pathophysiology. It is also important to highlight that a large number of MdDS female patients were experiencing perimenopause or undergoing hormonal replacement therapy when onset occurred [60]. Consequently limited information regarding reproductively active MdDS patients, including those that are undergoing pregnancy, are available, as they are regarded as the atypical MdDS patient. Nevertheless, given the suggestion of possible hormonal influences on symptom fluctuations as discussed in the section 4.1 we believe that assessing MdDS sufferers that are pregnant or have been pregnant while having MdDS

may help with our understanding of the underlying mechanisms of MdDS. From the previous reported retrospective survey, a small number of respondents who reported to be pregnant while suffering from MdDS, reported symptoms improvement during the 9 months of pregnancy. This specific preliminary find suggested that MdDS symptoms might be affected during pregnancy.

With regards to the pathophysiological mechanism underlying MdDS, two main theories have been developed [54]. MdDS has been hypothesised to be the result of a maladaptation of vestibular ocular reflex (VOR) (described in Chapter 2 as Theory 2), responsible for gaze stabilization during rotation of the head around the three axes (e.g. yaw, pitch and roll)[53]. The VOR is subjected to adaptation depending on the context, and this “contextual” VOR adaptation is long lasting [73, 74, 169]. For example, when a person is adapted to a specific context (e.g. cross-axis adaptation present on a cruise ship), a similar cross-axis re-adaptation will have to occur when returning to a static environment. However, in MdDS patients the latter described mechanisms seems to fail [54]. In relation to this, the failing mechanism is considered within the velocity storage mechanism, for more information please refer to Dai's et al 2014 [53].

According to the other hypothesis (described in Chapter 2 as Theory 1), MdDS is believed to be a disorder of abnormal functional connectivity; this has been supported by neuroimaging and neuromodulation studies on MdDS patients. According to these findings, MdDS can be defined as a disorder of over-synchronization of brain networks. This has been confirmed with MdDS patients responding favourably to neuromodulation [65]. The key areas attributed to MdDS are the entorhinal cortex (EC) and amygdala. The EC is particularly relevant for spatial information processing located in the medial temporal lobe [49] and together with the amygdala they are involved in learning and memory. Each has a successive connection with the hippocampus. Experimentation

using F-fludeoxyglucose positron–emission tomography has demonstrated hypermetabolism within the left EC and amygdala, parallel to a decrease metabolic activity within the prefrontal and temporal lobes[49].

Despite formulation of these primary hypotheses to elucidate the underlying pathophysiology of MdDS, a unifying and clear theory has not been established. Similarly it is still unclear why MdDS patients are known to report symptoms fluctuations [90], specifically, why female MdDS patients report an aggravation of symptoms during menses and ovulation [59] as reported in section 4.1. Symptom fluctuations in relation to female hormones have been previously described in other vestibular disorders such as in patients affected by Ménière's Disease (MD) [36]. The influence of hormones upon MdDS symptomatology is also supported by the high prevalence of migraine within MdDS patients [170]. Migraine occurrence is known to be sensitive to hormonal changes throughout the menstrual cycle in association with the "estrogen withdrawal theory" [39]. This theory was proven more than 30 years ago, when selected female migraine sufferers, who reported symptoms fluctuations during the menstrual cycle, were given estradiol, which resulted in the delay of associated pre-menstrual migraine attacks until the estradiol concentration declined [39, 171, 172]. These results served to postulate that the withdrawal of estrogen served as a trigger for migraine in vulnerable women. On the contrary, when considering pregnancy, between 55 to 90% of migraine sufferers report having an improvement in their migraineous symptoms, regardless of the type of migraine they suffer from [173]. This suggests that pregnancy has a beneficial effect on migraine.

In addition to this, hormonal changes alter neurological structure and functionality, and such changes have varied effects throughout the reproductive lifespan of a woman

It is important to acknowledge that ovarian hormones are involved in maintaining a specific neuroendocrine milieu throughout the woman's life span; as a result their levels

influence brain structures and functions in different ages and hormonal status. Motherhood is one of the most complex periods of cross talk between hormones and the brain in adult life [118]. During pregnancy women are subjected to a unique and limited condition, characterised by physiological and biochemical changes [158]. An extraordinary modifications in plasma levels of numerous hormones is reported, including progesterone, estradiol, prolactin, oxytocin, relaxin, and glucocorticoids [158]. These hormones influence brain changes, particularly in the hypothalamus [118], where plastic neuronal and glial remodelling is involved in the regulation of hormonal changes during motherhood. Functional magnetic resonance (fMRI) studies have begun elucidating the influence of ovarian hormones on the activation of the female brain during the reproductive years in response to emotional and cognitive processing. Furthermore, the maternal brain has been shown to decrease in size during healthy pregnancy and to increase in size after delivery [174]. Recently, grey matter (GM) structural changes have been considered in pregnant women; comparing different data point before, during and after pregnancy [175], it has been reported that women who experienced pregnancy for the first time are subjected to a pronounced change in their brain structure, not simply in size. These observations may be relevant if considering MdDS as neuroplasticity disorder, where ovarian hormones may be able to influence or modulate brain functions and thus to generate symptom changes. However, to date, the role of ovarian hormones and their relation to brain function remain largely unknown and speculative. In the 9 months of pregnancy, the cyclical fluctuations of hormones are absent and a raise in estrogen and progesterone is observed. These hormones in particular remain at high concentration until after delivery, when they are then decreasing. Estrogen and Progesterone during pregnancy are known to be involved in affecting not only brain structure and to induce physiological changes, but also to affect pain perception [176, 177]. If considering

migraine, 11% of migraine patients are reporting an improvement of symptoms within the first trimester, rising to 53% in the second and 79% in the third trimester, which is especially seen in women with menstrual migraine [178]. During the postpartum phase, the estrogen levels rapidly fall leading to an exacerbation of symptoms with 34% of women suffering a relapse of migraine symptoms, reaching up to 55% within a month after delivery [178].

The improvement reported in migraine as in other clinical pain conditions is termed pregnancy-induced analgesia [179], where hormones changes as well all as changes in neurotransmitters (GABA, serotonin, 5-HT, as well as endorphins) are believed to be responsible for changing symptoms and pain perceptions in various pathologies [179].

Currently, it is unclear how hormonal fluctuations during pregnancy may or may not influence female MdDS patients. As a result, this study aimed for the first time to conduct a preliminary pilot questionnaire, in order to evaluate if MdDS patients report symptoms changes during their pregnancy. This study also aimed to examine how many women developed MdDS while being pregnant and if hormonal changes are involved in triggering the onset itself. Lastly the purpose of this study was also to compare the two onset groups (SO and MT) and evaluate potential differences where possible.

We hypothesised that MdDS patients will report a similar pattern of improvement as described in migraineous patients, during their pregnancy. This study may provide us with valuable information about MdDS and hormonal fluctuations, which could lead to the improvement of patient care during pregnancy.

Materials and Methods

Ethical approval / study population and recruitment

Ethical approval was provided by the Ethics Committee of the University Hospital Antwerp Belgium (IRB number 15/44/454) and by the Western Sydney University Human Ethics Committee (H11962). Each respondent gave informed consent. All investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Patients diagnosed by specialists or believing to suffer from MdDS (also referred to as self-diagnosed patients) were included in the study. Patients were recruited across the USA, Europe, and Australia. MdDS patients were recruited through the Department of Otorhinolaryngology at the University Hospital of Antwerp, Belgium. Patients were also recruited globally through the main MdDS support groups: MdDS Australia Facebook Support Group, MdDS UK Facebook Support Group, website of MdDS Research Group at Mount Sinai Hospital, Western Sydney University MdDS Research Group Facebook page, website and Facebook of Vestibular Disorders Association (VEDA), and website and Facebook of Whirled Foundation and the REACT Community Facebook.

The inclusion and exclusion criteria are reported below (Table 18).

Inclusion and exclusion criteria

<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>
Patient with complaints of persistent (>1 month) Mal de Debarquement; reporting a prolonged sensation of self-motion (rocking, swaying and bobbing) after the exposure to passive motion, most frequently a boat trip, or travel over air or land	Male MdDS patients.
Patients with MdDS symptoms, which occurred spontaneously or with atypical onset refer to [21] for details	Female MdDS patients who were not pregnant while suffering from MdDS.
Female patients reporting sensations of self-motion (rocking, swaying and bobbing) for longer than one month, where the symptoms could not be explained by another diagnosis.	Patients reporting symptoms, which do not fit the previously published MdDS guidelines [21]
Only patients ≥ 18 years old were included	< 18 years
Self-diagnosed respondents were also included in the questionnaire. A series of questions were used to screen out the patients who did not meet the criteria to be included in the study.	

Table 18: Reported the Inclusion criteria used for this study based on the most updated diagnostic guideline [21], followed by the exclusion criteria applied in this research.

Questionnaire

The questionnaire was distributed online using the survey platform, Qualtrics. The questionnaire consisted of 45 questions (see supplementary material) which was divided into separate categories for both subtypes (MT and SO): epidemiology (demographic details), diagnosis (i.e. who made the initial diagnosis), onset triggers, symptom triggers (i.e. symptom fluctuation, assessments of potential triggers), hormonal influences, symptom comparison (level and type) between pregnancy and when not pregnant, and symptom fluctuations (e.g. how symptoms modulated during the 9 months of pregnancy and after). Respondents were also given the chance to add comments (open-ended comment section) regarding their symptoms, triggers or to anything they considered relevant (more details Annex 3).

Statistical analysis

Statistical analysis was performed with SPSS version 24 (IBM Corp). Non-parametric Chi Square was used for comparison between MT and SO groups. When the minimum expected count in Chi Square analysis was <5, the 2-sided significant was then considered. If no statistical significant difference was observed between the two groups, the group data was merged and analysed as one. Independent Samples t-test was used to evaluate the improvement in rating symptoms (Δ symptoms rate during pregnancy – symptoms rating prior to pregnancy on a 'Good' and 'Bad' day). Repeated measures analysis was used to analyse how symptoms changed according to triggers (e.g. different positions) before as well as prior to pregnancy.

Results

Epidemiology and diagnosis

A total of 20 respondents were selected following the inclusion and exclusion criteria presented in the methodology section, among the 75 patients that responded to the questionnaire. The majority of the subjects were excluded, as they did not meet the principal criteria of reporting MdDS symptoms during pregnancy. The majority of the respondents were from North America with 57% (number of respondents = n 12), 19% (n=4) equally from Europe from Australia. The average age was 37 years (SD=5.19 Minimum 27 years old – Maximum 46 years old). 4 of the respondents were of the SO subtype and 14 of the MT subtype. Given the small number of SO respondents a comparison between onsets was not always possible.

The majority of the respondents (n= 18 – 85.7%) had MdDS prior to being pregnant, while only 2 respondents (9.5%) reported that their MdDS symptoms started during pregnancy and 1 participant did not answer this question, but confirmed to have been having MdDS while pregnant. 8 respondents who participate in the study had been previously pregnant whilst experiencing MdDS symptoms (previously pregnant). On the contrary, 10 MdDS respondents were currently pregnant at the time of completing the questionnaire (currently pregnant). Both groups were treated the same. The majority of the currently pregnant women were between the 5th and the 6th months (week 18-21), when they completed the questionnaire. Diagnostic wise, only 2 respondents (1 MT and 1 SO) were self-diagnosed, all the others had received an official diagnosis from a health care professional. The majority were diagnosed by neurologists - 42.9% (8 MT and 1 SO), followed by otolaryngologists -19% (2 MT and 2 SO); 9.5% (2 MT) respondents were diagnosed by General Practitioner (GP) and 4.8% (1 MT) by a physiotherapist. Only 2 subjects (1 MT, 1 SO) were self-diagnosed (9.5%).

Onsets

As reported in Table 19, the majority of the respondents had a MT onset from a cruise (47.6%), followed by a combination of vehicles (14.4%).

Onset Triggers	MT	SO
<i>Cruise</i>	47.6 % (n10)	
<i>Flight</i>	4.8 % (n1)	
<i>Combination of Vehicles</i>	14.4 % (n3)	
<i>Traumas - Anxiety - Panic Attacks</i>		9.8 % (n2)
<i>Total number of respondents = 16</i>	14	2

Table 19: Onset triggers reported by respondents within the MT and SO groups expressed as the number of respondents (n) and percentage of respondents for both groups.

Respondents were asked about how long they had suffered with MdDS symptoms. The majority reported that they had experienced MdDS for 3 to 4 years; the results are reported in Table 20.

Onset Type	MT n	SO n	Total %
<i><6 months</i>	1	1	9.50%
<i>1/2 years</i>	4	1	23.80%
<i>3/4 years</i>	4	2	38.10%
<i>> 5 years</i>	2	0	9.50%

Table 20: Duration of MdDS before pregnancy reported by respondents within the MT and SO groups expressed as the number of respondents (n) and percentage of respondents for both groups.

Hormonal Contraceptive Used before Pregnancy

Respondents were asked: "Were you on any form of hormonal contraceptive prior to being pregnant?" 42.9% (n = 9) answered positively to this question (77.7% using oral hormonal contraceptives, 11.1% implant and 11.1% hormonal patch). 38.1% (n=8) did not use hormonal contraceptives. On average, the respondents assuming hormonal contraceptive were using it for 6.5 years (SD 4.9 years), and 19% (n=4) did not answer the question.

Symptom Changes throughout Pregnancy

Respondents were enquired about their symptoms during pregnancy:

"What are/were your symptoms like during pregnancy compared to before pregnancy"

The data for this question was combined as only 2 SO respondents answered this question, 18 answers were collected in total. 66.7% (n = 14) reported that their symptoms improved during pregnancy, specifically 28.6% felt *slightly better* and the majority 38.1% reported to feel *significantly better*. Only 9.5 % (n = 2) perceived *no changes* in their symptoms and 9.6% (n = 2) had an *aggravation of symptoms* during pregnancy. Data are reported in the table below.

What are your symptoms like during pregnancy compared to before	(n)	%
<i>No improvement or Changes</i>	2	9.50%
<i>Better first trimester</i>	1	4.80%
<i>Better during the first 2 trimesters</i>	4	19%
<i>Better overall during pregnancy</i>	7	33.30%
<i>Better after delivery</i>	1	4.80%

Table 21: Symptoms during pregnancy compared to during pregnancy, (n) the number of respondents and (%) the percentage of respondents is indicated. In total 15 respondents answered this question.

The majority of respondents indicated that their symptoms were 'better overall during pregnancy' compared to before pregnancy.

In addition to this, respondents were asked if experiencing dizziness according to different positions (e.g. standing, seated, lying down). The majority reported to have no dizziness during pregnancy (10 respondents – 58.8%), with no differences among onset groups. A small percentage equally from the MT and SO group reported to be dizzy while seated (2 respondents 11.7%), standing (2 respondents 11.7%) or lying down (3 respondents 17.6%)

MdDS respondents were also enquired about the nature of their symptoms, for example if they reported symptom fluctuations *day by day* or if their symptoms were *stable*.

18 respondents answered this question; the answers of the respondents are described in Table number 22. The majority reported to have stable symptoms.

Symptoms nature	MT n	SO n	Total %
<i>Cyclic symptoms</i>	2	0	9.50%
<i>Fluctuations related to stressors</i>	0	1	4.80%
<i>Fluctuations day by day / or during the same day</i>	4	1	23.80%
<i>Stable symptoms</i>	6	1	33.30%
<i>Symptoms can vary randomly</i>	2	1	14.30%

Table 22: Nature of Symptoms (e.g. fluctuation, stable symptoms) in MdDS pregnant respondents is reported as number of respondents (n) and the percentage (%) of the respondents for both onset groups.

The majority of respondents indicated that their symptoms were stable during pregnancy.

Heightened symptoms throughout the day

Respondents were asked when they experienced heightened symptoms during the day (e.g. as soon as woke up, mid-morning, evening etc.). The majority (38% - 8 respondents) reported to have symptoms fluctuating day by day and to be unable to specify an exact time throughout the day when symptoms were perceived as higher. This was followed by higher symptoms in the evening (23.8% -5 respondents), mid-afternoon (14.3% - 3 respondents) and morning (14.3% - 3 respondents).

Symptom Rating Good / Bad Days

Respondents were asked to rate (0 = symptoms free / 10=most severe) their overall symptoms perception during a good day (MdDS symptoms are low). Specifically they were asked to rate their symptoms prior and during their pregnancy. A statistical difference (pvalue= 0.002 – One sample t-test) was reported. A great reduction in symptoms was reported the mean rate prior to pregnancy was 2.36 (SD=1.9), compared to mean rate during pregnancy of 0.84 (SD=1.53). Similarly, respondents were enquired to rate their overall symptom perception during a bad day (higher symptoms), during and prior to pregnancy. No statistical difference was reached (mean rate prior to pregnancy= 5.53 SD=2.79; mean rate during pregnancy 4.31 SD= 3.03).

Motion perception

Respondents were also asked which motion symptoms they experienced the most (e.g. bobbing, swaying, rocking, or a combination of them) prior and during pregnancy. When compared the type of motion symptoms between prior to and during pregnancy, a statistical significant difference was recorded (pvalue= 0.044 – repeated measurement analysis). Despite the small number of SO respondents, we decided to

present the difference among the two onset groups as reported statistically significant prior as well as during pregnancy (pvalue before pregnancy= 0.005; pvalue during pregnancy=0.006). The major difference was that the SO group reported more rocking than the MT, while the MT reported to have a greater sensation of mixed directions prior to pregnancy, which decreased during pregnancy (Figure 13).

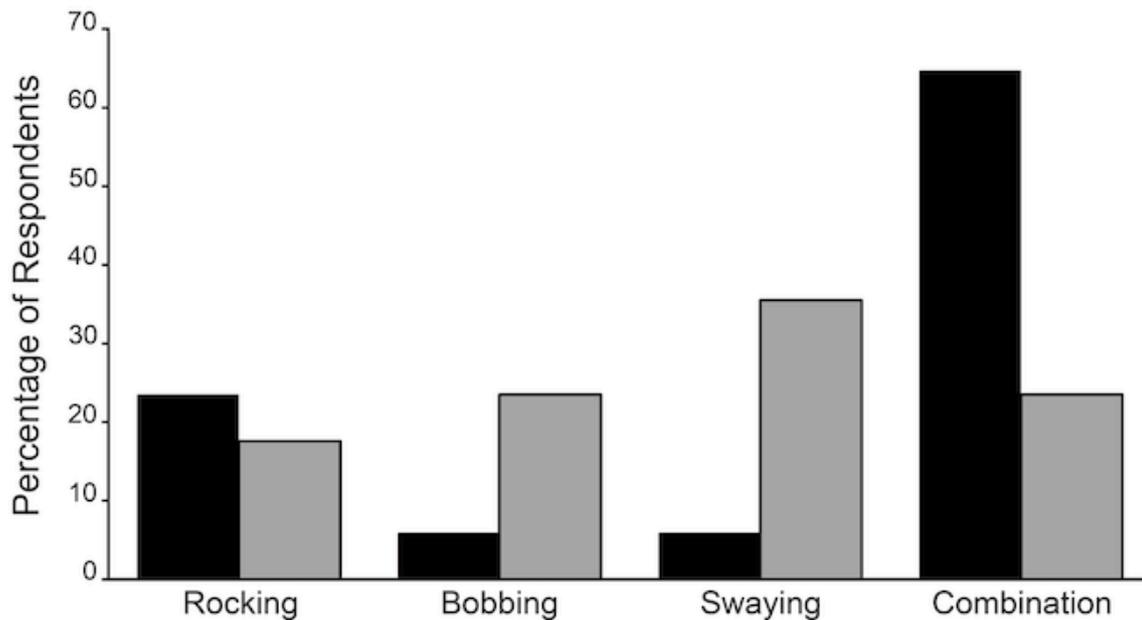


Figure 13: Reported perception of motion by the respondents before and during pregnancy. The number of respondents reporting more mixed / combined sensation of motion decreased during pregnancy, where the perception of motion seems to become clearer and solely involved one direction (e.g. only bobbing or swaying).

Triggers

Respondents were also asked in which position they reported most of their motion symptoms (e.g. standing, laying down, seating) prior as well as during pregnancy and statistical significant value was reported (pvalue=0.03 – repeated measurement analysis). Due to the small number of SO respondents, the differences among the two onset groups were not considered. The greatest changed occurred for the seating and lying down position, where more pregnant women reporting to have no symptoms while being pregnant.

In addition to this, respondents were also asked about other triggering factors: e.g. caffeine, travel by car, being in a supermarket, scrolling on their phones, etc. Symptoms were mainly aggravated by: scrolling on their phones, being in a supermarkets or in department stores, by the lack of sleep, weather changes and flashing lights (for details see Table 23). Similarly, due to the limited number of SO patients the two onset groups were not distinguished.

Triggers	Yes Triggered	No	Missing n respondents
<i>After a car ride</i>	0	19% (n5)	17
<i>Drinking caffeinated beverages</i>	9.5% (n2)	23.8% (n5)	14
<i>Drinking 1-2 drinks of alcohol</i>	33.3% (n7)	14.3% (n3)	11
<i>In a supermarket or grocery store</i>	33.3% (n7)	9.5% (n2)	12
<i>In a department store</i>	38.1% (n8)	9.5% (n2)	11
<i>Watching movies</i>	19% (n4)	23.8 % (n5)	12
<i>Weather changes</i>	28.6% (n6)	19% (n4)	11
<i>Stress</i>	52.4% (n11)	0	10
<i>Lack of sleep</i>	52.4% (n11)	0	10
<i>Dehydration</i>	14.3% (n3)	23.8% (n5)	13
<i>Hunger</i>	23.8% (n5)	23.8% (n5)	11
<i>Noises</i>	9.5 % (n2)	28.6% (n6)	13
<i>Flashing lights</i>	33.3% (n7)	9.5% (n2)	12

Table 23: A series of triggers that could aggravate MdDS symptom are here listed. Reported the number (n) and the percentage (%) of the respondents indicating if triggering factors would make or not make their symptoms worse during pregnancy. In the last column the missing number (n) of respondents is reported, indicated the respondents who did not complete this question.

Mood

Respondents were asked: "Does or did your mood influence your symptoms? " The majority of respondents (70% (8 MT; 4 SO) indicated that mood influenced their symptoms during pregnancy.

Symptom management

Respondents were enquired if they have discussed their symptoms with a gynaecologist, the majority (70%) answered negatively to this question. Thus, those who discussed their condition with their gynaecologist 52.4% reported that their gynaecologist was not aware of this syndrome.

Open – End comments

19 comments were left from the respondent in total, 8 comments explicitly reported that they felt better during pregnancy (*examples reported: symptoms went away during first two trimesters and came back in the last trimester; zero symptoms while being pregnant; overall I feel my symptoms are improving, but my symptoms were already improving prior to falling pregnant; overall my symptoms were much better during pregnancy, which I contributed to hormones*). One respondent commented to be concern for her symptoms to return after delivery.

5 subjects reported aggravation of symptoms due to stress, anxiety, weather changes and mostly visual triggers (e.g. scrolling, working on the computer, watching action TV, being in a supermarket).

Discussion

This was the first pilot study made available to pregnant women affected by MdDS. The recruitment of this study was challenging, as a result to collect a great number of respondents an international multi-institutional collaboration was set up. The result presented a small number of respondents who fitted the criteria; this number was achieved with great difficulties, highlighting the rarity and complexity in researching an entity like MdDS. From the results collected our hypothesis is confirmed, with a high number of MdDS sufferers reporting changing and improvement of MdDS symptoms during pregnancy.

Epidemiology-Diagnostic and Onset

The majority of respondents were from North America; this could reflect the greater awareness in USA and Canada compared to Europe and Australia. With regards to diagnosis, specifically, the health care professionals, providing MdDS diagnoses, our results are in line with the recently published questionnaire on MT and SO diagnostic investigation, where neurologists and otolaryngologists were the primary health professionals providing most of the diagnoses [21]. Also considering the onset triggers, the majority of the respondents were triggered by a motion event, namely after a cruise or sea travel, and this data are in also line with the data recently published from our group [21]. Overall, in the current study, the number of SO respondents engaging in the study was small, as a result our aim of comparing the two onsets was not realistic.

Most of the MdDS patients engaged in this pilot study had been suffering from MdDS prior to becoming pregnant, with most of them reporting to have MdDS for 3 to 4 years. Only two respondents reported that their MdDS symptoms began during pregnancy. Thus, given the small number of respondents, it is difficult to know if pregnancy and the

associated hormonal changes exist as a trigger for their MdDS symptoms.

Respondents were enquired about the usage of hormonal contraceptive prior to pregnancy. This data proved insignificant, preventing a correlation between hormonal contraceptive use prior to pregnancy and the influence on MdDS symptoms to be established.

MdDS symptoms during pregnancy and underlying theories on the mechanism involved

From the presented results the majority of MdDS respondents, regardless of their onset type, reported an improvement of symptoms during pregnancy, this can be considered the key findings of this study. The majority were not able to report accurately when the greatest improvement occurred, with a high number of respondents stating to perceive an overall improvement during the whole 9 months of pregnancy, which was further supported by the open-ended comments. The second largest number of respondents reported to have felt better within the first two trimesters of pregnancy and only 2 respondents reported to have their symptoms aggravated throughout the pregnancy period. If considering that from the very beginning of pregnancy, the trophoblast releases Human Chorionic Gonadotropin (hCG) hormone, allowing the corpus luteum within the ovary to continue to produce estrogen and progesterone until the formation of the placenta is complete [39]. The levels of estrogen and progesterone are maintained high and are stable; it is possible that MdDS symptoms improved as a result of steady hormonal concentrations achieved during pregnancy. This could potentially confirm our hypothesis, that MdDS patients, similar to migraine patients [168], are subjected to symptom improvement during pregnancy and sensitive to hormonal fluctuations when in their normal reproductive cycle. The placenta is responsible for producing the majority of estrogen and progesterone necessary for the progression of pregnancy [180]. The rise in estrogen and progesterone begins during the 6th to 8th

week of pregnancy and continues to gradually increase to peak levels during the third trimester; serum estradiol levels during the third trimester of pregnancy are 30–40 times higher and progesterone levels are 20 times higher than their highest levels during natural menstrual cycles [39, 158]. It can therefore be suggested that the absolute level of these hormones experienced during pregnancy, contrasting normal cyclic fluctuations [176] and the high levels of estrogen and progesterone could be responsible for symptom reduction demonstrated in this pilot study. The high and stable level of estrogen and progesterone matches with symptoms improvement reported by MdDS respondents enquired in this pilot study.

The higher level of estrogen may also reflect or induce central changes. Estrogen acts via two nuclear receptors, estrogen-receptor α and β [145, 146], which have excitatory action within the central nervous system [147]. These receptors have been found in brainstem vestibular nuclei concerned with optokinetic, vestibular-ocular and vestibulo-spinal reflex [142]. Additionally, estrogens are known to facilitate the glutamatergic system, potentially enhancing neural excitability. Progesterone is able to activate GABAergic systems, suppressing neural activity [39]. In one of the hypothesis presented the pathophysiology of MdDS was regarded as a maladaptation of the VOR and velocity storage. The nuclei involved within VOR and the velocity storage are GABA_b sensitive neurons, located in the medial and superior vestibular nucleus [77]. Those could be subjected to the GABAergic system changes induced by hormones [53]. Furthermore, if considering that MdDS is theorised to be a disorder of neuroplasticity [49], it is possible that the hormonal receptors activated by female hormones, may also affect the hippocampal and EC interneurons, however up to date estrogen receptors have not been specifically found in the EC area. However it could be possible that these projections could influence firing patterns within the EC-hippocampal circuit. Therefore, more specifically, as GABA-mediated neurons are hypothesised to have a

prominent inhibitory role in spatial navigation, their deregulation [150], by altering hormonal levels could hold some significance in the aggravation or improvement of MdDS symptoms. In this questionnaire, it has also been clearly reported that a great number of MdDS patients described to have no symptoms of dizziness during pregnancy, strengthening the positive effects of pregnancy.

This pilot questionnaire provides foundation for further assessments, which are necessary, given the limited number of respondents. The next assessment should examine at how symptoms may change in MdDS patients during each trimester as well as after delivery.

Symptom nature

With regards to the nature of symptoms, most patients reported stable or symptom changes (day by day). The fluctuation of symptoms or the fact that the majority reported higher symptoms in the evening could indicate that symptoms fluctuations are associated with neuroendocrinological modulations for example of cortisol. The necessity to evaluate the daily symptoms modulation could lead not only to greater insights in MdDS pathophysiology but also improvement of treatment options. Additionally, the respondents were required to rate the severity of their symptoms on a scale of 0 to 10, during what they considered a good day and a bad day, prior to and while pregnant. Considering the symptoms fluctuations characterising MdDS patients [47], both during prior being pregnant. A statistical significant difference was reported when considering a good day prior to pregnancy and during the pregnancy period. This indicates that a great reduction in symptom discomfort is perceived by MdDS patients while pregnant. Similarly, when comparing the participant's motion perception, a substantial difference was reported, mainly indicating that during pregnancy for the MT group the mixture of different motion perception (e.g.

combination of swaying and bobbing) reduced to the prevalence of mainly one direction (e.g. only mild swaying). This could be the result of the overall reduction of symptoms. Another interesting difference was that most of the SO respondents reported a rocking sensation, something less common from the MT group, which described no rocking sensations during pregnancy. The number of respondents however was too limited to draw firm conclusion, but suggests that further examinations about direction and phantom motion perception should be explored and the two onset groups should be further evaluated.

Furthermore, respondents were asked if different positions (e.g. standing or lying down) affected the level of their symptoms. Our results showed that different positions did affect respondents' symptoms. The majority of respondents reported to experience higher symptoms predominantly while lying down during pregnancy, something that was not common prior to being pregnant. No differences among the two onsets groups were considered due to the small number of SO participants. These results could be due to Supine Hypotension Syndrome (also referred to as Aortocaval Compression Syndrome), which is caused when the gravid uterus compresses the aorta and inferior vena cava when a pregnant woman lays down in a supine position [181]. This leads to a decrease of venous return and a reduced blood flow. Within 3 to 10 minutes in the supine position, symptoms such as dizziness, pallor, low blood pressure, sweating and nausea and an increase in heart rate occur [181, 182]. 8% of pregnant women within the 2nd and 3rd trimesters of pregnancy may experience this [182]. In our research cohort, it is possible that some respondents may have experienced supine hypotensive syndrome when lying down, rather than experiencing increases in MdDS symptoms per se. However, we did not ask pregnant MdDS respondents if they were aware of Supine Hypotensive Syndrome, it is hard to argue if this is the primary cause for increasing their symptoms in the supine position. Not all women experience supine hypotension during

pregnancy, as pregnant women also have protective mechanisms, such as the development of paravertebral pelvic collateral circulation or a change in baroreflex gain. Overall, pregnant MdDS women should avoid conditions that can naturally increase the risk for triggering dizziness, such as lying down in the supine position, but should be advised to move to the left side position.

Triggers - mood

The respondents were also asked if during pregnancy they were more sensitive to a series of triggers known for disturbing MdDS patients [52]. From the results collected, most respondents seemed to report a heightened sensitivity to visual stimuli, which is something known for MdDS patients [44]. It was also reported that mood could influence patients symptoms, and stress was considered as a trigger, similarly to what is previously described in Chapter 3 [21]. High levels of anxiety were also expressed in the open-end comment section: again anxiety is considered a major trigger in influencing MdDS symptoms (as reported in Chapter 3).

Symptom Management

From our preliminary results, it is clear that the majority of gynaecologists are not aware or familiar with MdDS. However given the drastic changes in MdDS symptoms potentially related to hormonal changes, it may be relevant to assess patient's hormonal profile and to pursue follow ups in the puerperium phase in collaboration with gynaecology consult. After delivery, hormonal levels drop and as observed in migraine [168], similarly for MdDS patients' symptoms may return.

Limitations

The survey questions sometimes requested information about events which occurred many years prior and we included no specific strategies for reducing recall bias. The number of MT and SO respondents was limited due to the difficulties in recruiting respondents, thus our analysis should be considered preliminary. A larger cohort should be recruited for future studies. Respondents were only enquired to how symptoms changed during pregnancy in respect to prior to being pregnant. A future assessment should also consider follow up on how symptoms might change after delivery.

Conclusion

This was the first pilot study made available to pregnant MdDS women. Valuable information about symptoms fluctuations and changes throughout the pregnancy were observed. MdDS patients regardless of their onset type (MT or SO), reported overall an improvement of symptoms during the their pregnancy compared to before pregnancy, suggesting the beneficial influence of higher estrogen and progesterone concentration and absence of cyclic fluctuation. This preliminary data may provide incentive for further investigation into the role of hormones in the symptom profile and pathophysiology of MdDS.

4.3 Challenges and next steps for future research

Challenges

The greatest limitation to the study presented in section 4.1 and 4.2 was the difficulty encountered in the recruitment of patients. Despite in study 4.1 we were able to engage a great number of respondents overall the number of SO patients was smaller compared to the MT. Similarly the SO respondents engaging in the pregnancy questionnaire were less than the MT. Thus further research should continue international collaboration and perhaps dedicate research solely to the SO group, gaining more information about the SO subtype would ultimately help the classification of this specific group.

Future studies

With regards especially to the findings obtained in section 4.1 future studies should consider the implication of estrogen within the vestibular system, for example focusing on estrogen receptors found in brainstem vestibular nuclei, brain areas concerned with optokinetic, vestibulo-ocular and vestibulospinal reflex [142] as well as influencing central neurotransmitters (i.e. GABA). Neuroimaging studies, coupled with estrogen testing, could prove useful in assessing the effect of estrogen on hippocampal and EC interneurons, which have been theorized to be involved in MdDS pathophysiology [54]. We also encourage future research to conduct a detailed analysis of the perimenopausal phase and pre menstrual syndrome (PMS) in MdDS sufferers; in order to elucidate what other potential causes may be implicated with MdDS symptom fluctuations and onset. The difference in irregular and regular menses for MT and SO subtype should be further evaluated. Additionally, testosterone testing could prove beneficial for male and female MdDS patients alike to provide detail concerning its effect on cognitive functions and memory [166] [156], which are also described as impaired following MdDS onset. Overall, a clinical assessment of female and male hormonal profiles should be performed to elucidate possible mechanisms behind the development of MdDS, and provide direction for potential hormonal treatment strategies for MdDS.

Considering study 4.2, future studies should consider to focusing on assessing female MdDS patients not only during pregnancy but also in the postpartum phase. Such extended overview will provide more insights on the hormonal influences upon MdDS symptoms in female subjects.

MdDS patients – Blood Sampling Hormonal Research

Here we propose a methodology to objectify hormonal influences in MdDS patients, though hormonal assessment via blood sampling. This study is currently on-going therefore the data are not included in this manuscript.

Methodology Blood Samples Study in female MdDS patients.

Study Population and Recruitment

Patients diagnosed by specialists or believing to suffer from MdDS were recruited for the study. Inclusion criteria for this study are summarized in the table below and are based upon the most recent guidelines and diagnostic criteria for MdDS [21].

1)	≥18years old
2)	Female patients reporting sensations of self-motion (rocking, rocking, swaying and bobbing) for longer than one month, where the symptoms could not be explained by another diagnosis, Patients reporting MdDS symptoms after the exposure to passive motion (<i>MT group</i>). Patients reporting similar symptoms without a clear motion event or any obvious cause (<i>spontaneous</i>). Patients reporting the initial symptoms after a strong emotional or stressful event (e.g. childbirth, physical or emotional trauma, surgery, etc.) (<i>Other</i>) (<i>Combined = SO group</i>).
3)	Female patients in their active reproductive years free from contraceptives.
4)	Female patients assuming hormonal contraceptive, which allow for one monthly week break in their dosage.

Table 24: Inclusion criteria used for the study. See guidelines [21, 44].

MdDS patients were recruited through the Department of Otorhinolaryngology and Head and Neck Surgery, a tertiary referral centre, at the University Hospital of Antwerp, Belgium. Recently, due to the limited number o respondent's patients are now also recruited across the USA, Europe, and Australia. Ethical approval was provided by the Ethics Committee of University Hospital Antwerp Belgium (IRB number 15/44/454). Each patient provided informed consent. All investigations have been conducted according to the principles expressed in the Declaration of Helsinki.

Patients were asked to provide to two-blood sampling over their menstrual cycle.

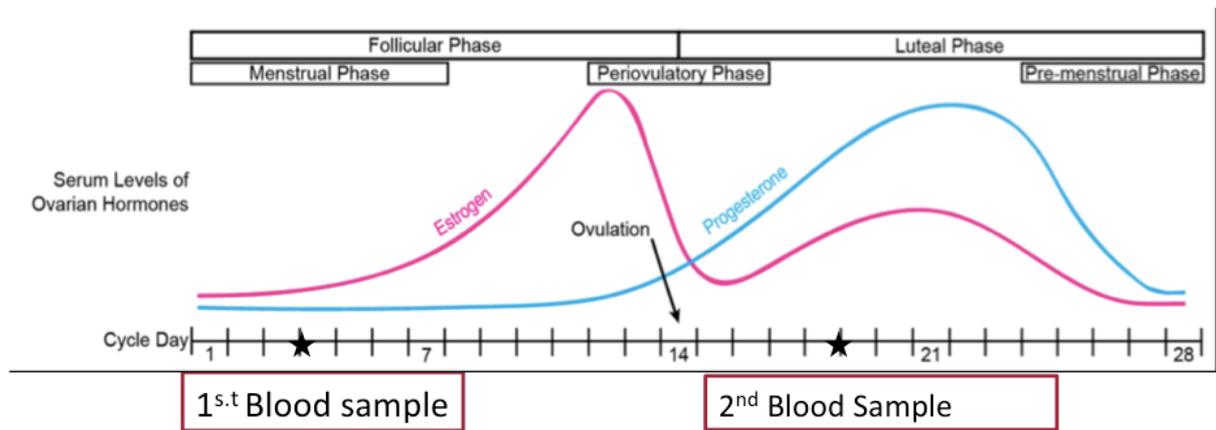


Figure 14: A graphical representation of the hormonal fluctuations. With the star symbols the moment when the two blood samples are taken are here presented. (Mucci et al 2018 unpublished)

As reported in the figure above hormonal blood levels are subjected to changes during the simple menstrual cycle as during different stages of life. Addressing the fluctuation of hormones is extremely relevant to understand when and how the perception of the symptoms are changing or aggravating.

Patients free from contraceptives

Hormonal check-up only for the patients free from contraceptive pill is here reported.

These patients are asked to collect a blood sample twice during a menstrual cycle:

- 1st Step - 1st Sample: collect the 1st sample of blood on the 3rd day of their menstrual cycle. A blood sample for common routine hormonal analysis: Estradiol (E2), Hormone- Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Progesteron (P).
- 2rd step - LH detection: In order to detect the period after ovulation, the patients are asked to use a commercial ovulation prediction strip (<http://www.early-pregnancy-tests.com/inovtesstrip.html>), detecting LH levels in the subject's urine. Ovulation prediction kits are very popular and easy to use. Just before ovulation there is a surge in the LH levels. When this is detected ovulation usually occurs within the next 36 hrs.
- 3rd Step - 2nd Sample: following 5 days from the surge LH surge patient are asked to provide another blood sample. In this specific moment of the menstrual cycle after the ovulation peak Estradiol (E2) is decreasing and Progesteron (P) is increasing. We aim to observe if a decrease in E2 would be related to aggravation of symptoms and also to investigate if MdDS patient's hormonal cycle is behaving normally.

Patients using hormonal contraceptives

Patients currently under the prescription of hormonal contraceptive therapies (in the form of monthly pills) are advised to undertake two blood samples in two different moments of the month.

- 1) 3-4 days during contraceptive suspensions
- 2) 10 days after day 1 of the contraceptive - the second assessment should be performed while they are in the middle of the usage of their contraceptive.

Remark: if patients are not having any suspension of the contraceptive pill or hormonal replacement therapy they will be excluded from the hormonal investigation.

We hope that by gaining more data on patients symptoms fluctuations and hormonal levels through blood sampling in different menstrual phases, we will be able to confirm not only empirically the estrogen withdrawal theory previously proposed.

5. CHAPTER OPTOKINETIC TREATMENT FOR MdDS PATIENTS:

- Optokinetic Treatment for MdDS

Part of this chapter has been submitted and is currently in the final stage of review:

Sham-controlled study of optokinetic stimuli as treatment for Mal de Debarquement Syndrome

Mucci, Viviana, Perkisas Tyché, Jillings, Steven, Van Rompaey Vincent, Fransen Erik., Vereeck, Luc, Wuyts, Floris L., Van de Heyning Paul.H., Browne Cherylea J., and Van Ombergen, Angelique. March 2018.

Part of this research focused on one of the few currently available treatment options for MdDS patients. This treatment has been built on Theory number 2 presented in Chapter 2. The treatment is named Optokinetic stimuli (OKN treatment) and MdDS patients are exposed to repetitive optokinetic stimuli to re-calibrate the believed disrupted Vestibular Ocular Reflex (VOR).

5.1 Sham-controlled study of optokinetic stimuli as treatment for Mal de Debarquement Syndrome

Abstract

Introduction: Mal de Debarquement Syndrome (MdDS) is a neurological condition, characterised by a perception of self-motion, with two onset types: Motion-Triggered (MT) and Spontaneous (SO). Currently, the pathophysiology is unknown and consequently, the therapeutic options are limited. One proposed treatment, developed by Dai and colleagues in New York, USA, is based on optokinetic (OKN) stimulation. This study aimed to reproduce the same treatment, for the first time, and to assess if a placebo effect was present. We also aimed to further explore and evaluate if a standardisation of the OKN treatment was possible as well as to gain more information about MdDS patients (previous treatment trialled as well as hormonal status).

Method: 25 MdDS patients (13 MT; 12 SO) were exposed to five consecutive days of OKN treatment (consisting of exposure to OKN stimuli with head movements). Eleven of these 25 patients were exposed to two days of a sham protocol prior to the treatment. Patient's posturography and symptoms were assessed throughout the treatment with the visual analogue scale. Posturography data were compared with 20 healthy controls. Female patients were enquired about their hormonal status during onset.

Results: No placebo effect was recorded with any changes in postural data and VAS scale. After the OKN treatment, a significant improvement in postural control (pvalues: AUC_AP= 2E-04; AUC_ML=1E-03, CEA=6E-05, Velocity=2E-05) was observed in 48% of patients, of whom 70% were of the MT subtype. Some of the participants were exposed to other treatments such as vestibular rehabilitation, with poor results. Women reported to be perimenopausal and menopausal when onset started.

Conclusion: A standardized OKN treatment was effective in approximately half of the patients with no placebo effect recorded. The MT group responded better to treatment than the SO group. Respondents reported to have tried other treatments (e.g. antidepressant, vestibular rehabilitation) with poor or no improvement; this strengthened the need to further assess the OKN treatment. As a result, this study has demonstrated the validity of OKN treatment. A potential hormonal risk factor has been hypothesised following the results collected with regards to the female patients.

Introduction

Despite the growing awareness and investigations into MdDS, the knowledge of this condition among health care professionals is still limited, resulting in a high number of misdiagnosed patients [21]. Consequently, treatment options and symptom management strategies are poor and inadequate. The latter is further strengthened by the scarce knowledge and understanding of the underlying pathophysiological mechanisms of MdDS.

Up to now, two main theories have been hypothesised with regards to MdDS pathophysiology. One theory developed through neuroimaging and neuromodulation investigations, has proposed MdDS to be a disorder of abnormal functional connectivity within the brain, limbic abnormalities involving the hippocampus and the entorhinal cortex in particular, a key area for mapping one's spatial environment [49, 65]. Additionally MdDS patients have been reporting functional connectivity reduction, and therefore responded favourably to neuromodulation such as repetitive transcranial modulation (rTMS), indicating that MdDS may be a disorder of over-synchronization of brain networks [23, 49, 54]. This over-synchronization may have been driven by entrainment to background low-amplitude oscillating environments, such as

experienced on water [49]. rTMS is currently considered one of the few treatment options available for MdDS patients (for more details please refer to Chapter 2 & Chapter 8).

Another theory formulated by Dai and colleagues [53, 73], and supported by research in subhuman primates [73, 74, 78] suggests that MdDS is the result of maladaptive coupling of multiplanar information of the vestibular-ocular reflex (VOR). This maladaptation results in a disrupted velocity storage mechanism. The VOR is the reflex responsible to ensure gaze stabilization during rotation of the head around the three axes relative to the centre of gravity (e.g. yaw, pitch and roll) [52]. During normal head rotation the eyes rotate in the opposite direction of the head, thus cancelling the head motion visually [183], ensuring image stabilization on the retina. The VOR is able to adapt depending on the context, and this "contextual" VOR adaptation is long lasting [74, 169]. For example, when a person is adapted to a specific context (e.g. cross-axis adaptation present on a cruise ship), a similar cross-axis re-adaptation typically occurs when returning to a static environment, e.g. after disembarking. However, this mechanism seems to fail in MdDS patients. In particular, it is believed that this failing mechanism is related to processes within the velocity storage mechanism. This could suggest that cross-axis-coupled stimuli (e.g. being on a boat) have the ability to alter the velocity storage mechanism of the VOR.

The velocity storage mechanism is defined as a multisensory element comprising of central pathways that are responsible for extending vestibular inputs and retaining vestibular information, which enables the adjustment of postural stability in specific contexts [184]. Its function is to compute and accurately estimate rotation velocity by using multiple sensory cues, e.g. canal signals, otolith signals, and visual inputs [184]. Its

key feature relies on the sensitivity of the orientation of the head relative to gravity [54]. When considering the higher central control of the VOR, the vestibular nuclei, inferior olive and cerebellum are the neuronal centers, which are proposed to be involved in the disruption of normal VOR function [53, 73]. Particularly, two types of neurons are involved in processing vestibular information: Type I, which receives convergent input from the lateral, anterior, or posterior canals of the vestibular apparatus, and Type II, which are vestibular-only (VO) neurons, involved in vestibulospinal functions, velocity storage and perception of self-motion [77, 185]. As a result, the central pathways of the velocity storage include indirect and direct pathways that drive the VOR [186]. From previous animal studies [77, 78], it is now possible to understand the velocity storage also serves as an input for the sympathetic nervous system and that it is able to influence the descending vestibulospinal projections [77] (e.g. modulating the VOR with repetitive rotation in protocol to reduce motion sickness susceptibility). Interestingly, and of particular significance, is the fact that several MdDS patients have reported to physically move (rocking or swaying) at a frequency of 0.2 Hz, showing that the velocity storage integrator not only is associated with spatial orientation, eye movements and activation of the sympathetic nervous system, but also with descending vestibulospinal projections, influencing postural instability in the case of MdDS subjects [77]. Thus, Dai and colleagues hypothesised that the velocity storage is aberrant in MdDS patients, after the exposure to passive motion (e.g. being on a cruise). Its alteration is as such considered responsible for the reported postural instability in MdDS patients [53].

Taking this into account, it has been theorised that the velocity storage and the VOR can be readjusted by manipulating the VOR (velocity storage) time constant. Based on these observations and hypothesis, a treatment protocol was created. The treatment involved the re-adaptation of the VOR in MdDS patients using optokinetic (OKN) stimulation, in combination with passive head roll movements, this was first installed by

Dai and colleagues in 2014 [53]. This treatment will be referred in this manuscript as OKN treatment. It is known that in large fields visual inputs have the ability to drive the VOR, which is called the optokinetic reflex (OKR), and this visual input can elicit a false perception of motion [187]. OKN stimulation was hypothesised to be able to readjust the VOR due to the interference with the velocity storage. The OKN stimuli used in Dai's protocol are vertical stripes rotating to the right or left, or horizontal stripes moving upwards or downwards.

Optokinetic stimuli consist in repetitive visual patterns that can have different shapes and form, which are used to induce optovestibular stimulation. Vestibular patients are often exposed to repetitive optovestibular stimulation as part of a vestibular rehabilitation (VR) program. This often includes optokinetic stimulation as well as ocular pursuit, and position exercises [188].

The literature described favourable results in patients with vestibular disorders after being exposed to optokinetic stimulation using a rotating drum with vertical white and black stripes [53, 188]. This specific type of optokinetic stimuli has been described to be beneficial especially for MdDS patients [53], an example is reported in Figure 15.



Figure 15: Representation of the optokinetic drum exposing vertical stripes [53].

However other vestibular optokinetic stimuli can be used for different VR [88] as well as for reducing motion sickness during sea travels [189]. The type of the optokinetic and vestibular rehabilitation can be modelled for each specific vestibular disorder and patient according to their primary needs [190].

In Dai's protocol patients were also subjected to passive head movements in the form of a head roll, a representation is reported in Figure 16.

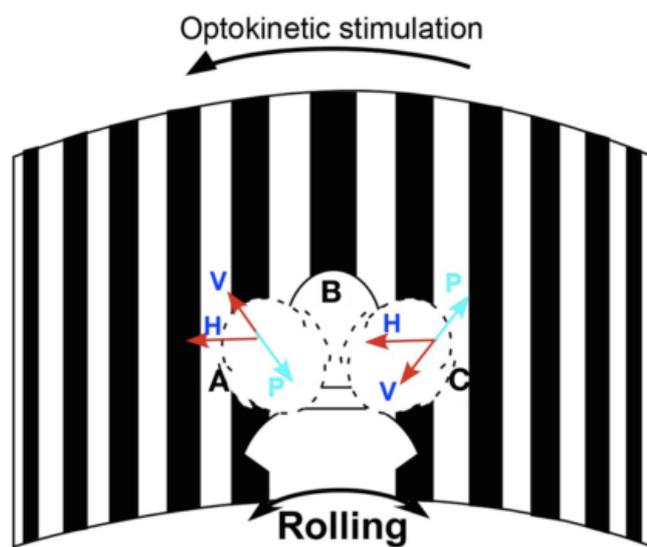


Figure 16: Schematic paradigm of head roll applied during the protocol of Dai et al 2014 on MdDS subjects [53].

In this hypothesis, MdDS patients were believed to have a pitch orientation vector transformed from its original position along gravity to a tilted position in roll [73]. Consequently, in order to induce a change in the velocity storage, the combination of the OKN stimuli (in the form of stripes) with patient's head roll was required.

In particular, Dai and colleagues developed a personalised protocol where the head roll oscillation frequency matches the patient's internal sensation of motion also named self-motion or gravitational pull (rocking, swaying, etc.) [53]. In this way, it was proposed that the patient's gravito-inertial acceleration (GIA) would be modulated, as the patient is subjected to an OKN stimulus that rotates around the spatial vertical against the direction of the vestibular imbalance reported by the patient (when possible) [73]. In the OKN protocol for MdDS, the researcher rolls the patient's head at $\pm 20^\circ$ according to the patient's rocking or swaying frequency, while the patient is asked to passively watch the moving stripes projected on a wall [53]. MdDS subjects are asked to repeat their exposures for 4 to 5 consecutive days. This first setting was tested in 2014, on 24 MdDS patients, 70% of which reported an improvement of MdDS symptoms [53]. Following this initial investigation, a second assessment from the same team (Dai and colleagues) was conducted in 2017; this involved a larger sample size of patients [52]. They included 120 MT and 21 SO MdDS patients [52]. In this second study, patients were followed up to roughly 11 months following the treatment. In both studies the treatments were delivered over 4-5 consecutive days and the patients were treated 10–120 min a day, where each session was customised [52, 53]. The study demonstrated that the improvement rate after about 1-year followed up decreased to 42% from the original 70% recorded in 2014 [52]. So far no other studies have ever been performed on the OKN treatment and in order to further validate this therapy for MdDS patients, more studies are requested. Additional research could provide evidences that the results obtain by Dai and colleagues are reproducible [191].

Taking this into account, our research intended to elucidate the validity of the OKN treatment by reproducing a similar methodology proposed by Dai's and colleagues. Secondly, as Dai's investigations lacked of a placebo control group, we aimed to

assess if the OKN treatment can induce a placebo response in MdDS patients, through the implementation of a sham protocol. Posturography data [192] were used to objectify postural changes of MdDS patients and posturography measurement validity were compared with healthy controls.

Our study also aimed to standardize Dai's protocol by using a more strict procedure of combination of stimuli and number of exposures; this would allow us to have a reproducible protocol easy to be implemented in clinical setting. Thus, contrary to Dai's protocol, where the OKN stimuli and head movements were personalised for each patient, we assessed if standardization would interfere with the treatment outcome by keeping a fixed frequency for the head roll among all subjects.

Lastly, a series of investigative questions were asked (e.g. what other treatment have been trialled, symptoms, etc) to the MdDS patients, and to female MdDS patients a series of hormonal related questions were proposed, in order to gain more information about the characteristics of our group of patients.

We hypothesised to obtain similar results to the one gained by Dai and colleagues in their previous studies and that no placebo effect was present for MdDS patients with our setting.

Methodology

Ethical approval/ Patient Recruitment/ Study population/ Study Size

Ethical approval was obtained through the Ethics Committee of Antwerp University Hospital, Antwerp, Belgium (IRB number 15/44/454). Each patient gave informed consent prior to the study. All investigations have been conducted according to the principles expressed in the Declaration of Helsinki. Patients with MdDS were recruited during vertigo-specific consultations at the department of Otorhinolaryngology and Head and Neck Surgery at the University Hospital of Antwerp, Antwerp University, Belgium. Patients were diagnosed with MdDS, implementing the earlier published guidelines by our group [21, 44]. In the first study from Dai and colleagues (2014) [53], 24 MdDS subjects were included, as a result in this study we aimed to replicate the same number of patients, including 25 MdDS subjects. Only patients from the Euro zone (flight distance less than 5hrs from Brussels) were included in the study, to diminish the possibility to triggers patients symptoms with a long journey while returning home. Our inclusion and exclusion criteria are reported in the Table below (Table 25).

<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>
Patient with complaints of persistent (>1 month) Mal de Debarquement; reporting a prolonged sensation of self-motion (rocking, swaying and bobbing) after the exposure to passive motion, most frequently a boat trip, or travel over air or land,	< 18years,
Patients with MdDS symptoms, which occurred spontaneously or with atypical onset refer to [3] for details,	Epilepsy diagnosis,
Clinical research with micro-otoscopy and video-oculography with normal results,	Visual impairments that cannot be corrected with glasses or contact lenses,
Tonal audiometry speech audiometry and tympanometry with normal results,	Pregnant women,
Standard MRI posterior fossa, performed pre-treatment with normal results,	Female patients experiencing menstruation (on the days of treatment) due to a potential the aggravation of symptoms [3] and increase motion sickness sensitivity [26],
Electronystagmography (ENG), vestibular evoked myogenic potentials (VEMP) with normal results,	Patients taking antidepressant drugs (e.g. Selective serotonin reuptake inhibitors (SSRIs), Monoamine oxidase inhibitors (MAOIs), Tricyclic antidepressants) – however could be included if they temporarily ceased taking the medication during the treatment week.
Patients whose complaints cannot be explained by another diagnosis.	

Table 25: Inclusion criteria based on the published update guidelines [21, 44]. Exclusion criteria based on clinical observations.

Research Methodology

Questionnaires

A series of intake questionnaires were given to the patients prior to the study. They included epidemiological questions as well as questions related to their onset, symptom fluctuations and triggers (see Annex 4 for more details). Patients were also enquired about migraine and in general the existence of other pathological conditions. Patients were also asked to complete a Misery Scale (MISC) questionnaire [193] on each day of the treatment. Similarly, a Visual Analogue Scale (VAS) questionnaire describing symptoms severity (0= being symptoms free, 10=severe symptoms) [193] was provided to the patient each day before and after the OKN stimulation. Female MdDS patients were also enquired about their hormonal status during onset. For more details, please consult Annex 4. In addition to the intake questionnaire, follow-up questions regarding symptoms (3 months post treatment) were presented after the treatment.

Here reported the follow up questions:

Follow up symptoms:

1. *Please state how your symptoms have changed (improved or become worse) since the treatment?*
2. *Since the treatment, do you feel dizzy when watching busy traffic intersections, scrolling on your phone, walking in a supermarket?*
3. *Have you experienced brain fog since the treatment?*
4. *Have you experienced headaches since the treatment?*
5. *Have you experienced migraine since the treatment?*

Posturography

Posturography was measured with the use of a Wii Balance board® (Nintendo Co., Ltd), as it has been shown to be a valuable tool in measuring postural sway and the velocity rate of sways in vestibular patients [192]. The data was analysed with a program based on the Colorado University Wii Balance Board code developed at the

Neuromechanics Laboratory at Colorado University [194]. After acquisition, the data was filtered using a Butter filter of fourth order and a cut-off frequency of 0.17 Hz. The software suite of choice was MATLAB (Release 2017b, developed by The MathWorks, Inc., Natick, Massachusetts, United States). For the posturography measurement, patients were asked to stand upright for 60 seconds, with feet apart (hip width) on the Wii Balance board [192], with eyes closed, and barefoot, similarly to Dai's and colleagues' protocol [53]. All patients remained on the board for a minimum of 60 seconds, although, if a patient had severe postural instability he/she could step off after 30 seconds. At all times, patients were closely observed by the researchers to avoid injuries such as falling off the board. Following previous publications, we believed the Wii Balance board was the best too to compare individual measurements, assess postural sway and easily track health status changes of the patients [84, 192, 195, 196]. This measurement was performed before and after each exposure to the OKN stimuli as well as before and after the sham protocol. To avoid injuries, patients with poor postural stability were asked to remain on the balance board for as long as they possibly could (a minimum of 30 seconds), additionally patients were carefully monitored by the researcher and could stop at any time if needed it. Posturography data was recorded every day before and after the exposure to sham protocol as well as before and after each exposure to the true OKN stimulation during the five days of treatment. Eight posturography measurements in total were recorded for the Sham protocol and on a range of 24 to 40 posturography measurements were performed over the five days of treatment (more information are presented in Table 26 below).

The following five postural parameter variables were recorded:

- 1) Area under curve Anterior-Posterior (**AUC_AP**)
- 2) Area under the curve Medial-Lateral (**AUC_ML**)

AUC_ML and AUC_AP represent the area under the curve of a power spectrum, assuming that patients suffering from MdDS reported aberrant medio-lateral sways, it is valid to assume that abnormal movements will result in aberrant frequencies of oscillation reported by the Area under the Curve in the power spectrum [197].

- 3) Confidence Ellipse Area (**CEA**): has been widely used before when assessing posture and this variables provides with 95% confidence ellipse area for the mean of the centre of pressure (CoP) anterior, posterior, medial and lateral coordinates [195].
- 4) **Path Length**: the CoP path length (mm), which is the absolute length of the CoP path movements throughout the testing period [198].
- 5) **Velocity**: this variable is also named the *Sway Velocity*, represented the sway rate (mm/s) defined as the mean speed of movement of the CoP throughout the testing period [198].

Twenty-five patients with MdDS were analysed considering these five postural parameters. These parameters are hereafter referred to as 'outcome parameters' in the remainder of the manuscript. The patients received the treatment over five consecutive days, and on each day, outcome parameter measurements were recorded before (Pre) and after (Post) treatment. An example of the posturography recordings of a healthy subject and an MdDS patient are shown in Figure 17 (Fig A= Healthy Control and B= MdDS Patient).

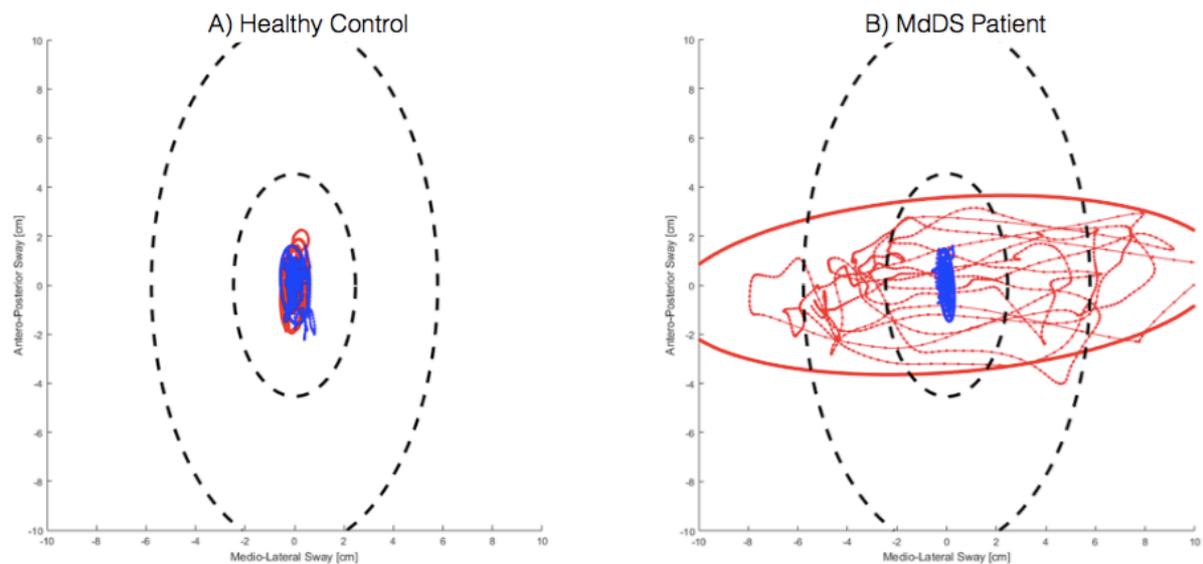


Figure 17: Example of the posturography recordings from a (A) Healthy control and (B) a MdDS Patient– (Female / 43yr. old perimenopause). The colour red represents the posturography prior to the treatment and in colour blue the posturography after the treatment.

Posturography - Control group

Twenty healthy control individuals were tested (test-re-test method) twice (on Day 1 and Day 2) within a two-week interval; however, they did not receive the OKN or the sham protocol. These subjects were age-matched (mean age: 44.5 years – range from 24 to 66 years) with the patient group. With this assessment we were able to evaluate if any learning effect were presents.

Treatment (True and Sham)

True Optokinetic Treatment Duration

All patients underwent five consecutive days of OKN stimulation. During the five days of treatment, patients received various sessions per day: two sessions on Day 1 (treatment day), slowly increasing to 4 sessions on Day 2 and up to 6 to 8 or more sessions on Day 3. Thus, all patients underwent a gradual increase of exposure time and number of sessions throughout the five days. Following Day 3, the numbers of sessions were

modulated according to their subjective feeling of internal oscillation (e.g. if a patient was feeling better and his/her posturography improved, only 4 sessions were performed on Day 4 and Day 5, on the contrary if a patient's subjective feeling and postural outcome measures were not improving, patient's sessions were increased). A 30-minute interval was provided between each session of OKN stimulation.

Sham Treatment Duration

Among the 25 patients that received the true OKN stimulation, 11 of those were randomly selected for the Sham treatment, which involved two additional sessions prior to the true OKN treatment. Participants were exposed to the same OKN stimulus but without the stripes moving, they were asked to stare passively at static OKN vertical stripes, while their heads were rolled at same frequency as during the true OKN stimulation. We hypothesized that introducing the patients to the same environment and being in contact with the patients (by holding and rotating their heads), could be a strong factor that could potentially induce a placebo effect.

True Optokinetic Treatment Setting

During the treatments, the patients were seated in a chair in a darkened OKN drum, specifically built for the experiment (for details see Figure 18).



Figure 18: Set-up and full-field optokinetic stimuli as implemented in this study.

A full-field OKN visual stimulus was projected on the drum walls, filling the visual field of the patient, including peripheral vision as reported in the Figure 18, similar to what proposed in Dai's setting [53]. Patients were seated at 60 cm from the wall of the drum; the drum was composed of a rotating wall of 3 meters (Field of View (FoV)= 71.56° , 1.249 rad).

During the treatment, the OKN stripes moved with a speed of $10^\circ/\text{sec}$. The patients were required to stare passively at the stripes; they were instructed prior to the study on how to look straight in front of them without following the stripes movement with their eyes or starting at a fixing dot. The patient's head was rolled at a constant frequency of 0.165Hz by the researcher with the help of a metronome. This frequency was chosen, as it was considered the closest frequency to 0.167Hz, a known frequency for emetic incidence [199], that was not able to induce any discomfort for the patients.

During the first three days, patients were only exposed to vertical OKN stripes moving right or left for 240 seconds (4 minutes) per session. The direction of the OKN stripes (e.g. stripes starting from the left or right first) was determined by two main variables - the Fukuda Stepping Test or the description of the patient's feeling of internal oscillation considering the direction of the phantom motion (swaying, rocking, etc.). For the

Fukuda Stepping Test, patients were asked to march in one spot for 45 seconds, with eyes closed and arms held out straight. An analysis was made of whether the patient rotated dominantly towards one side with a deviation $>20^\circ$ [53], as reported in the study of Dai and colleagues. It is known that normal population usually has a deviation with an average of 24.2° ($SD=16.1^\circ$) and that normally this test is considered abnormal only when the deviation is greater than 45° [200], thus we assumed as proposed by Dai and colleagues that a deviation greater than 20° may indicate an horizontal imbalance in the VOR [53]. The OKN stimulation was then programmed to start in the opposite direction to the one indicated by the results of the Fukuda Stepping Test. If an abnormal Fukuda Stepping Test was not observed in a patient, but they described a constant motion perception in one main direction, this variable was considered. In those cases, the OKN stimulation would start in the opposite direction to the patient's subjective perception.

Throughout Day 1 and Day 3 the same stimulation was gradually increased, meaning that it was repeated multiple times. For more details about the OKN sessions performed each day please refer to Table 26.

	Sham 1	Sham 2	Day 1	Day 2	Day 3	Day 4	Day 5
Duration	240 sec	240 sec	240 sec	240 sec	240 sec	Customize d*	Customize d*
Stripes Movement	None	None	Vertical – moving right and vertical – moving left	Vertical – moving right and vertical – moving left	Vertical – moving right and vertical – moving left	Customize d*	Customize d*
Head Roll	0.165Hz	0.165Hz	0.165Hz	0.165Hz	0.165Hz	Customize d*	Customize d*
	Break	Break	Treatment end/ Shorter treatment on Day 1	Break	Break	Break	Break
Duration	240 sec	240 sec		240 sec	240 sec	Customize d*	Customize d*
Stripes Movement	None	None		Vertical – moving right and vertical – moving left	Vertical – moving right and vertical – moving left	Customize d*	Customize d*
Head Roll	0.165Hz	0.165Hz		0.165Hz	0.165Hz	Customize d*	Customize d*
	Break	Break		Break	Break	Break	Break
Following sessions				Repeat as above	Repeat as above	Repeat as above	Repeat as above

Table 26: Scheme of the stimulation performed throughout the sham and the true OKN treatments. Patients who were not included in the sham group, started from Day 1 of the true OKN treatment.

Following the first three days, where patients were only exposed to vertical OKN stripes moving right or left for 240 seconds per stimulation (see Figure 19 for stripes direction-movements; a and b), the OKN treatment protocol was customized for each patient if required. As a result, on Day 4 and 5, patients were exposed to horizontal stripes moving upward or downward according to their subjective perception with a passive head roll at 0.165Hz (see Figure 19: when patients subjected feeling was matching with c and d). Horizontal stripes were not implemented in the same drum structure as for the horizontal stripes, but on a large flat screen, which was able to cover fully the patient's visual field. Patients were exposed to a reversed direction of the horizontal or vertical stripes, if they

reported worse symptoms following one direction. When the horizontal stripes were used, no head movements were performed and those sessions lasted for 1 minute with 30 minutes interval between sessions. In total 10 patients needed it to have horizontal stripes in addition of the standardised protocol with vertical stripes moving right and left.

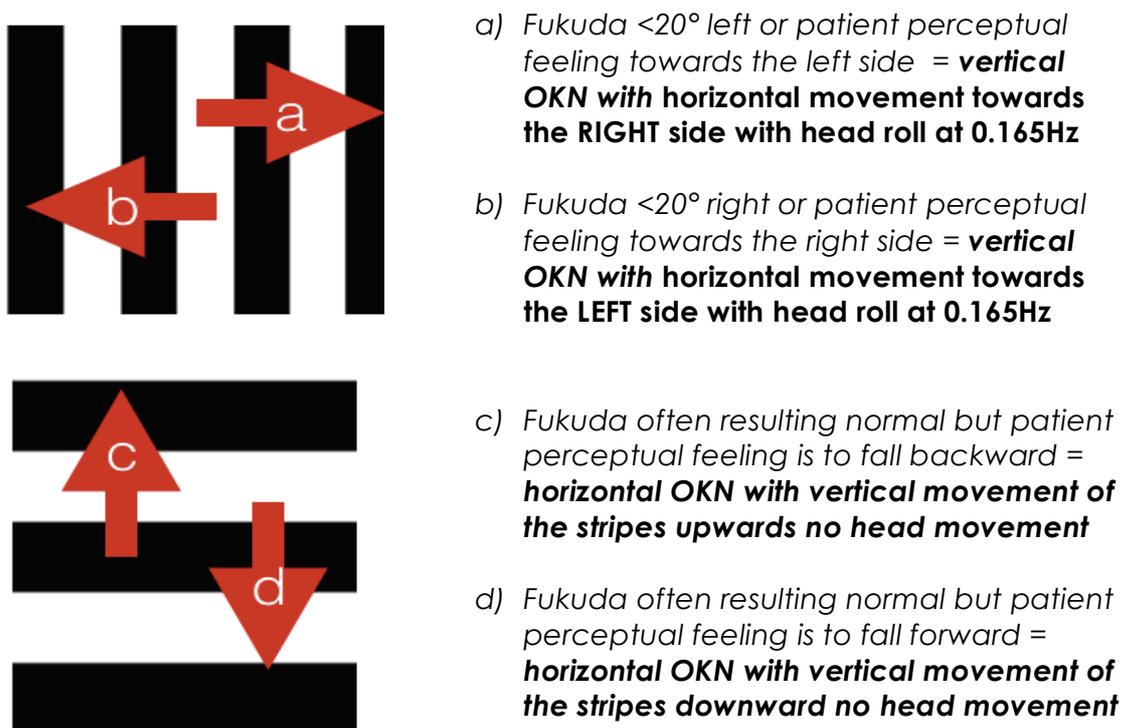


Figure 19: Schematic representation of the applied stripe movement according to the Fukuda Stepping Test results or patient's perception of movement Directions a) and b) were used during Day 1 to 3. While directions c) and d) were only implemented when required during the customized sessions on Day 4- 5.

Sham Treatment Setting

After the posturography recording, the patients were seated on a chair in an OKN drum. The full-field OKN visual stimulus was then projected on the walls directly in front and surrounding the patient exactly the same as during the true OKN treatment. During the sham treatment, the OKN stripes were not moved and patients were required to stare passively (as described earlier) at the stationary stripes. The patient's head was rolled at 0.165Hz frequency for 240 seconds, during which the researcher made use of a

metronome to maintain this frequency. After this, the patient's posturography was measured for a second time. The patient was then re-exposed to the stripes for another 240 seconds with the same head movements. This was repeated in two sessions with 30 minutes interval. For more details please refer to Table 26.

Statistical Analysis

The responses to the questionnaires proposed (for details see Annex 4) were analysed using Chi Square analysis, this was used when comparing different onsets. While when considering the group as a whole, one-sample binomial tests analysis was performed. In addition, nine main research questions (RQ) were created with regards to the treatment protocol. Patient n24 was excluded from posturography analysis, as the data collected resulted inaccurate, yet data from patient n24 regarding symptoms and other co-factor questions were taken into account. For each RQ, we report the statistical analysis that was performed and each RQ.

- **RQ1: Does the true OKN treatment over 5 days have an effect on the subjective outcome measures and on the posturography data? Do those match with VAS questionnaires representing subjective feeling?**

Non-parametric statistical tests, due to the small groups sizes was used. Postural outcome measures were interrelated and as a result, in most cases, when one changed, the others also showed a similar change. Together with this, a significant improvement in the patient's VAS score and statistical significant difference between Pre and Post VAS score was necessary to qualify as 'success'. Patients were also asked to express their subjective feeling about their symptom perception. A correlation analysis was also performed.

- **RQ2: Does the 2-day sham treatment involving a passive head roll at 0.165 Hz have a significant effect on patient posturography and on their subjective feeling of motion?**

Non-parametric test analysis was used (Wilcoxon Signed-Rank test).

- **RQ3: Do postural changes occur between Pre and Post OKN treatment? Are they different from healthy controls that performed a test-re-test of the postural data?**

Mann-Whitney U testing for a difference in test-retest values between the control and the patient group was used and followed a Bonferroni correction for 5 hypothesis tests.

- **RQ4: After how many days from the start of the treatment did outcome parameters from the posturography measurements indicate a difference?**

We tested for a difference between the *pre-treatment* measurement and the *first* measurement on each day separately using a linear mixed model, followed by a posthoc analysis with Dunnett correction. This allowed us to observe where potential changes were retained until the morning after the last treatment when each pre treatment measurement was taken, as well as to evaluate if the constant testing on the posturography was inducing an improvement.

In addition the Wilcoxon signed rank test (with Bonferroni correction) was used for the null hypothesis that within the day there is on average no change in postural outcome within the subjects, this analysis allowed us to observe when the changes occurred within the five days of treatment.

The success rate was defined as an improvement of postural stability when comparing the measurements recorded before and following the treatment. The

patient needed to report a postural improvement, which is defined by a significant improvement in at least one of the postural outcome measurements.

➤ **RQ5: Do SO or MT MdDS patients behave similarly in terms of postural control and do they respond similarly to the OKN treatment?**

For RQ5, fixed effects included days (continuous variable), onset type and their interaction. To test for a different slope between the onset types, we tested the significance on the interaction term onset type*days. To test for a systematic difference in outcome between the onset types, the significance of the main effect for onset type was tested (in a model where the interaction term was omitted).

➤ **RQ6: Is there a gender or age influence over the posturography?**

For RQ6, the effect of gender was modelled by including days (continuous variable), gender and their interaction as fixed effects. The effect of age was modelled by including age, days and their interaction as fixed effects. Similar to the strategy followed in RQ6, the significance of the interaction term indicated if the change in outcome over the days is dependent on the gender (respective age). The main effect of gender (respective age) across all days is tested for significance in a reduced model where the interaction term is omitted.

➤ **RQ7: Is the success rate equal between onsets groups (MT versus SO)?**

For RQ7 the effect of success rate was considered. Patients were asked about their symptoms at a 3 months follow-up point. In the follow-up, no posturography data was recorded, thus only reports of the subjective feelings of the patients

were collected. These two time points for success rate (i.e. end of treatment and 3 months follow-up) were compared using a McNemar's test.

- ***RQ8: Is there an association between duration of symptoms (Duration Onset) and success rate?***

The association between duration of symptoms and success rate was considered and Mann-Whitney U test was used.

- ***RQ9: Which hormonal phase are the MdDS patients while enrolled in the study? Were female MdDS patients in a particular hormonal status when onset occurred (e.g. menstruation, perimenopausal, ovulating), were they assuming contraceptive or medications?***

Chi square analysis and descriptive statistics were used to compare variables.

Results

Epidemiology

During the course of 2.5 years, 25 MdDS patients were recruited in the study. 48% of the patients were from Belgium, 24% from Netherlands, 8% from Denmark, and in total 16% of patients were from Germany, France, Italy and Israel (flights duration within 4.5 hrs). Within those 25, 14 patients were treated without the sham protocol and 11 with the sham protocol prior to the true OKN treatment. More details about the patient's epidemiology and onset type are reported in the table below (Table 27).

Epidemiology	MT and SO	
Mean Age	42.3 years	
SD	11.3 years	
Female	17 (68%)	
Male	8 (32%)	
Symptom Duration (mean)	3.9 years	
SD	4.5 years	
Minimum	3 months	
Maximum	19 years	
MdDS	MT	SO
Number of patients	13	12
Onset distinction		
Cruise	4 (30%)	
Flight	7 (53%)	
Car ride	1 (7.6%)	
After a trampoline + train ride	1 (7.6%)	

Table 27: Epidemiological data and details about MdDS onset type of the patients enrolled in the study are reported.

Treatment outcome

Research Question (RQ) 1: Does the true OKN treatment over 5 days have an effect on the subjective outcome measures and on the posturography data? Do those match with VAS questionnaires representing subjective feeling?

We compared pairwise the data obtained prior to the first session on Day 1 and after the last session on Day 5. The variables AUC_ML, AUC_AP, CEA, Path Length and Velocity significantly improved when the first and last measurements were compared ($p= 0.025, 0.006, 0.010, 0.026$ and 0.003 respectively, Wilcoxon Signed-Rank test). The CEA changes before and after the treatment (Day 1 pre vs. Day 5 post) are represented in Figure 20, as example to show the individual changes before and after treatment.

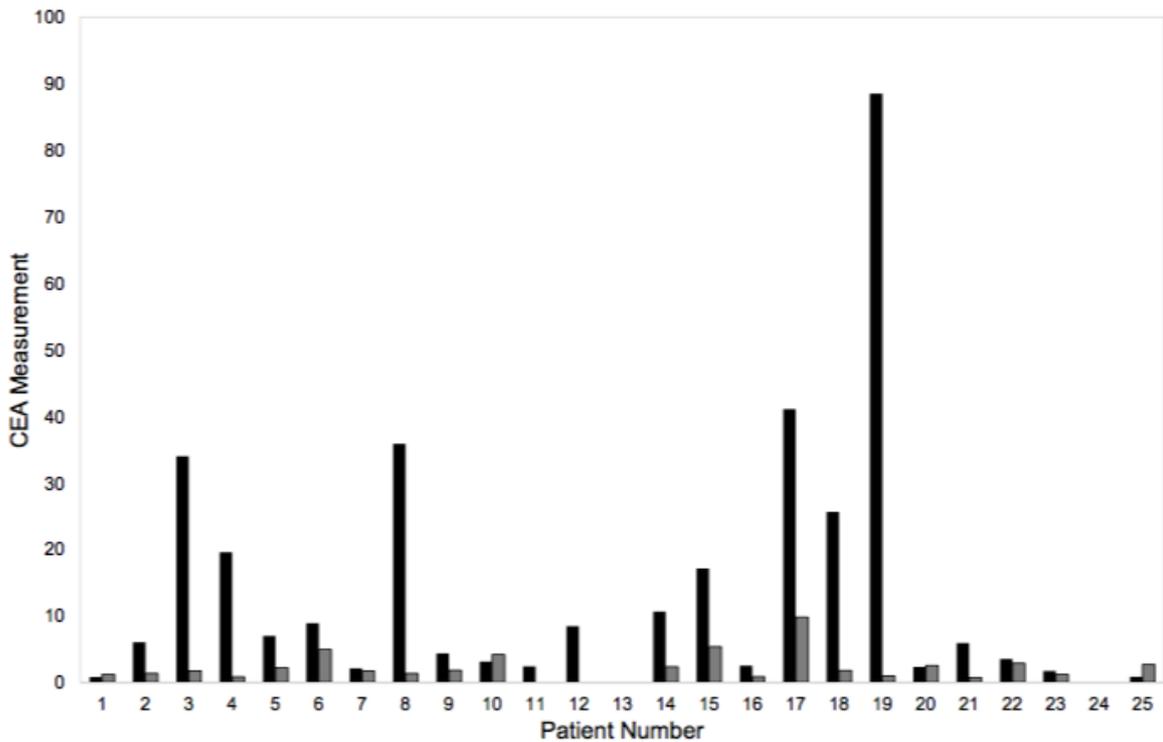


Figure 20: Breakout of CEA (95% confidence interval) changes for each individual patient Pre (Day 1 – black bars) and Post (Day 5 – grey bars) Treatment in the 25 MdDS patients.

A large difference is reported considering those two time points. The measurement collected on Day 5 shows the great reduction compared to the Pre measurement on Day 1 across the majority of patients.

A reduction in subjective feeling, through symptoms rating using the VAS score (0= no symptoms; 10= severe symptoms) is reported in Figure 21.

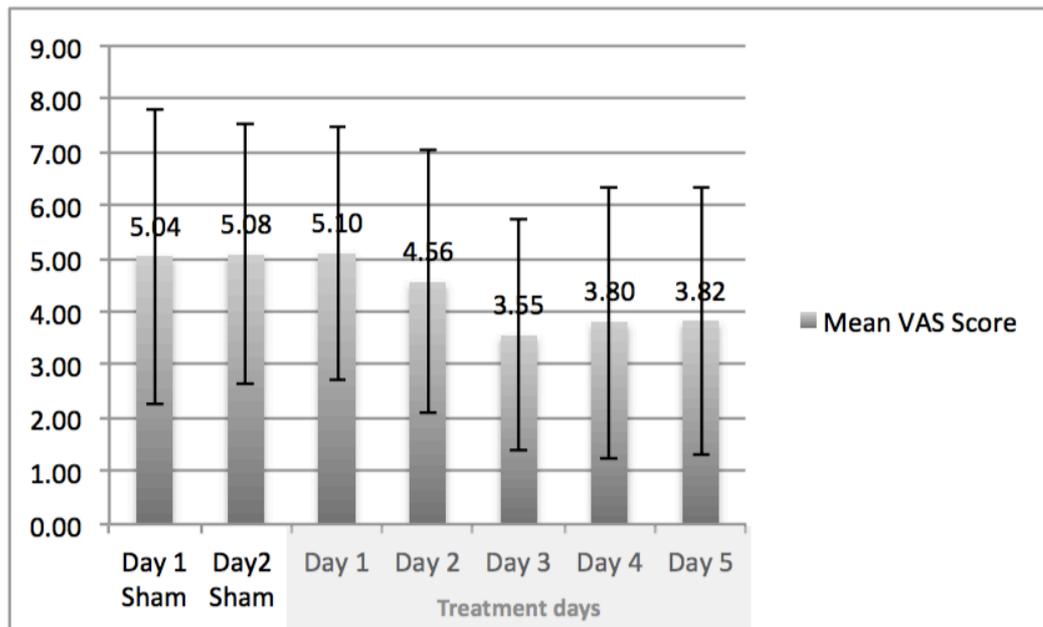


Figure 21: Visual Analogue Scale (VAS) Score Mean Representation from Day 1 of treatment to Day 5 of the treatment from the 25 MdDS patients (Sham days are excluded).

These posturography measurements are in line with the subjective scale VAS questionnaire, where a reduction in the VAS score indicates a reduction in symptom severity. The VAS score reported a statistically significant change ($p=0.004$) from Day 1 to Day 5, but Spearman correlations between posturography outcomes and VAS were very weak (data not shown).

MISC questionnaire results did not differ significantly between baseline and the follow-up measurement.

RQ2: Does the 2-day sham treatment involving a passive head roll at 0.165 Hz have a significant effect on patient posturography and on their subjective feeling of motion?

No significant differences were observed between the baseline measurement (prior to sham) and the last measurement following the second sham treatment (all pvalues > 0.05, Wilcoxon signed rank test). The subjective score VAS score had a mean of 5.03 (SD=2.08) on Day 1 of the sham and remained similar on Day 2 post sham with an average score of 5.08 (SD=2.44), as a result no significant differences in VAS were found (Figure 21). The reduction in scores may suggest that no changes occurred, however given the small number of participants to the sham protocol, these data should be interpreted carefully.

RQ3: Do postural changes occur between Pre and Post OKN treatment? Are they different from healthy controls that performed a test-re-test of the postural data?

The third research question was to test if the postural changes between baseline (before starting the treatment on Day 1 of the treatment week) and post treatment (last recording collected after the treatment on Day5) in the patient groups were different from the test-re-test (with two weeks interval) results in the healthy controls group. The mean, standard deviation and the pvalue obtained after performing Mann-Whitney U test between the repeated measurement for healthy controls and the measurements obtained each day post treatment (Δ =measurement day 5 post – measurement Day1 pre) indicates that patient postural changes are significantly larger compared to healthy subjects (see pvalues in Table 28) also after the Bonferroni correction for CEA and Velocity outcome measure. Sham days were here excluded from this analysis.

	Contro l Day 1 Mean	SD	Contro l Day 2 Mean	SD	Patien t Pre Day 1 Mean	SD	Patien t Post Day 5 Mean	SD	pvalue (unadjusted)	pvalu e (BF Corr.)
AUC_M L	0.09	0.1	0.16	0.31	0.64	1.06	0.1	0.12	0.083	0.415
AUC_AP	0.51	0.36	0.42	0.35	1.51	1.8	-1.09	1.77		
CEA	3.61	3.12	4.19	5.77	14.44	20.1 8	2.47	2.12	0.002	0.01
Path Length	132.07	42.7 4	128.42	44.1 9	82.76	65.6 8	58.34	35.5 6	0.028	0.14
Velocity	2.16	0.7	2.08	0.74	1.71	0.99	1.05	0.4	0.006	0.03

Table 28: Postural Outcome Measurements Pre-Post Treatment. This table represents the mean and standard deviation (SD) of the case and control group at the two points of measurement. Significant pvalues (Mann-Whitney U) testing for a difference in test-retest values between the two groups are reported and highlighted in bold. The last column shows the pvalues after Bonferroni correction for 5 hypothesis tests.

Abbreviations: AUC_AP= Area under curve Anterior-Posterior, AUC_ML= Area under the curve Medial-Lateral, CEA = Confidence Ellipse Area, BF Corr. = Bonferroni Correction.

An additional example of the differences between control and patient's posturography (CEA 95% confidence ellipse) is reported in Figure 22.

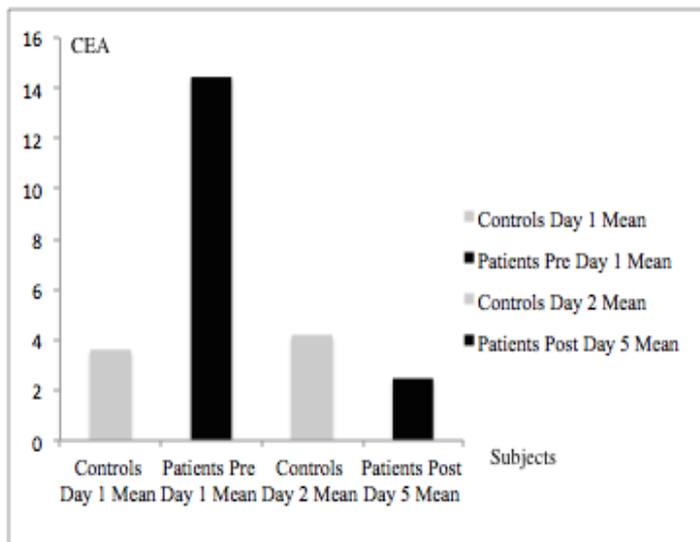


Figure 22: The CEA 95% ellipse mean value of control subjects on Day 1 and 2, compared with MdDS patients are here represented.

Abbreviation: CEA = Confidence Ellipse Area.

Figure 22 clearly showed a great postural change (CEA outcome variables – Day 1 versus Day 5 mean) in the patient group.

RQ4: After how many days from the start of the treatment did outcome parameters from the posturography measurements indicate a difference?

In the patients, we tested for a difference between the *pre-treatment* measurements on each day. Patient postural tests performed everyday, prior to the treatment, was compared with the first postural measurement of the following day. The relevant p-values are reported in Table 29 after Bonferroni correction.

Postural Parameters	pvalue	pvalue Bonferroni - corrected (bold=significant)
AUCap	4E-05	2E-04
AUCml	3E-04	1E-03
CEA	1E-05	6E-05
PathLength	3E-01	2E+00
Velocity	5E-06	2E-05

Table 29: pvalues from linear mixed model, testing the null hypothesis that the mean outcome does not differ between days.

Abbreviations: AUC_AP= Area under curve Anterior-Posterior, AUC_ML= Area under the curve Medial-Lateral, CEA = Confidence Ellipse Area.

Postural changes were significant considering the outcomes postural variables: AUC_AP/ AUC_ML; CEA and Velocity. Thus, a posthoc test considering Dunnett Correction was performed, pvalues are reported in Table below (Table 30).

	pvalue	pvalue	pvalue	pvalue (bold=significant)
	$\Delta= 2-1$	$\Delta= 3-1$	$\Delta= 4-1$	$\Delta= 5-1$
AUC_AP	0.3705	0.0289 *	<0.001	<0.001
AUC_ML	0.464	0.0184 *	<0.001	<0.001
CEA	0.3449	0.0064 **	<0.001	<0.001
PathLength				
Velocity	0.02247 *	0.00101 **	< 0.001	< 0.001

Table 30: pvalues for the pairwise comparison of the measurements on Day2, 3, 4 and 5, (obtained prior to the intervention) to the first postural measurement prior to the onset of treatment (Day1) (posthoc analysis with with Dunnett correction).

Abbreviations: AUC_AP= Area under curve Anterior-Posterior, AUC_ML= Area under the curve Medial-Lateral, CEA = Confidence Ellipse Area.

Postural changes are detectable from the third day of treatment and the patient postural improvement remained significant throughout day 4 and 5 for AUC_ML, CEA, Path Length and Velocity.

From these analyses most changes occurred relatively quickly after the second day of OKN exposure and they were maintained until the morning of the following day, when the first measurement (pre) was recorded. This means that after two days of treatment patients posturography significantly changed.

In addition to this, we have calculated the pre and post treatment differences for the postural variables considering Day 1 of the treatment and Day 5 the last day of the treatment. Results are reported in Table 31.

Days	AUC_A P pvalue	AU C_A P BF	AUC_ML pvalue	AU C_B F	CEA p Value	CEA BF	PL pvalu e	PL BF	Vel pvalu e	Vel BF
1			0.052	0.26	0.01	0.046	0.01	0.041	0.002	0.01
2										
3	0.02	0.13	0.03	0.15	0.01	0.037	0.08	0.4	0.07	0.34
4										
5										

Table 31: pvalues for the difference between pre-treatment and post-treatment values for the 5 outcome parameters variables throughout the 5 days of measurements (Wilcoxon signed rank test with Bonferroni correction for 5 measurements). The statistical significant values with $p < 0.05$ after the Bonferroni Correction are bolded (CEA, Path Length, Velocity on Day 1 and on Day 3 CEA). Sham days are excluded.

Abbreviations: PL= Path Length, Vel= Velocity, BF= Bonferroni Correction, AUC_AP= Area under curve Anterior-Posterior, AUC_ML= Area under the curve Medial-Lateral, CEA = Confidence Ellipse Area.

Changes were observed from Day 1 considering CEA, Path Length and Velocity variable. Suggesting that the greatest change in postural control among patients was almost immediate (From Day 1).

RQ5: Do SO or MT MdDS patients behave similarly in terms of postural control and do they respond similarly to the OKN treatment?

This research question aimed to evaluate if SO or MT patients behave similarly in terms of postural control. The relation between outcome and time is shown in Figure 23. The figure shows that upon log transforming the outcome variable the relation is approximately linear, and linear regression of outcome vs. time is valid.

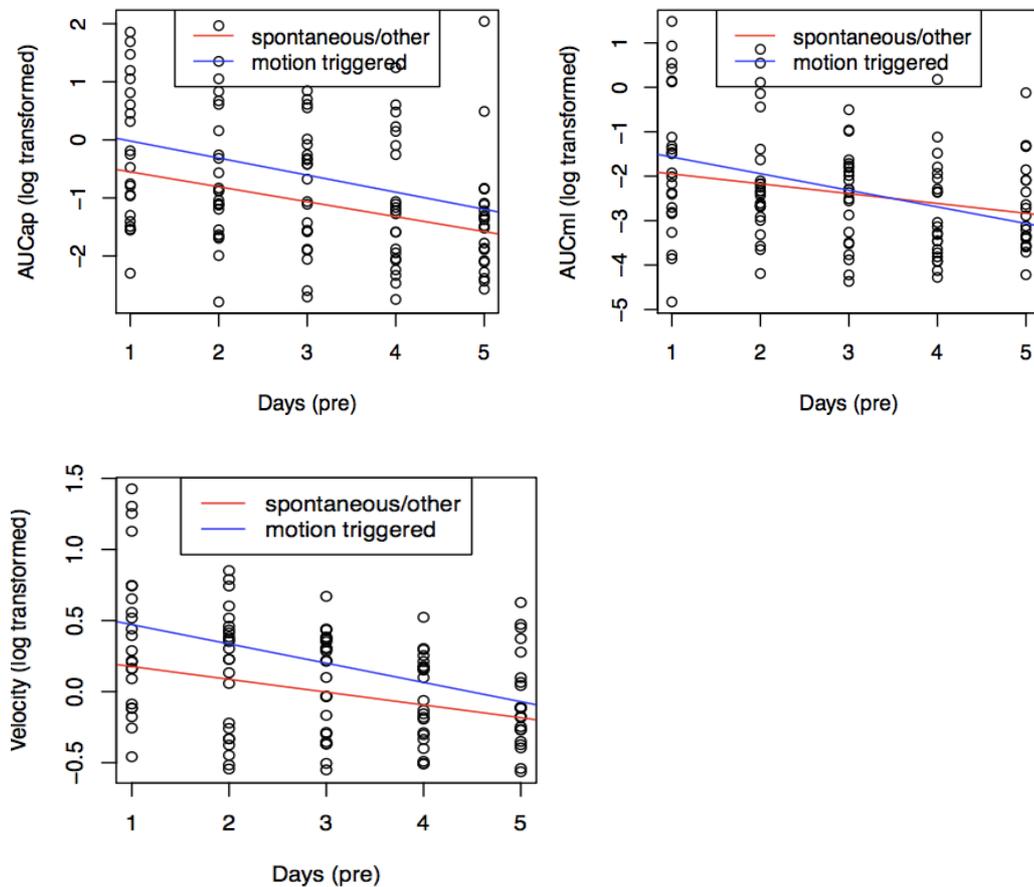


Figure 23: AUC_AP/ML and velocity for SO and MT over 5 days of Treatment is reported. Here plotted the (log transformed) outcome versus time, with two separate regression lines for the two onset types (red=SO, blue=MT) for AUC AP/ML and Velocity. The two onset groups responded similarly.

Abbreviations: AUC_AP= Area under curve Anterior-Posterior, AUC_ML= Area under the curve Medial-Lateral.

Modelling the change in postural outcomes versus time in both groups, showed a significant change over time in all outcomes measured. However, the rate of change

did not differ between both two groups. Moreover, there was no significant difference in outcome measures between the two groups across all days.

RQ6: Is there a gender or age influence over the posturography?

After modelling the posturography outcomes versus time, accounting for age and gender, significant effects of age and gender across all days were not observed. In addition, the rate of change in posturography outcomes measures was not different between the two genders, and was not dependent on age. A representation of the equal response of female and male subjects is here reported.

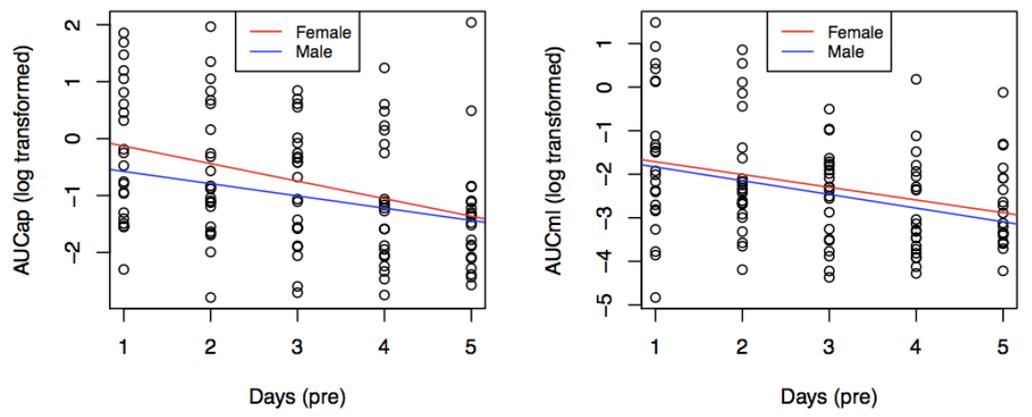


Figure 24: AUC_{AP} and AUC_{ML} for female and male MdDS patients over 5 days of treatment, the graphs report an equal postural adjustment throughout the days. No gender differences were reported.

Abbreviations: AUC_{AP}= Area under the Curve Anterior – Posterior; AUC_{ML}= Area under the Curve Medio-Lateral.

As report in Figure 24, female and male patients behaved similarly in response to the optokinetic stimulation.

Treatment success rate and follow up

Success rate

RQ7: Is the success rate equal between onsets groups (MT versus SO)?

With regards to the *success rate* (=remission of symptoms), two success rates were evaluated. The first success rate was noted on the last day of treatment and a second after a 3-month follow up, patients were enquired about their symptoms. Overall, 48% of the success rate was observed considering the last day of treatment, with 70% of the patients improving symptoms being of the MT subtype. The same success rate (48%) was maintained after the 3-month follow up. There is a significant association between both the last day of the treatment and the follow up ($p=0.009$, Chi-square test), but among the patients reporting a different result between the two success measurements, no trend was observed. The number of patients shifting from success to failure was not significantly different from the number of people shifting from failure to success ($p>0.05$, McNemar's test). Specifically, three patients reported remission of symptoms in the 3 month follow up and in one patient where the phantom motion perception resolved but reported severe migraine and brain fog.

RQ8: Is there an association between duration of symptoms (Duration Onset) and success rate?

We have used a Mann-Whitney U test to test if the duration of the symptoms was significantly different between both groups. No significant effect was found ($p=0.13$, Mann-Whitney U test).

Follow-up symptoms

Within the follow up questionnaire (3-months follow up), patients were enquired about their symptoms after the treatment (questions presented in the methodology section). A statistically significant difference was reported between SO and MT subtypes with regards to the follow up symptoms (pvalue=0.010), with only 70% of SO patients reporting the same level of symptoms as prior to the treatment while 7% of MT reported the same symptoms. This matches with a higher success rate among the MT group. Within the MT subtype, 46% of the patients who benefitted from the treatment, meaning that their perception of motion greatly reduced or disappeared, still reported secondary symptoms after the OKN treatment. The symptoms reported during the follow up included: migraine, heightened visual motion sensitivity, brain fog, and headaches.

Hormonal aspect of MdDS in a small female group

RQ9: Which hormonal phase are the MdDS patients while enrolled in the study? Were female MdDS patients in a particular hormonal status when onset occurred (e.g. menstruation, perimenopausal, ovulating), were they assuming contraceptive or medications?

Given the female predominance in MdDS, a series of questions (consult Annex 4 for details) related to the hormonal aspects for female MdDS patients were asked. From our cohort the majority of patients involved in the study were menopausal ($p=0.008$) and a great number was in perimenopausal phase. In addition to this, 70% of the MT respondents reported to have been travelling during menses, during the believed event that triggered the onset for MdDS symptoms. A small percentage of those (35%) were also assuming other medications (e.g. antibiotics, psychotherapeutic drugs used for attention deficit disorder and depression). No differences between the two onset groups were noted, with no statistical significant difference was reported between the two groups.

Patients profiles

Reported below the answers to the *intake questionnaire* asked to patients prior to the treatment.

Symptom Fluctuations	Total	MT	SO	(p<0.01) Chi-Square
Yes	100% (n=25)	100% (n=13)	100% (n=12)	
No	0%	0%	0%	
Motion Sickness Susceptibility	Total	MT	SO	
Yes	60% (n=15)	46% (n=6)	75% (n=9)	
No	40% (n=10)	53% (n=7)	25% (n=3)	
Reporting Migraine	Total	MT	SO	
Yes	60% (n=15)	61% (n=8)	58.3% (n=7)	
No	40% (n=10)	38% (n=5)	41.6% (n=5)	
Reporting Tinnitus	Total	MT	SO	
Yes	64% (n=16)	61.5 % (n=8)	66.6% (n=8)	
No	36% (n=9)	38.5% (n=5)	33.3% (n=4)	
Being Diagnosed with Depression	Total	MT	SO	
Yes	20% (n=5)	15.3% (n=2)	25% (n=3)	
No	80% (n=20)	84.6% (n=11)	75% (n=9)	
Used Antidepressant in the past	Total	MT	SO	
Yes	44% (n=11)	38.5% (n=5)	50 % (n=6)	
No	56% (n=14)	61.5% (n=8)	50 % (n=6)	
Using Antidepressant drugs now (when enrolled for the study)	Total	MT	SO	
Yes	24% (n=6)	23% (n=3)	25% (n=3)	
No	76% (n=19)	76.9% (n=10)	75% (n=9)	
Being more anxious since MdDS onset	Total	MT	SO	(p<0.01) Asymp. Sig.
Yes	80% (n=20)	84% (n=11)	75% (n=9)	
No	20% (n=5)	15% (n=2)	25% (n=3)	
Lifestyle affected after MdDS onset	Total	MT	SO	(p<0.01) Chi-Square
Yes	100% (n=25)	100% (n=13)	100% (n=12)	
No	0%	0%	0%	

Table 32: Percentage (%) and the number of responses (n) collected from the intake questions enquired to patients are here reported.

From the data presented in Table 32 all 25 patients reported that they generally experienced symptom fluctuations throughout the day (p<0.01). Motion sickness

susceptibility was reported to impact a greater number of SO (75%) compared to MT (46%). No statistical significance was observed. Subjects were enquired about migraine experiences and no statistical significance was recorded. Patients were asked whether they experienced tinnitus and SO and MT patients reported such symptoms equally. Participants to the study were also asked if they had been diagnosed with depression before their MdDS onset. The majority of MT (84.6%) and SO (75%) patients answered negatively to this question. No significant differences were observed between the MT and SO patients. Patients were asked if they were currently using antidepressant drugs and if they used them before getting MdDS. 50% of SO and 61% of MT had not used antidepressant drugs in the past (prior to MdDS), although 23% MT and 25% SO were using it when recruited for the study. Patients were asked if they felt more anxious since their MdDS onset, the great majority (84% MT - 75% of SO) reported to be more anxious since their onset ($p = 0.003$). All 25 patients reported to have had to modify their lifestyle after onset.

Patients were also enquired about what aggravate their symptoms and other treatment that they have been trying before being enrolled in the OKN treatment.

Triggers

Patients were enquired about triggers that aggravate their symptoms (e.g. watching the screen of a laptop, being stressed during busy days, sleep deprivation, watching crowds) for details refer to Annex 4. Patients from both onset subtypes answered to be greatly disturbed by visual inputs, specifically SO - 50% and MT -84%. When considering all patients as one group, the triggers that were observed to be significant in triggering symptoms were *scrolling on a phone* (p value = 0.014), *stress* (p value = 0.072) and *strong emotions* (p value = 0.014).

Other treatments experienced by the patients before being enrolled in this study

Patients were asked about medications that they had trialled to manage their MdDS symptoms. The most common medications trialled by the patients from both onset subtypes were benzodiazepines, antidepressant drugs (non-specific noradrenergic, serotonergic antidepressants, tricyclic antidepressants), and beta-blockers (commonly used for migraine). The most used drug, which was reported to improve patient's symptoms, were tricyclic antidepressants. MdDS sufferers were also asked if they had trialled any vestibular rehabilitation (VR) programs prior to the intervention, only a small number of patients tried VR (22.2%MT / 40% SO). With the exception of one SO patient, all the other reported no symptoms improvement after VR therapy.

Discussion

Our study is the first that has successfully reproduced the OKN treatment that was developed by Dai and colleagues. We have shown that patients respond well to a standardized OKN treatment, both subjectively and objectively, and that a placebo effect is not observed in patients that received the sham treatment.

Epidemiology

From the results collected, our patient group reflected the epidemiological description of previous studies. Similarly to what has been described before [21, 47, 50, 52, 53] a female predominance was also present in our study sample. The mean age of our patient sample was also similar to what has been previously observed in MdDS patients (mean 42.3 years), i.e. in the 5th life decade [47, 52]. A similar number of MT and SO patients were included. Patients' data was collected over two years and half of research and the patients included were travelling from multiple countries, highlighting the currently difficulty in recruiting this category of patients.

In this study, the first cause for triggering symptoms in the MT group was travelling by plane, followed by cruise, contrary to what previously observed. In most cases in the literature, sea travel has been described as the primary trigger for onset [21]. However, our data suggests that any passive motion trigger may be able to induce MdDS.

OKN Treatment – Main findings

During treatment, patients reported an increase in postural stability and a decrease in symptom severity, as indicated by the VAS score results. These findings corroborate with earlier results by Dai and colleagues [53], i.e. that the patient's symptoms reduce significantly during the course of the treatment. These subjective observations matched the posturography measurements. Considering postural data, in order to observe where

potential changes were retained until the morning after each treatment day, we compared the pre-treatment measures. The most relevant changes were observed in AUC_AP, AUC_ML, CEA and Velocity, indicating that the patient postural changes were retained until the day after. With a reduction in sway (movement on the platform) and sway velocity, it is possible to assume that patients became more stable due to the re-adaptation of the VOR, as also discussed in Dai's study [53]. In addition to this, a poshoc analysis was carried on, where we compared each day with the first initial postural measurement recorded. Significant postural changes occurred on the third day. A second analysis comparing pre and post OKN variables demonstrated that a significant postural change was detectable after the first exposure on Day 1 with respect to velocity, indicating that the sway velocity of the patients changed rapidly. This is particularly relevant, as it suggests that a shorter treatment protocol may be possible.

Control versus MdDS Patients

In order to exclude that the changes observed could have been attributed to a learning effect [201], the data was compared with a group of 20 healthy control subjects. From the results of this group, it is clear that no changes were reported in postural outcome parameters as presented in the example Figure 17. There is a clear discrepancy between the posturography results in the patients as compared to the healthy control group. The latter suggests that no learning effect was present.

Consequently, we hypothesize that the changes detected in the MdDS patients were genuinely attributable to the real OKN treatment involving the combination of optokinetic stimuli and head movements at the fixed frequency of 0.165Hz. A limitation to our study was that after Day 3, when required, we exposed patients to subjective and customized stimuli, potentially affecting the integrity of a fully standardized

protocol. However, the number of patients who underwent additional horizontal stripes and customised sessions on Day 4 and 5 was limited (10 patients in total).

A limitation to this study was the relatively small sample size; further testing with a larger sample of patients is therefore encouraged for future studies. Nevertheless, we hope that these results provide a basis for a more structured protocol that will make this treatment easier to be implemented in multiple centres.

Mechanisms and theories behind the OKN treatment

Currently it remains unclear what are the exact mechanism inducing these beneficial effects on MdDS patients, however, we followed the previous theory developed from Dai and colleagues. Thus we similarly can hypothesized that the VOR and the velocity storage were modulated by the OKN exposure and thus inducing a postural change.

The VOR respond to optokinetic stimuli with the activation of the optokinetic reflex (OKR). The VOR and the OKR work together synergistically to maintain a stable retinal image, regardless of the type of motion one is subjected to [187]. The VOR, as previously described, is a very fast acting reflex that serves to compensate for head movements in the 1-7 Hz range [202], despite being less accurate at lower frequencies.

On the contrary, the OKR has the opposite performance characteristics [202]. The OKR has a longer latency due to the required evaluation of visual information to determine a response. Another relationship between VOR and OKR is related to VOR adaptation: it is known that the VOR response can adapt and accommodate sensory arrangements, as shown in a study by Draper [203], where VOR adaptation to virtual environments was tested. Draper's study showed that the VOR response could modulate gain values to adjust the sensory re-arrangements occurring during the stimulation, more specifically, an adaptation to visual magnification corresponded to VOR adaptation and the visual adaptation was related with simulator sickness. Equally,

it is also possible to consider that the primary motion trigger of MdDS patients involved a head motion while being subjected to different passive motion frequencies and an aberrant organization of visual and somatosensory integration may have resulted in the disruption of the VOR and velocity storage. Thus, we propose that the OKN stimulation and head roll is able to induce the VOR adaptation process by altering the performance of the OKR through visual anomalies.

The side-to-side (roll) head movements during vertical OKN stripes at 0.165Hz frequency has proven to be effective for improving MdDS symptoms (e.g. sensation of motion-swaying- rocking-bobbing). This frequency was adapted as previously described, as it is considered to be closest to one of the most emetic frequencies. As previously hypothesised in another theory, the gravito-inertial acceleration (GIA) vector in MdDS seems to be restored with the use of a roll the head, while activating the velocity storage integrator with a low frequency, constant velocity, full-field, OKN stimulus. Thus, a pseudo cross-coupling mechanism seems to be able to restore the velocity storage mechanism. However, contrary to what Dai's group proposed [73], in this study, a fixed frequency (for the head rolls) has been able to improve motion symptoms by inducing avection sensation, and restoring the believed conflict between the tilted orientation vector and the spatial vertical that has resulted in MdDS.

The VOR and GIA theories however are for now only hypothesis. Future testing is required to further assess how patients may change their subjective feeling and postural response after the OKN treatment, for example by measuring the VOR gain or the optokinetic after nystagmus (OKAN) changes.

Success rate and onset differences

In line with Dai's findings [52], no differences among genders groups were noted. Both genders responded equally to the OKN stimulation. However a difference in success rate was recorded when considering onset type, despite the onset groups responded similarly to the OKN stimuli, this is the reflection that some SO patients still benefitted from the OKN treatment.

Our success rate, when considering both onset groups, was lower to the one obtained in 2014 Dai's study [53]. We had a 48% of the success rate (both MT and SO) on the last day of treatment. Although considering the study of Dai from 2014, it was not specified if SO patients were included, so it is presumed they only included MT subjects. Thus, when compare to the MT subgroup in our cohort, our success rate is similar to their findings (70% improvement in both studies). As such, we can assume that there are no major differences between a customised head frequencies [73] and our standard head frequency of 0.165Hz and OKN exposure.

Overall, when considering both onset groups, MT patients respond better to this type of treatment, with a higher success rate as compared to SO patients as reported in Dai's follow up study [52], suggesting that this treatment may be more suitable for MT patients. However, it should be noted that both groups indicated an improvement in postural outcome measures over the course of the treatment. As a result, this treatment should not be excluded from SO patients, but these patients should be aware of the lower positive response rate. This difference in success rate between the groups may suggest a potential difference in the underlying pathophysiology of the two onset types [48]. It has been previously recognised that migraine is affecting more SO than MT patients and that most SO patients report to have been migraine sufferers before onset compared to MT [51], as a result it could be theorised that the pathological pathways

for the SO group may be interrelate with migraine, and that this may be a substantial difference with the MT group.

The most recent studies on resting-state functional magnetic resonance imaging (rsfMRI) studies have shown an increased functional connectivity in MdDS patients between the left EC/amygdala and visual / vestibular processing areas, as a result of a decreased connectivity in multiple prefrontal areas [49]. At this stage, it is unclear if the VOR maladaptation, which is a brainstem manifestation of MdDS, may also be implicated in a cortical manifestation with aberrant functional connectivity. It is possible that MT and SO shares abnormal brain functioning and physiology, although entering by different pathways or mechanisms [51], which may explain why they different response to OKN intervention.

Sham protocol

Our study has also demonstrated that the sham protocol performed on MdDS patients from both onset subtypes does not induce a placebo effect. If a placebo effect were to occur, we would expect a postural improvement after two days of sham sessions, this was not the case as no significant posturography changes were recorded after the exposure to the sham protocol. In addition, the subjective sensations as reported by the VAS did not change, nor improve during the sham days. We hypothesized that, if patients were susceptible to a placebo effect, the interaction with the researchers and being enrolled for the study could have influenced his/her posturography outcomes measure and subjective perception of internal oscillation, however it seems that this hypothesis can be rejected. Nevertheless a limitation to our study regarding the sham analysis is that the non-significance of the statistical test reported when assessing the VAS (sham Day 1 versus Day 2) does not formally prove there is no sham effect. Small

effects of the sham treatment, for which the statistical test did not offer sufficient power, cannot be excluded. However, the further analysis where patients were compared versus the control group, we obtained a significant difference in delta (pre-post) between the two groups. This kind of analysis accounts for the possibility of a sham/placebo effect in the non-treated group. So our conclusions remain valid.

We also acknowledge that the perfect sham protocol should have lasted the same number of days as the treatment. Unfortunately, given that most patients were travelling from abroad we were logistically incapacitated to perform a longer sham protocol.

In conclusion, from our results, the head movements alone do not seem to induce any significant postural changes. This supports the previous hypothesis that the combination of the OKN stimulus and head movements, in this case a head roll at 0.165Hz frequency, is believed to be involved with the re-adaptation of the VOR [19].

Follow up

A follow-up was performed three months after cessation of the treatment, during which patients were able to report any fluctuations or changes in their treatment response. A greater number of SO patients reported the same symptom type (constant sensation of motion) and the same symptom levels upon follow up; similarly to what previously observed, overall the success rate in the SO was much smaller [52]. This is in line with the success rate of our study, with 48% of patients reporting improvement of symptoms (70% of which were MT), a percentage that remained stable after follow up. For the MT patients, the level of symptoms reported during the follow up was much lower, indicating that the OKN treatment was able to reduce their MdDS symptoms. However, despite a general improvement (in postural stability and self-perception), MdDS patients from both onset groups still reported other associated symptoms such as

migraine, which prevented us to define them as fully 'symptom-free'. This has been previously observed from the follow up study of Dai and colleagues [52]. These associated symptoms seem to remain after the OKN treatment, even when the intervention is believed to be successful as patients' complains are greatly reduced. These secondary symptoms might indicate that a more complex neural basis may be implicated in the pathophysiology of MdDS [54]. However, from the follow up report of Dai and colleagues, patients were examined also at after two week from the end of the treatment and they observed that patients who were not subjected to long distance journeys after the treatment were less likely to develop additional symptoms [52]. In our study, a two-week follow up was not performed. Moreover, a potential limitation of this study was that most of the participants were commuting from abroad and subjected to flight or car trips following the last day of treatment.

This study was performed on a small sample size and a short-term follow up, therefore, further testing should include a larger sample of patients and continuous follow up to up to 2 years after the treatment is encouraged.

General patient overview

Equally, both onset subtypes reported to be greatly impacted by MdDS in terms of lifestyle, in line with previous research [21], in which MdDS was reported to have high levels of intrusiveness of an individual's life [56, 80]. In order to gain more information about the patients enrolled in our study, the subjects were enquired about depression. From our results, the number of patients previously diagnosed with depression was not significant. We also asked them about symptomatology and in line with previous findings, symptoms fluctuations throughout the day [21] was reported by most patients. Additionally, they reported to be more anxious after MdDS onset, as expected based upon previous studies [55]. The majority of patients from both onset subtypes reported

to be triggered by visual stimuli, suggesting that they may have developed a heightened visual sensitivity (potential overlap with Visually Induced Dizziness) [59, 98]. Further research and additional therapeutic approach should closely evaluate the overlap of high visual sensitivity symptoms in MdDS patients. For example, some MdDS patients who reported these symptoms could benefit from an additional desensitization technique based on repetitive optokinetic stimuli to cope with their visual sensitivity (later proposed in Chapter 6) [32].

Lastly, we asked patients about their previous treatment history, prior to this OKN treatment. From the responses collected, MdDS patients enrolled in our study received other treatments such as vestibular rehabilitation (VR) and antidepressant medications. However, the majority reported no improvement. Overall, the number of patients who tried these types of intervention was limited. With regards to VR, more research is needed to establish if and which type of vestibular rehabilitation may help MdDS patients. Considering medications wise, antidepressant drugs, benzodiazepine and beta-blockers were reported from the patients. Tricyclic antidepressants were indicated to be the most successful in helping patients cope with their symptoms, as previously reported from other studies [80, 204]. However, the patients main complaints were not entirely solved by these drugs [47]. Potentially, these drugs have the ability to ease MdDS symptoms as they are known to help in the management of migraine [80]. The fact that the patients in this study have received multiple unsuccessful treatments strengthens the need to explore novel treatment options, such as the OKN treatment described in this study.

Female MdDS patients - Hormonal status

Considering the female preponderance of patients affected by MdDS, we examined by means of questionnaires at the hormonal profiles and status of the recruited patients. Most of the female patients engaged in our study were in the menopause and perimenopause in line with previous research [47, 80] indicating that this phase may be crucial for the developing of MdDS. The hormonal influences in vestibular disorders for women has been previously suggested, in particularly the predominance of vestibular related disorders in perimenopausal and menopausal phase (i.e. vestibular migraine) [117] as presented in Chapter 4. It has been well established that steroid hormones are able to modulate the physiological and neuroplastic properties of the central nervous system, and affects the existence of specific intracellular steroid receptors in the cerebral cortex, the limbic system, cerebellum and preoptic part of hypothalamus and brainstem [117]. Another interesting aspect related to hormonal fluctuation was to consider if menstruation was occurring during with the travelling event that triggered the onset for the MT group. The majority of MT patients in this investigation reported that during their onset they have been travelling while experiencing their monthly menstruation.

Endogenous estrogens are known to influence the hippocampal white matter measurements [153]. One hypothesis to explain this could be that low levels of estrogen, as during the luteal phase, may have altered the brains adaptability to new environments. Additionally, if considering that the velocity storage is an integrative network of GABA_b sensitive neurons receptors, it is important to consider and further evaluate whether low GABA plasma levels may be implicated in MdDS pathophysiology. From previous studies it is known that low GABA plasma is associated with depression [149], and that low GABA plasma levels are a characteristic in Pre Menstrual Syndrome (PMS) sufferers in the luteal phase [148]. Taking this into account

and considering that most MT patients may have already suffered from irregular menses during perimenopause, we could hypothesise that MdDS patients, who developed their onset while menstruating, may also report low plasma GABA levels. As reported in Chapter 4 this explains why drugs acting on the release of GABA such as clonazepam may be effective for MdDS patients [47]. In addition to experiencing menstruation during the onset event, a small number of patients were also assuming other medications. These could have also been interfering with GABA receptors. A further detailed investigation is here encouraged.

Conclusion

This study is the first to validate the OKN treatment in MdDS patients and to implement the same treatment protocol.

Our study has shown that no placebo effect is induced in patients when exposed to the OKN treatment. Secondly, our study proved that a personalisation of the head roll according to patient's frequency of oscillation or perception is not needed to improve both objective (posturography) and subjective (VAS) symptoms. Thus, the use of a standard frequency can simplify the protocol for treatment purposes and still provide the same beneficial effects on MdDS subjects. We have also shown that a gradual and standardized OKN treatment is able to reduce MdDS symptom levels, especially in the MdDS patients with an MT onset. The latter suggests a potential difference in pathophysiology in MT and SO MdDS; however, future studies should directly assess this. Furthermore, we have shown that postural improvements occur almost immediately, within the first days of exposure to the OKN treatment. As such, a short and effective standardized protocol (head roll maintained at 0.165Hz) may be beneficial and feasible for MdDS patients. Future studies should consider a larger sample size and should investigate if these improvements are long term. With regards to the pathophysiology and onset triggers mechanism of MdDS, specific hormonal status (e.g. during menses or perimenopause) should be further explored.

5.2 Guidelines for future OKN treatment on MdDS patients

MdDS patients can benefit from the repetitive exposure to optokinetic stimuli in the form of stripes moving side to side and up and down, in combination with head roll at fixed frequency of 0.165Hz.

The treatment can last a total of 3 days. Patients posturography should be evaluated before and after each exposure to understand how OKN is impacting patient 's balance.

Patients should be asked to perform the Fukuda Step Testing before each exposure to evaluate if changes are occurring. When unsure if the patient is not feeling a direct gravitation pull to one clear direction, ask to report their subjective feeling. As illustrated in Figure 19 decide accordingly in which direction to start the moving stripes. We recommend patients to be exposed to a maximum of 4 sessions on day 1, to avoid overstimulation. Between sessions we advise to give a breaking time of minimum 30 minutes, in order for the patient to adjust.

Patients should be followed in the first few months after the treatment and if heightened visual motion sensitivity or migraine symptoms are reported, these should be further considered and when possible followed by a therapeutic intervention (e.g. VR for visual stimuli, medications for migraine).

Considering the data proposed in Chapter 4, female patients in their reproductive years, should not be treated during the week of menstruation or during the suspension week of hormonal contraceptives, as symptoms may be heightened during these specific periods.

Patients who reported to be menstruating when onset occurred should be encouraged to evaluate their hormonal levels (see Chapter 4.3 for details), in order to further explore a potential relation between hormonal fluctuations and onset triggers.

6. CHAPTER 6 VISUAL SENSITIVITY:

- Visually Induced Dizziness in MdDS

This chapter is part of a larger project, which is currently ongoing:

Visually Induced Dizziness and Optokinetic Treatment

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As reported in Chapter 5, most of the MdDS patients who participated to the OKN treatment, reported secondary symptoms such as high visual sensitivity. In the current chapter the main triggers of VID symptoms are going to be presented. Additionally, an overview of one of the few treatment currently available and used in vestibular patients reporting VID symptoms will be presented. This treatment is based on optokinetic stimulation, customized exercises and behavioural changes. These preliminary data on other vestibular patients could support a future implementation of a similar protocol for easing heightened visual motion sensitivity in MdDS patients.

6.1 Visually Induced Dizziness

Introduction

The human vestibular system integrates sensory information provided by vision, proprioception and the peripheral vestibular organs in the inner ears. The incorrect integration of these is observed in patients reporting peripheral vestibular dysfunctions or central vestibular disorders, which are known to often lead to the development of high visual field dependency [85]. Symptoms such as disorientation and panic can occur in situations where movement of an object near the person may be mistaken for self-movement. In those cases, people are experiencing the so called Visual Induced Dizziness (VID), which literarily means that visual stimuli such as computer screens, optic flow and visual motion in general can trigger dizziness [83]. The definition of VID included the use of different terms over the years. It was firstly named Visual Vertigo (VV) by Bronstein in 1995 [98], it was also called space and motion discomfort [205], and lately it has been referred to as Visual Vestibular Mismatch (VVM) [84]. In 2009 the Barany Society adopted the term Visually Induced Dizziness (VID) to describe these symptoms and included them under the umbrella of Persistent Postural-Perceptual Dizziness (PPPD). However despite this, in the current manuscript VID symptoms will be described not in combination or relation to PPPD, but as VID symptoms per se.

In order to identify how patients are reacting to complex visual stimuli, it is important to be aware of the visual surroundings most responsible for triggering dizziness during every day life. Examples of situations rendering patients dizzy are looking at passing trains or flickering lights, being subjected to repetitive visual patterns, walking in supermarket aisles (from where it derives the name: The Supermarket Syndrome), watching movies or scrolling phones and laptop screens [83]. Disorientation and dizziness may also simply occur when a person's visual field is overwhelmed (e.g. if the wallpaper of a room uses

repetitive patterns) or due to the lack of point of fixation (e.g. in intense darkness, wide open spaces, or as experienced with snow blindness) [98]. In patients affected by peripheral vestibular disorder, VID symptoms are commonly observed, and patients also report symptoms being triggered while they are passengers in a car, due to the numerous stimuli moving at high speed [84, 206]. If considering MdDS patients, VID symptoms have been named and identified as motion sensitivity, meaning that MdDS patients are more sensitive to visual motion and that visual inputs are able to aggravate MdDS symptoms of self-motion (e.g. rocking, swaying etc.) [44]. Visual motion normally occurs after MdDS onset [52, 54]. However contrary to other vestibular patients affected by VID, MdDS subjects are not subjected to VID symptoms when in a moving vehicle (e.g. while being passenger in a car), as they normally report a reduction of symptoms when exposed to passive motion [21]. Some examples of the major triggers for VID are reported below.

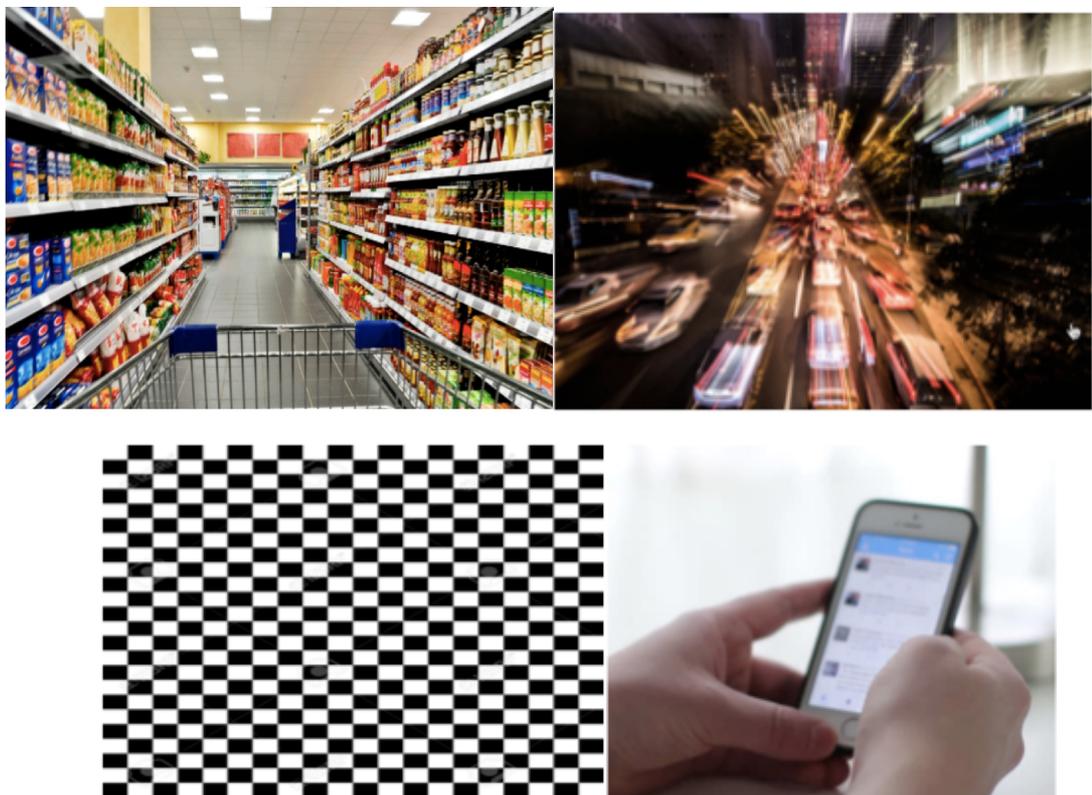


Figure 25: Four typical figures are here reported about usual triggers for Visually Induced Dizziness patients.

Subjects affected by VID report excessively relying on visual cues for perception and postural control, especially in situations causing visual–vestibular conflicts [207] for example in environments with rich visual inputs as reported in the figures above.

Treatment options are still under exploration, and more so for the MdDS patients. In Dai's and colleagues' study, performed in 2017, they reported successfully reducing visual motion sensitivity in MdDS subjects by introducing desensitization treatment for motion sickness [52]. However, specifically for visual sensitivity, previous studies have shown that the use of repetitive optokinetic stimulation (OKN) has the ability to counteract the effect of disorienting visual stimuli in VID patients, with an improvement in postural stability [83]. In the study of Pavlou [208] a full-field rotating visual environment was used as OKN and this treatment was compared with a DVD protocol where the patients watched OKN stimuli at home. This proved to be successful and that customized rehabilitation was able to improve patient's postural stability. Additionally, a supervised intervention (OKN + physical rehabilitation) was assessed versus unsupervised rehabilitation. It was noticed that supervised intervention was more successful [208].

It is important to specify however that the optokinetic stimuli in this study used for VID symptoms are not the same as the one use for MdDS patients for the OKN treatment described in Chapter 5. The purpose of the use of OKN is also different for VID patients. In the OKN MdDS treatment, the purpose of the optokinetic moving stripes is to induced a potential recalibration of the VOR [53, 73], through passive exposure to moving OKN. On the contrary, the OKN treatment used for VID patients is based on sensory integration, where the present mismatch is improved by introducing multi sensory stimuli training (visual and proprioceptive) to the subject [209] at the same time. Through optokinetic exposure and a combination of exercises, patients are expected to decrease the excessive weight given to visual information, which is activated, to compensate for the erroneous vestibular inputs. As a result the VID OKN exposure

should be considered a rather active exposure, rather than passive as for the MdDS OKN protocol. From the literature the OKN technique for VID showed to induce a significant improvements in both perceptual and postural responses [188] in VID patients. This rehabilitation is believed to induce plastic, adaptive changes that decrease the magnitude of visual dependency [32]. Reported below is a typical optokinetic stimuli used for OKN treatment in VID patients [207].



Figure 26: Image of optokinetic disk used for desentising visual dependency [207] where the subjects focuses on the stable central dot, while the other dots are rotating around.

Despite these positive findings, it remains unclear which one is the best type of OKN stimulation for VID patients, for example for how long patients should be stimulated or what other additional countermeasures patients should adopt.

As a result with this study we aimed to assess a customised OKN intervention, which included not only the OKN stimuli but also behavioural and lifestyle changes for vestibular patients reporting VID symptoms. Our purpose was of developing a successful program that could also be of benefit for MdDS patients, who are reporting continues heightened to visual stimuli also after resolving their self-motion symptoms.

From clinical observation, MdDS subjects should not be exposed to OKN VID stimuli before receiving the OKN MdDS treatment, as the exposure to OKN VID stimuli resulted in the aggravation of MdDS symptoms. It is essential that MdDS patients have first solved the major MdDS complaints of self-motion (e.g. internal sensation of rocking, swaying and bobbing) and only in a second stage, if a VID component remains, this could be further addressed with a new customized optokinetic and vestibular rehabilitation program.

VID is often affecting migraineous patients. Migraine and particularly vestibular migraine patients reported to have higher susceptibility to both movement-induced and visually induced motion sickness or VID [101, 210]. Similarly, as previously described MdDS patients have a high prevalence of migraine [51]. As first noted almost 150 years ago by the English physician Edward Living, dizziness coexist in numerous migraineous patients. He reported that six out of 60 patients with migraine had spontaneous attacks of vertigo [101]. Vertigo is two to three times more common in patients with migraine than in headache-free controls and in patients with tension type headaches [101]. It is therefore clear that migraine and dizziness are often coexisting pathologies. It remains unclear if the VID component in MdDS patients may be the result of a higher prevalence of migraine in this group of patients. More research is needed to identify the aspect of VID symptoms in vestibular migraine and MdDS subjects.

As migraine is highly prevalent in women [39], we hypothesised that similarly more female patients would report VID symptoms. Thus, this research also aimed to include hormonal related questions to VID patients.

Overall the intention of this research was to increase the current knowledge about VID patients and the use of OKN as a treatment to reduce visual dependency in different vestibular patients.

Methodology

The inclusion and exclusion criteria used to select patients are reported in Table 33. Patients with multiple vestibular disorders were selected, through an intake screening form (more details in Annex 5). The patients included had to report symptoms of visual motion sensitivity and fit into the VID criteria according to the guidelines described in Table 33 [96].

<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>
Patients age range between 18 and 70 years old	Patients aged < 18 years or > 70
Patient diagnosed with VID, thus with complaints (postural instability) while being exposed to complex visual fields: (super market, cinema, roundabout), as well as complete the intake questionnaires (Annex 5). The criteria to diagnose VID were following the Barany Society Criteria [96].	Patients with epilepsy or other neurological disease, visual impairments
Patient with standard diagnostic MRI imaging of the brain.	Pregnant women/ breast feeding women
Patients diagnosed with VID symptoms even if reporting associated other vestibular disorders. The criteria to diagnose VID were following the Barany Society Criteria [96].	People reporting substances abuse

Table 33: Inclusion criteria for the VID protocol following the guidelines for VID patients [96] (more information on the questionnaire used in Annex 5).

Ethical Approval /Patients Recruitment

Ethical approval was obtained through the Ethics Committee of Antwerp University Hospital, Antwerp, Belgium (IRB number 17/11/134). Each patient gave informed consent prior to the study. All investigations have been conducted according to the principles expressed in the Declaration of Helsinki. Patients with MdDS were recruited during vertigo-specific consultations at the department of Otorhinolaryngology and Head and Neck Surgery at the University Hospital of Antwerp, Antwerp University, Belgium. Patients were diagnosed following the VID guidelines [96], the detailed process for diagnostic intake procedure is described below.

Diagnostic Process:

- Detailed history of complaints (based on the SO STONED history taking [211] – in combination with the standardized intake form (Annex 5);
- The criteria to diagnose VID were following the Barany Society Criteria [96];
- Clinical research with micro- otoscopy and video oculoscopy;
- Tonal audiometry speech audiometry and tympanometry;
- Standard MRI posterior fossa with extended rsfMRI and DTI sequences if appropriate. A pre treatment MRI scan was performed in order to observe retrocochlear pathologies and distinct features of VID patients compared to healthy controls;
- Normal Electronystagmography (ENG), vestibular evoked myogenic potentials (VEMP) and unilateral centrifugation where appropriate.

Posturography

The patients were assessed using a Wii Balance board® for Posturography measurements. The patients were asked to stand upright for 1 minute on the Wii balance board, with eyes closed, barefoot. As outcome measures, the postural balance and the dominant frequency of rocking / swinging are calculated. This was done by calculating the swings / movements (sway path) from the center of pressure (COP). Additionally, the area under the curve of the frequency analysis will be calculated. A dedicated Matlab program was used as described in Chapter 5, with the required information from each subject at each time point. The same outcome measures as described in Chapter 5 were considered:

- 1) *Area under curve Anterior-Posterior (AUC_AP)*
- 2) *Area under the curve Medial-Lateral (AUC_ML)*
- 3) *Confidence Ellipse Area (CEA)*
- 4) *Path Length*
- 5) *Velocity*

On each day, outcome parameter measurements were recorded before (Pre) and after (Post) OKN exposure.

Questionnaires

Patients were asked to complete a series of intake questionnaires, where they were asked about their previous diagnosis and symptoms. Female patients were also asked about their hormonal status and if they reported symptom changes during hormonal fluctuations (e.g. aggravation of symptoms during menses). Visually Induced Analogue Scale was used during every treatment session to monitor patients changes (Annex 5), while the Visual Analogue scale for Visual Vertigo was used pre and post treatment to evaluate the treatment effect on VID triggers.

Optokinetic stimuli:

Patients were exposed to a minimum of 5-optokinetic sessions to a maximum of 12 sessions according to patient subjective feeling and speed of adaptation to the optokinetic stimuli. Each session lasted for about 45 minutes.

Sessions Structure:

During the treatment the patient was placed in front of the rotatory disk at 60 cm distance, as reported in Figure 27. The patient was placed in total darkness, where only the fluorescent dots on the rotatory disk remained visible. The total darkness was a key factor in inducing the best stimulation and also to create an environment that is free from any point of reference for the subject.



Figure 27: Rotatory disk with optokinetic fluorescent dots to induced desensitization in VID patients.

Patients are exposed for a specific time and they are required to inform the researcher when the induced dizziness decreases. In this way the researcher will take note of the desensitisation decay (time), when possible, during each session.

The rotatory speed of the disk was set between 30°/sec during the first session, up to maximal speed of 60°/sec. The subject was assessed at different speeds starting from

the lowest (30°/sec) up to 50°/sec during the first session. The initial speed was customised, as each subject had a different baseline threshold point. By observing the patient's reactions and verbal feedback, the researcher then gradually adjusts the speed of the disk. The speed was always able to trigger for a few seconds a sense of dizziness and often a sense of rotation in the patients, but it was not inducing sickness or total disorientation. If the speed was too quick for the level of the patient, the subject often reported an upset stomach and the session was temporarily stopped, then the speed had to be adjusted. The most beneficial "optokinetic rehab" seemed to be customized from previous studies [208], and involved a gradual rehabilitation, where the subject is not over stimulated. Therefore, the current study was based on a gradual exposure and on patient feedback.

An example of the procedure performed with the patients is reported below:

- Exposure to right and left side randomized at 30 degrees/sec SEATED POSITION for 1 min each side
- Exposure to right and left side randomized at 30 degrees/sec STANDING POSITION 1 min each side
- Exposure to right and left side randomized at 30 degrees/sec STANDING ON FOAM (Later stages) each side
- Exposure to right and left side randomized at 30 degrees/sec STANDING ON FOAM WITH 1 LEG (Later stages) each side.

Additionally, patients were also provided with behavioural instructions to implement changes at home as well as with a series of customised exercises from Cawthorne Cooksey.

Behavioural Instructions:

VID patients were pushed to abate their avoidance techniques and to go back to their normal life through behavioural instructions. VID patients often avoid being exposed to stimuli that triggers symptoms, such as going to certain shops, crowds, watching movies and playing sports involving balls (such as tennis or basketball). During and after the OKN rehab, they were encouraged to walk and to subject themselves to busy visual fields and to anything that triggers symptoms. The course of exposure was encouraged to be gradual.

Walking Protocol:

Week 1 -3: Subject was asked to walk twice a day to the bottom of the road where he/she lives. They were asked to walk twice a day up a hill, or a road close to their home. If they have a treadmill at home, they were asked to try to use it or to attend a gym. They were asked to walk on inclination 5 – speed 4.5km/hr. They were asked to walk to the end of the road and cross over the main road.

Week 4 to 6: Subjects were asked to walk to the local shops, progressively to a post office of medium size and thirdly to walk halfway to town – (4Km) crossing busy roads.

Week 7 to 8: Subjects were asked to walk in the centre of a busy city, to take busy roads, and to take the bus/metro back home.

If patients were in need for extra training of their gaze, VOR, smooth pursuit extra exercises were given. The exercises were mostly customised but they included the Cawthorne and Cooksey sequence reported below.

Cawthorne Cooksey Exercises
- Visual; Inner Ear; Postural – Proprioceptor exercises -

A. *Sitting (if very impaired in bed)*

1. *Eye movements -- at first slow, then quick (10 times)*

1. *up and down*
2. *from side to side*
3. *focusing on finger moving from the nose away from face (approximately the hand moves forward up to 60-90cm)*

2. *Head movements at first slow, then quick, later with eyes closed*

1. *bending forward and backward*

2. Turning from side to side.

B. Sitting

3. Eye movements and head movements as above
4. Shoulder shrugging and circling
5. Bending forward and picking up objects from the ground

C. Standing

6. Eye, head and shoulder movements as before
7. Changing from sitting to standing position with eyes open and shut
8. Throwing a small ball from hand to hand (above eye level)
9. Throwing a ball from hand to hand under knee
10. Changing from sitting to standing and turning around in between

D. Moving about in a large room

11. Circle around a central person who will throw a large ball and to whom it will be returned
12. Any game involving stooping and stretching and aiming such as bowling and basketball

Diligence and perseverance were required but the earlier and more regularly the exercise regimen was carried out, the faster and more complete they were returning to normal activity. Individual patients should be accompanied by a friend or relative who also learns the exercises if doing it at home for safety reasons.

Video: <https://vimeo.com/120610194>

ADDITIONAL EXERCISES FOR VISUAL-EYE TRACKING:

<https://www.youtube.com/watch?v=-0af865XuWY>

PATIENTS NOTE:

Your balance is good! You are not swaying about! If you get dizzy, stop and rest and do some breathing and relaxation exercises.

When you go to town pick a shop to visit in which you feel comfortable (e.g. a flower shop)

If patients were following training regimens they were asked to report their compliance every week to the researchers via email (for details please see Annex 5).

Follow up:

After three months from the last optokinetic treatment patients were asked about their symptoms (follow up) (Annex 5).

Control group:

Summary Methodology:

Number of subjects:

Male and female healthy subjects were recruited in equal number.

Recruitment:

Healthy subjects were invited through the University channels. In order to participate they will also have to sign the info & consent form.

Exclusion criteria healthy control:

- Subjects affected by vestibular disorders
- Subjects affected by migraine (without VID)
- Pregnant women or breast-feeding women
- Subjects reporting recent injuries (6 months musculoskeletal injuries) that can affect their balance and fitness level
- People with sensory deficits
- Subjects with chronic disease.

Inclusion Criteria:

- Subject aging ranging: Age > 18 and < 70
- Healthy Subjects

OKS Stimuli:

In order to make the OKS stimulation enough challenging for healthy subjects, the exercises given were similar to the last sessions of the VID patients, which are considered to be the most challenging. Healthy subjects were exposed at a fixed speed of 60°/sec, which is considered the most difficult for VID patients.

Duration:

Subjects were invited once a week for two consecutive weeks, possibly during the same day of the week and specific time.

Session Structure for healthy participants:

-Before: VAS questionnaire 1 + Posturography (1 minute eyes closed: feet open, 1 minute eyes closed feet closed – with no shoes)

Exercises:

- 1) Seated 2min Right and Left rotation of the disk
- 2) Standing 1min Right and Left rotation of the disk
- 3) Marching on the foam for 1min Right and Left rotation of the disk
- 4) Standing on 1 leg 30sec per leg Right and Left rotation of the disk
- 5) Standing still 1 min Right and Left rotation of the disk

Statistical Analysis:

Posturography and VAS data were analysed using the Sample t-test ($\Delta = \text{Day 5} - \text{Day 1}$) non-parametrical analysis. Descriptive statistics was used for evaluating the group age mean, as well as the type of primary vestibular input reported prior to VID symptoms.

Results

Twenty-eight VID patients were assessed in total. The average age was 48.5 years old (minimum 27 years – maximum 70 years) standard deviation (SD) of 12.66 years. 21 females (75%) and 7 male (28%) engaged in the study. Some of the patients involved had different other vestibular diagnoses prior to manifesting VID complaints, thus 46.4% of the patients had previously been trying vestibular rehabilitation, which were unsuccessful and did not involve OKN exposure. While 53.6% never tried any form of vestibular rehabilitation.

The table below shows the diagnosis of the patients. One MdDS patient who had been previously enrolled in the OKN MdDS treatment, and after having resolved his self-motion MdDS symptoms, the patient was then included in the VID OKN study.

<i>Diagnosis</i>	<i>% n</i>
VM	17.9% (n=5)
VP	7.1 % (n=2)
BPPPV	10.7% (n=3)
VN	3.6% (n=1)
Post MdDS	3.6% (n=1)
VID only	28.6% (n=8)
VID + unclear diagnosis	25% (n=7)
Unilateral vestibulopathy	3.6% (n=1)

Table 34: Primary vestibular input reported in VID patients is here presented.

Abbreviations: VM= vestibular migraine; VP= vestibular paroxysmia; BPPV= benign positional paroxysmal vertigo; VN= vestibular neuritis.

When compared the posturography data ($\Delta = \text{Day 5} - \text{Day 1}$, sample non-parametric t – test) pre and post treatment a significant change was reported in regard to the following outcome measures: the area under the curve anterior posterior (AUC_AP) (pvalue < 0.001), Confidence Ellipse Area (95%- CEA) (pvalue=0.009), Path Length (pvalue=0.085) and Velocity (pvalue=0.020). While the area under the curve medio-lateral AUC_ML did not significantly change after treatment (pvalue=0.223). These postural changes indicate that the patient postural stability increased.

An example of postural changes is reported in the figure below, where CEA 95% ellipse confidence in a typical VID patient is compared with a healthy control subject, before (in red) and after OKN exposure (in blue).

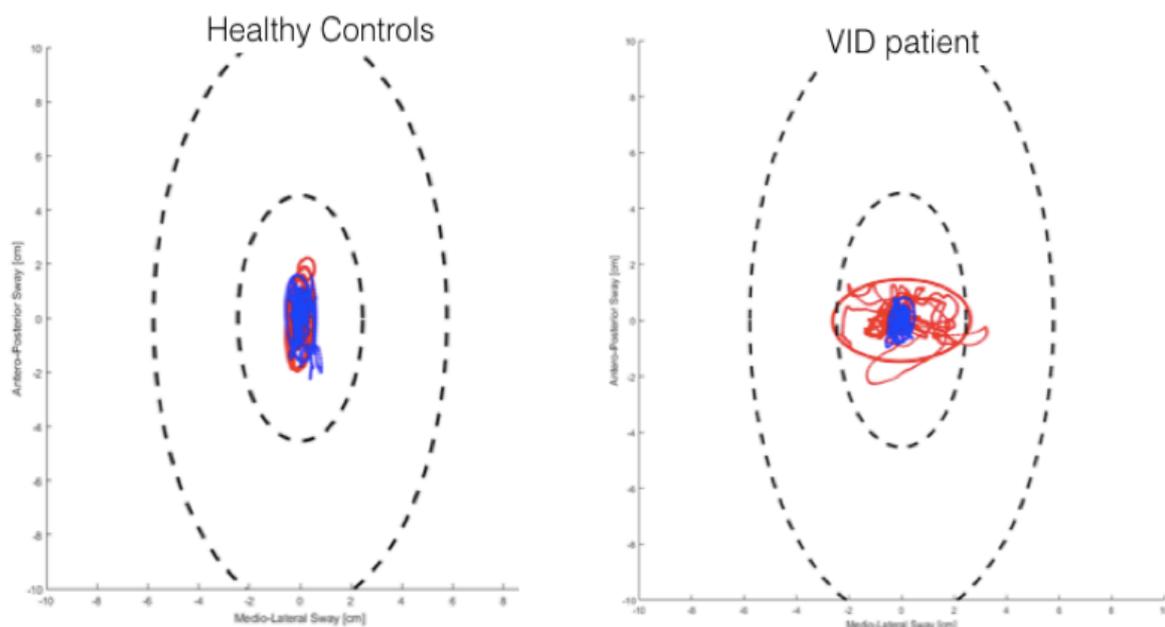


Figure 28: Example of the posturography recording from Healthy control and VID patients (female). The red line represents the recordings prior to the treatment and the blue line represents the recordings after the treatment.

In consideration of patient perception of improvement using the VAS score (0 severe symptoms – 10 no symptoms) this also improved (pvalue < 0.001), with a mean on day 1

of 6.10 (SD=1.68) reaching on average a score of 2.3 (SD=0.95) on the last day of treatment.

Healthy controls on the other hand reported no postural changes after OKN exposure. As observed in Table 35, overall no significant changes were reported. This indicates that the optokinetic exposure did not impact healthy controls.

	Control Day 1 Mean	Control Day 2 Mean	pvalue
AUC_ML	0.093	0.16	NS
AUC_AP	0.508	0.417	NS
CEA	3.61	4.194	NS
Path Length	132.069	128.419	NS
Velocity	2.161	2.083	NS

Table 35: Mean of each outcome measure and pvalue are here reported.

Abbreviations: NS = not statistically significant, AUC_AP= Area under curve Anterior-Posterior, AUC_ML= Area under the curve Medial-Lateral, CEA = Confidence Ellipse Area.

When considering the follow up data, 14% (n=4) of patients reported to no longer have VID symptoms, 52% (n=13) reported to have improved but still reported occasional dizziness, and 44% (n=11) reported to have the same symptoms as prior to the treatment. The majority of the patients' who did not improve were patients with an unclear diagnosis (number of patients not improved n= 4; yes improved n=3) and one patient with unilateral vestibulopathy. While patients improving were patients suffering from VM (yes improved n=4, not improved n=1); VP (yes improved n=2; not improve n=0); BPPV (yes improved n=3; not improved n=0), VN (yes improved n=1; not improved= 0) and VID and all patients reporting solely VID symptoms also improved (yes improved n=5; not improved n=3).

Hormonal Status in VID patients

A great predominance of female patients was reported among the VID patient group (21 female patients). Female subjects were asked if they were perimenopausal or menopausal, the majority were in their reproductive years (5 patient reported to be in perimenopausal and 5 in menopause) ($p < 0.01$ – Chi Square analysis). Patients were enquired about symptom aggravation and 10 female (83%) ($p < 0.01$ Chi Square) subjects, still in their reproductive years, reported to have higher visual motion sensitivity during menses and 8 subjects (66%) ($p < 0.01$ Chi Square), who were still in their reproductive years reported to suffer from irregular menses.

Discussion

This study proposed a customised rehabilitation protocol for patients reporting VID symptoms. Twenty-eight patients were engaged from different ages (mean age: 48.5years old) and with a different primary vestibular insult. 46.4% of the patients enrolled had previously tried other vestibular rehabilitation protocol (not including OKN stimulation), which were unsuccessful in reducing their symptoms. This strengthens the need for new defined and specialised protocol to reduce patient's visual sensitivity.

From the objective postural measurement collected it is clear that OKN intervention in combination with exercises and lifestyle changes can improve patient postural stability. These matched with the subjective feeling reported through the VAS score, suggesting that the patients also perceived an improvement. The numbers of sessions for each patient were customized, meaning that each individual received a number of sessions according to their subjective feeling and to how quickly they adjusted to the stimuli. Our findings are in line with previous studies [190].

Considering the follow up data, the majority reported an improvement of symptoms (54%) and 14% complete recovery. The patients that improved were reporting VID associated to VM, BPPV and VN, or patients having solely VID symptoms. This suggests that regardless of the primary vestibular insult (e.g. vestibular migraine or vestibular neuritis etc.) inducing their VID symptoms, visual sensitivity can improve with OKN exposure in combination with the active training of proprioceptive / visual inputs integration, and with behavioural changes.

The patients that did not improve were patients with an unclear diagnosis, indicating that despite the VID symptoms being identifiable, a clear vestibular diagnosis was not possible, and therefore this treatment may have not been the most suitable for them.

Overall our study supports previous findings where OKN treatment was shown to reduce visual dependency [84, 188]. With this study, we also show that VID patients need to

receive customized interventions, for example a different number of OKN exposures and exercises.

When considering the rehabilitation, it is important to mention that rehabilitation works by inducing plastic changes in the brain [32, 212]. This plasticity changes the functional characteristics of the brain enabling normal function. With regards to the OKN treatment for VID, we know from animal studies on monkeys that OKN is defined as an eye movement that combines an initial response of a smooth pursuit component with a large resetting saccade [213]. However there is a more complex system underlying the optokinetic stimulation [214], which relies on a slower build-up in relation to the vestibular nuclei complex response to optokinetic stimulation. In humans the vestibular system and the optokinetic stimulation were demonstrated to interact via the activation of visual and ocular motor areas and simultaneous deactivation of vestibular cortex areas [213, 214]. Additionally, in our setting, OKN was not the only component, as for most vestibular rehabilitation programs; VID patients were encouraged to continue with normal daily activities to ensure they are exposed to visual and vestibular challenges. This sensory stimulation is believed to drive the adaptive change required for the recovery. However a more specific control group for evaluating that changes were attribute to the OKN exposure should have been performed.

OKN stimuli together with the encouragement to induce behavioural change (exposure to real world phenomena, e.g. going to shopping malls) may have been responsible for inducing such positive long lasting effects on the patient. Real world phenomena can never be fully reproduced with OKN or other settings in the lab. However a more concrete monitoring, perhaps via a patient online diary, should have been performed.

The current underlying pathophysiology of VID is still unclear, however from a preliminary study involving functional magnetic resonance (fMRI), VID patients reported alteration in the visual and vestibular cortical network, which could explain why these patients show amplification of their vestibular symptoms when being exposed to challenging visual stimuli [85]. These could also expound the overreliance on visual cues (visual dependency). In healthy subjects, when the vestibular system signals an input indicating “no motion”, this should impede a visual motion signal from indicating “self-motion”, however when the vestibular inputs are erroneous as in vestibular patients, visual inputs can override and provoke a sensation of self-motion when the visual stimulus occupies a large portion of the visual field and the subject lacks of point of fixation. This is in line with the neuroimaging finding proposing that a higher connectivity is present in the visual cortex and a decrease in the vestibular cortex [85]. MdDS patients reported alterations in gray matter volume in the visual-vestibular processing areas (e.g. V5/MT) [64], among others. Suggesting that these changes may be implicated in the high visual motion sensitivity.

However, why some patients go on to develop long term visual dependency and visually induced dizziness is not completely understood.

17% of the patients enrolled in our study were diagnosed with vestibular migraine, indicating that VID in vestibular migraine can be observed together. The neurobiological mechanism underlying visually induced dizziness symptoms and migraine as well as psychological components should be closely evaluated.

Whatever the nature of the visual motion stimulus, the observed modulation of cortical excitability may plausibly mediate the therapeutic effect of the proposed rehabilitation protocol that has been developed empirically.

OKN for VID Study Limitation

This study lacked of a patient control group that not only assessed the posturography reliability but also the OKN effectiveness. However, we assumed that as almost half of the patient's engaged in this study had been previously exposed to vestibular rehabilitation, a simple exposure to lifestyle changes and Cawthorne Cooksey Exercises, would not be enough to decrease VID symptoms and improve patient postural stability. However this assumption should have been tested with a control group of vestibular VID patients who would not receive OKN exposure, such comparison would have strengthened our results.

Hormonal component in VID patients

Similarly to what was observed in the MdDS population, within the VID cohort a gender disparity was reported with 75% of female subjects participating in the VID study. Contrary to the MdDS group, most of the VID patients enrolled in this study were not in perimenopausal or menopausal. When considering patients who were still in their reproductive years (including perimenopausal subjects) similarly to the MdDS group, VID patients reported symptom aggravation during menses and a high number of subjects reported to be subjected to irregular menses. However, these may be expected as the perimenopausal subjects were united to the younger female patients. From these preliminary data it may be possible that similarly to what is observed in MdDS female subjects, estrogen withdrawal triggers heightened visual motion sensitivity in VID patients.

Online patient diaries in relation to hormonal fluctuation could help to elucidate when exactly symptoms are aggravated within the menstrual cycle.

Conclusion and future research line

From the preliminary data collected in this study, the OKN VID treatment in combination with exercises and behavioural changes can improve VID symptoms in vestibular patients (with different primary vestibular insults). A limitation to our study was that we lacked of a control group, that did not receive the OKN treatment, to prove that the OKN exposure is the rehabilitative tool inducing the positive changes. However these data are proving that patients may be able to decrease their visual sensitivity with a non-invasive and non-pharmacological intervention. Similarly to what described in Chapter 4.1, VID female subjects reported that hormonal fluctuation aggravated their VID symptoms as observed for MdDS females. Thus, the hormonal component in MdDS and VID females should be compared and closely evaluated as it may be uniting a key aspect of both pathophysiologies.

Visual or motion heightened sensitivity present in MdDS patients may also benefit from such optokinetic and vestibular rehabilitation once MdDS self-motion symptoms are treated. We hope that this initial study will stimulate further research on MdDS patients to abate their VID symptoms.

7. CHAPTER 7 GENERAL DISCUSSION:

- General Interpretation and relevance

7.1 General Discussion

Introduction

This chapter aims to provide an overview of the main findings of the thesis as well as to discuss their clinical relevance.

7.1.1 MdDS Clinical Features, Diagnostic Guidelines and Clinical Relevance:

Purpose 1:

- 1) Gain more information about epidemiology, misdiagnoses, main clinical features and characteristics of SO and MT MdDS subtypes. Aim to improve the current diagnostic criteria for MdDS; when possible compare SO and MT patient groups.

Key Findings 1:

- Identified two potential different onset within MdDS: Motion Triggered (MT) and Spontaneous Other (SO) onsets;
- From the data collected it appeared that there is a lack of awareness of MdDS in the medical community, thus MdDS are highly misdiagnosed. This is especially true for the SO group, who on average also attend more visits to healthcare professionals before receiving the right diagnosis and remain longer without a clear diagnosis;
- Both MT and SO shared a key feature characterising MdDS symptoms, which I described as a temporal relief of symptoms when re-exposed to passive motion (e.g. being passenger in a car). From this observation, two new diagnostic guideline for MT and SO were created;
- Patient's lifestyle was reported to be greatly affected, in both subtypes (MT and SO);
- Depression and anxiety were highly recorded in MdDS respondents following onset;

- Stress resulted in heightening MdDS symptoms and it was considered as a trigger;

Summary 1:

For the first time with an international collaboration between Europe, Australia and USA, we were able to gain the largest amount of dataset of MdDS patients (Chapter 3). This study provided us with adequate data to clearly present and distinguish two onset types that were not fully described in the literature. The first is named Motion Triggered (MT) MdDS onset, indicating the most typical onset type resulting from disembarking after passive motion exposure. The second subtype is termed as Spontaneous Other (SO) MdDS onset, unifying the spontaneous onset, occurring without any clear event and the onset characterised by a non-motion event (e.g. surgery, childbirth).

Within this research, the lack of awareness of the disorder among healthcare professionals is highlighted, and therefore how difficult is for MdDS patients to receive the right diagnosis. More so for the SO onset group, which in comparison with the MT group, had a higher number of patients undergoing up to 20 - 40 medical appointments, with an average of 19 visits [56] before receiving a diagnosis. Overall the SO subtype is less acknowledged by the medical community and SO subjects reported to have been seeking for the right diagnosis (remained without a clear diagnosis) for longer compared to the MT group. Consequently, the SO group also resulted in a higher number of self-diagnosed patients in proportion. The amount of misdiagnoses was also very high in both onset groups. Generally, patients described their medical experiences as negative, indicating lack of support from healthcare professionals. We were also able to show that similarly both onset groups share the same prominent feature of temporary relief of MdDS self-motion symptoms when re-exposed to passive motion (e.g. being a passenger in a car). This key feature was not suggested as a typical MdDS trait in the previously published guideline from Van Ombergen [44, 58],

and as a result we proposed to integrate this feature and we formulated new diagnostic guidelines [21]. Within the guidelines we added a specific diagnostic criteria to help identify SO patients [21]. In Chapter 3, we also presented the strong interrelation that MdDS patients have with psychological factors. Firstly the great impact of MdDS on patient's lifestyle was reported. After that, secondary mood disorders were evaluated (e.g. depression and anxiety) and lastly we discussed the impact of stress in aggravating the MdDS symptoms. We theorised that MdDS patients due to the chronic stress deriving from a chronic illnesses may develop aberrant stress responses, leading to autonomic changes and brain function alterations.

Clinical Relevance

We believe that collecting data on patient's experience is fundamentally important for improving patient care. Proposing new diagnostic criteria may help physicians to diagnose and recognise MdDS patients (earlier), leading to a reduction in misdiagnosis, and subsequently in healthcare expenditure and ultimately in improving patient health management. From our data, the two onsets (MT; SO) did not report differences in major clinical features or traits.

The further insights about MdDS associated secondary mood disorders and stress are believed to be relevant for improving patient care and to promoting further research. Our proposed new theory may help to prompt new research into the stress component of MdDS.

7.1.2 MdDS Hormonal Component: New Theories & Clinical Relevance

Purpose 2:

2) 4.1 Examine a potential influence of gonadal hormones on MdDS pathophysiology, when possible compare SO and MT patient groups;

4.2 Evaluate if during pregnancy MdDS patients report a change in their symptoms and sensitivity to triggers.

In both study 4.1 and 4.2 a series of questions about the diagnostic procedures and current co-morbidities were also performed.

Key Findings 2:

Section 4.1

- Female predominance in the respondents (more than 80% were female);
- Female subjects were enquired about their hormonal phase when onset occurred. A high number of female patients reported to be menopausal.
- MdDS patients still in their reproductive years were asked if they were menstruating during onset. Considering the open-ended responses, several subjects reported to be travelling during menses;
- Female patients from the MT group were reporting aggravation of symptoms during menses and mid-cycle ovulation. While no statistical significance was reached for the SO group;
- Both onset groups reported no aggravation to triggers during different menstrual cycle phases;
- A higher number of SO participants reported to have irregular menses compared to the MT group;
- Preliminary data also suggested that male subjects might suffer from hypogonadism;

- Female MdDS patients may report a higher prevalence of PCOS compared to normal population. These data should only be considered preliminary due to the small number of respondents and for the retrospective nature of the data;
- Migraine should not be considered a predisposing factor for MdDS, but rather to be related to MdDS onset, as it seemed to develop after onset;
- Motion sickness was not a predisposing factor for MdDS;

Section 4.2

- Female MdDS patients during pregnancy reported less MdDS symptoms, regardless of their onset type;
- MT pregnant MdDS patients reported to shift from a subjective feeling of internal oscillation moving in multi-directions to a more stable and single direction feeling;
- Healthcare professionals caring from pregnant MdDS subjects are mostly unaware of this condition;

Summary:

From the epidemiological data presented in Chapter 3, a great female predominance was observed in both onset groups. It is known that MdDS is more prominent among females, this has been previously observed in numerous studies (9:1 female to male subjects) [45, 60]. Although this has been known for years, no studies have investigated the link between MdDS and gonadal hormones, which could help to explain this female preponderance. As a result, in Chapter 4 we presented our study based on assessing gonadal hormones in MdDS patients. This was the first study (Chapter 4.1) in the form of a retrospective questionnaire enquiring about hormonal related aspects in MdDS patients. The main aim was to gain preliminary data on how gonadal hormones

may influence MdDS symptoms and to evaluate if hormonal phases are interrelated in MdDS pathophysiology. Despite numerous studies having identified an MdDS gender disparity, up to date, no study has ever explored the potential role that hormones could play in developing or influencing MdDS. In female vestibular patients [36], it is suggested that gonadal hormones may have a potential influence on symptoms, for example, hormonal fluctuations have been found to play an important role in other vestibular disorders, such as vestibular migraine and Ménière's Disease [36]. Additionally, the predominance of vestibular disorders among women occurs often during perimenopausal years [117], suggesting an hormonal influence on the pathophysiology of certain vestibular disorders. Another aspect to consider is migraine. Numerous vestibular disorders have been associated with migraine [215, 216], similarly migraine is highly prevalent among MdDS patients [49, 51, 101]. Estrogen as well as ovarian steroid hormones have been implicated in migraine symptom fluctuation and pathophysiology [39]. As a result, our main hypothesis was that MdDS female patients would be vulnerable to hormonal changes, particularly to the fluctuations of estrogen, similarly to what is observed in migraineous patients with the so called estrogen withdrawal. Estrogen withdrawal has been implicated in aggravating migraine symptoms. Similarly estrogen drop (as is the case in the peri-menopausal - menopausal transition [172], and menstruation [39] has been hypothesised to aggravate female MdDS patients' symptoms. In addition to this, in our study we also enquired about the hormonal profile of male and female MdDS patients as well as motion sickness susceptibility and migraine.

From the data collected, despite being considered preliminary, a clear aggravation of symptoms was recorded in MT patients during menses and in the mid cycle, when estrogen are believed to be at its lowest [39]. This confirmed our hypothesis that estrogen withdrawal may be involved with symptom fluctuation in MdDS patients.

Additionally, the age of MdDS participants matched with the 5th decade of life previously reported [60], which suggests that the perimenopausal or menopausal phase should be closely considered as a potential risk factor for developing MdDS.

In the survey discussed in Chapter 4.2 we also asked patients about pregnancy. A small number of MdDS patients reported to experience pregnancy while suffering from MdDS and most of them indicated that they had an inexplicable reduction of symptoms during the 9 months of pregnancy. As a result, a pilot study designed for MdDS pregnant women was created (for details please refer to Chapter 4.2). As previously reported, the majority of MdDS patients are usually towards the end of the reproductive years (i.e. perimenopausal, menopausal), consequently limited information regarding reproductively active MdDS subjects, including those undergoing pregnancy are available in the literature. Consequently, the study presented is the first of its kind. Given the preliminary data reported in study 4.1 we hypothesized that assessing MdDS sufferers during pregnancy may help our understanding of the underlying interrelation of hormones upon MdDS.

Once again we considered the symptom changes observed in migraine patients, this time during pregnancy, and we hypothesised that a similar change would be observed in MdDS subjects. During pregnancy, between 55 - 90% of migraine sufferers report having an improvement in their migraineous symptoms [173], suggesting a positive effect of pregnancy on migraine. During pregnancy women are subjected to a unique and limited condition, characterised by physiological and biochemical changes [158]. An extraordinary modification of numerous hormones is reported [158], hormones that can influence brain regions such as the hypothalamus [118], where plastic neuronal and glial remodelling is involved in the regulation of hormonal changes during motherhood. This research aimed to provide valuable information about how hormonal changes during pregnancy may or may not affect women with MdDS, with the ultimate

goal of improving patient care during pregnancy. From the data collected, despite the small sample size, the majority of the patients reported an improvement of symptoms while being pregnant. The rise in estrogen and progesterone and the absence of cyclic fluctuations [39, 158, 176] is hypothesised to be responsible for the positive reduction in symptoms reported by MdDS patients.

From the data presented in Chapter 4, it is clear that hormonal fluctuation and hormonal changes affect MdDS symptoms in female subjects. If considering both studies together (4.1 and 4.2) hormonal changes (cyclic fluctuation during menses and the absence of fluctuation during pregnancy) are believed to be responsible for changes in MdDS symptomatology.

From recent studies, the interrelationship of estrogen on brain neurotransmitters has been confirmed [39], thus within Chapter 4 we propose a new theory on the implication of gonadal hormones in MdDS pathophysiology. MdDS has been defined as a disorder of neuroplasticity as well as the result of the VOR maladaptation [53]. Potentially, low levels of estrogen, as during the luteal phase, may alter the brain's adaptability to new environments, by influencing the subject's central neural control for the velocity storage mechanism that has also been implicated in the maladaptation of the VOR [52]. The velocity storage integrative network is constituted of GABA_b sensitive neuron receptors. For previous studies, low GABA plasma has been associated with depression [149] and Pre-Menstrual Syndrome (PMS) sufferers in the luteal phase [148]. GABA-mediated neurons are known to have a prominent inhibitory role in spatial navigation. Consequently their deregulation, by altering hormonal levels, could hold some significance in the aggravation of MdDS symptoms [150]. If GABA is implicated in MdDS pathophysiology, this could also explain why drugs acting on the release of GABA such as clonazepam may be effective for MdDS patients [47]. GABA and the

GABAergic system during pregnancy also changes. The GABAergic system is particularly subject to hormonal fluctuations, undergoing, in response, dramatic functional changes observed during pregnancy [217].

More research is needed to prove the hormonal influences on neurotransmitters (e.g. GABA) and how they correlate to MdDS symptomatology changes. Further evaluation of GABA plasma and its correlation with in vivo proton magnetic resonance spectroscopy (1H-MRS) is encouraged.

Clinical Relevance

The studies presented in Chapter 4 despite they should be considered preliminary they can be defined as a first milestone in the underlying MdDS pathophysiology.

Knowing that female MdDS patients are subjected to symptom fluctuation due to hormonal changes could help in understanding when to implement therapeutic interventions. Knowing that some female MdDS patients may report higher symptoms during menses suggest that therapeutic interventions at this particular time should be avoided or the changes in symptomatology should be considered. Furthermore, such information could also trigger new therapeutic interventions in regard to hormonal therapies.

With regards to pregnant women, the preliminary data obtained has further supported our theory of estrogen withdrawal. In order to examine how MdDS patients manage their symptoms, closer monitoring after delivery should also be implemented. Clinicians aware of such information could help patients with preventative strategies during breastfeeding if MdDS symptoms reappear. During breastfeeding, after delivery, the preferred therapeutic strategy should always be a non-pharmacological one, thus being aware of these symptoms changes, could also help patients seek mental health support, and to decrease the chance of developing depression, which in turn can

have negative consequences for the mother and the baby [177].

Despite being preliminary, this information provides new insights about MdDS symptom fluctuations and may bring about innovative research as well as new patient management strategies.

7.1.3 Optokinetic Treatment (OKN) for MdDS & Clinical Relevance:

Purpose 3:

- 3) Reproduce the OKN treatment for MdDS patients proposed by Dai and colleagues. To evaluate if patients are subjected to a placebo effect.
Create a standardised treatment protocol and evaluate its success rate in both onset groups.

Key Findings:

- MdDS patients benefitted from 5 days of OKN exposure (with head roll at the fixed frequency of 0.165Hz).
- The greatest changes occurred on the first days of the treatment, suggesting a shorter treatment may be possible.
- No placebo effect was recorded on MdDS patients within our setting, (no changes in posturography and subjective feeling after the Sham exposure).
- The postural data from the control group significantly differ from the ones from MdDS subjects, indicating that no learning effect was present for MdDS subjects.
- MT patients benefitted the most from this OKN treatment, with 70% of them reporting a reduction or remission of symptoms, upon three months follow-up.
- No gender or age influences were observed when considering the subject response to the treatment.

Summary:

Therapeutic options to ease or cure MdDS are still limited and under exploration, due to the scarce knowledge and understanding of the underlying pathophysiological

mechanisms of MdDS. In addition to this, MdDS as reported in Chapter 3, is still poorly recognised among health care professionals. Consequently, treatment options and symptom management strategies are poor and often inadequate. However, over the last few years, a potential treatment based on optokinetic (OKN) stimulation has been proposed. The treatment consists of exposing MdDS subjects to OKN stimuli in combination with head roll for five consecutive days. This protocol was developed by Dai and colleagues [53] in 2014. In Chapter 5, we present our clinical trial, which for the first time reproduced the same OKN treatment proposed by Dai and colleagues. The treatment is constituted on the hypothesis that MdDS is the result of the VOR maladaptation and that the exposure to optokinetic stripes and head movements induces the activation of the optokinetic reflex, thus it is able to restore the disrupted velocity storage and VOR. Additionally, patient's gravito-inertial acceleration (GIA) was hypothesised from Dai's group to be modulated by head roll matching the subjective motion feeling reported by the patients. As the patient is subjected to an OKN stimulus that rotates around the spatial vertical against the direction of the vestibular imbalance reported by the patient (when possible) [73]. GIA vector in MdDS seems to be restored with the use of a roll of the head, while activating the velocity storage integrator with a low frequency, constant velocity, full field, OKN stimulus. Thus, a pseudo cross-coupling mechanism is considered as the responsible for restoring the velocity storage mechanism.

This study aimed to reproduce the OKN treatment for the first time, as well as to assess patients for a potential placebo effect. This OKN treatment has never been tested for placebo before, thus, we implemented a sham control study prior to the real intervention. In addition to this, we also aimed to assess if maintaining patient head roll at a fixed frequency was able to induce the same positive results as previously observed from Dai's research group. Overall, this research aimed to standardise the

protocol to create a more practical and implementable treatment for clinical setting. Additionally, we questioned female MdDS patients about their hormonal status taking into account the findings presented in Chapter 4.

From our results, significant postural changes were detectable after the first exposure on Day 1 with respect to sway velocity, indicating that patients' self-motion was reduced rapidly. Other postural outcome variables changed after two days of exposure, resulting in an increase in postural stability in most patients. Overall, this suggests that the treatment effects of the OKN treatment are almost immediate. Secondly, we showed that in our setting no placebo effect was present, as patient postural and subjective feeling remained stable during the sham protocol. Lastly maintaining the head roll at a fixed frequency (0.165 Hz) did not affect the overall treatment outcome. Having a standard frequency can help in replicating this study in multiple centres. The fixed frequency for head roll helped in simplifying the treatment procedure from the original protocol formulated by Dai and colleagues.

We concluded that within our setting similar results to what had been observed in previous studies were achieved, with 48% of MdDS patients reporting symptom improvement, 70% of which were motion-triggered (MT) patients. This treatment has been previously observed to have a higher success rate among MT patients [52]. It is unclear why SO patients are less responsive to such treatment, future studies should consider the higher prevalence of migraine described in Chapter 5 and 4 among SO patients to estimate if the two subtypes are pathologically different. It is possible that MT and SO share abnormal brain functioning, symptomatology and physiology, although entering by different pathways or mechanisms [51], which may explain why they exhibit a different response to OKN intervention.

Despite our study being performed on a small sample size, we were able to show that OKN treatment is reproducible and we provided a basis for a more structured protocol

that will make this treatment easier to be implemented in multiple centres. Another crucial finding is that visual motion sensitivity continued to affect patients, including when the self-motion symptoms improved.

With regard to the hormonal status, the majority of MT patients in this investigation reported that during the believed onset they had experienced their monthly menstruation. Additionally, a great number of subjects were also in the perimenopausal and menopausal phase when MdDS onset began.

Clinical Relevance

The relevance of this study relies in proving that a short and effective OKN treatment is possible, as most of the postural changes occurred within the first two days of treatment. This indicates that more patients may be able to try this treatment as it could be implemented within only 3 days instead of 5. Another aspect with a high clinical relevance is the observation of extra symptoms. Despite 48% of patients reporting that their symptoms improved in the follow up data, most patients reported a heightened visual sensitivity as well as migraine. These extra symptoms seemed to remain even in subjects where the reduction of self-motion through OKN was successful. Similar findings have been previously observed in a year follow up study conducted by Dai and colleagues [52]. These observations strengthen the need to consider migraine and visual sensitivity more closely, as further discussed in Chapter 6. From our findings, patients reporting SO onset resulted less responsive to the OKN treatment, suggesting that further research in the pathophysiology of MT and SO MdDS is needed, to understand if MdDS subtypes are clinically different.

In this study, a female predominance was observed and most subjects reported to be in perimenopause or menopause, this strengthens our previous hypothesis described in Chapter 4, thus the hormonal status of MdDS patients should not be ignored.

7.1.4 Visual sensitivity in MdDS patients:

Purpose:

- 4) Aim to evaluate if vestibular patients reporting VID symptoms can ease their visual dependency with a combination of optokinetic stimuli, vestibular rehabilitation and behavioural guidance. A similar protocol could be used for MdDS subjects reporting VID symptoms.

Key Findings:

- VID patients affected by multiple vestibular disorders (e.g. vestibular migraine, vestibular neuritis etc), improved following OKN exposure combined to lifestyle and vestibular rehabilitation exercises.
- VID female subjects reported an aggravation of symptoms similarly to what described in Chapter 4 for MdDS female patients.

Summary:

As presented in Chapter 5, visual sensitivity affects numerous vestibular patients and similarly also MdDS patients report a high visual dependency since onset. In detail, subjects reported relying on visual cues for perception and postural control, especially in situations causing visual–vestibular conflicts [207]. Symptoms such as disorientation and panic can occur in situations where movement of an object near the person may be mistaken for self-movement. These symptoms have been described as Visually Induced Dizziness (VID).

In Chapter 6 we described the main characteristics of VID symptoms and presented one of the few treatments available based on OKN stimuli. As for MdDS, treatment options able to reduce subject visual dependency are still under exploration. The study of Dai and colleagues performed in 2017, reported to successfully reduce visual motion

sensitivity in MdDS subjects by introducing desensitization treatment for motion sickness [52]. However, specifically for visual sensitivity, previous studies have shown that the use of repetitive OKN stimulation has the ability to counteract the effect of disorienting visual stimuli in VID patients, with an improvement in postural stability [83]. It is important to mention that the purpose of the use of OKN stimuli in VID is also different for the use of OKN stimuli used in the treatment for MdDS. In the OKN MdDS treatment, the purpose of the OKN moving stripes is to induce a potential recalibration of the VOR [53, 73]. On the contrary, the OKN treatment used for VID patients is based on sensory integration, where the present mismatch is improved by inducing multisensory stimuli training (visual and proprioceptive), which are believed to induce plastic changes in the brain [32, 212]. Despite no concrete data having yet been published on a sample of MdDS patients, this study could be clinically relevant to promote the use of another treatment to alleviate MdDS secondary symptoms, once the self-motion perception has been treated.

In addition to this, similarly to the MdDS group, a female predominance was reported in the VID group. Most of the female VID patients contrary to MdDS were not in menopause, although similarly to MdDS patients, women in their reproductive years including perimenopausal women reported an aggravation of visual motion sensitivity during menses and to be subjected to irregular menstrual cycles.

Clinical Relevance

The study described in Chapter 6 shows that a combination of OKN stimuli with behavioural and lifestyle changes can help managing visual dependency in vestibular patients. It is possible to theorize that a similar protocol to the one proposed for VID patients could be implemented for MdDS patients after their self-motion symptoms are resolved. However, it is important to specify that the OKN stimuli used for VID symptoms

are not the same as the ones used for the MdDS OKN treatment described in Chapter 5. The VID OKN treatment involved an active participation from the patients, while in the MdDS OKN the subject was asked to watch passively the moving stimuli.

Similarly to the MdDS group, a female predominance was observed in the VID study. Patients reported a heightening of symptoms during menses. This could potentially suggest that the above described estrogen withdrawal theory could be applicable also for subjects affected by VID symptoms. In addition to this, MdDS patients should be asked in more details whether their aggravation of self-motion during menses is the consequence of an increase in visual motion sensitivity. The underlying susceptibility in both MdDS and VID patients to hormonal changes may be equally influencing the pathophysiology of both disorders. We hope that these findings will trigger more research in this field.

Gaining more insights into additional symptoms affecting MdDS patients and proposing effective countermeasures may facilitate patient management over time.

7.2 General Overview

The findings presented in this thesis broaden the understanding of MdDS.

MdDS is a complex disorder, with multiple aspects to be considered. With the research proposed we highlighted that MdDS has a strong psychosocial impact for the patients, which should not be underestimated. Patient's management from the survey presented is still poor and often inadequate. To address this issue, we launched a first international online questionnaire for MdDS patients with MT and SO onset. From the results collected we gathered valuable information about patient's clinical features, onset triggers and associated mood disorders. Thus, we proposed an update of the diagnostic guidelines for MdDS previously published by Van Ombergen [44]. Our guidelines also include the SO onset subtype. Overall with these more broad and comprehensive guideline, we aimed to provide a tool for health care professional to identify MdDS and ultimately to reduce the number of misdiagnosed patients. Within our investigation into associated features influencing MdDS, stress was reported as a strong trigger for aggravating MdDS symptoms. MdDS patients as most patients affected by a chronic illness, report chronic stress [49]. Chronic stress is known to be able to inhibit normal brain plasticity, leading to detrimental changes in the brain [109]. Thus, it could be potentially implicated in MdDS pathophysiology per se. Future studies should focus on assessing if MdDS patients report aberrant stress responses, ideally before and after a successful intervention. The second purpose of this thesis was to assess if MdDS gender disparity was related to a potential link among hormonal fluctuations and MdDS symptoms or pathophysiology. The great prevalence of female subjects affected by MdDS is not coincidental and has been clearly indicated in previous studies [60].

In order to address this, a series of questionnaires were released to investigate this hypothesis as well as to evaluate the hormonal profile of MdDS subjects. We were able to set up the first global survey, with the highest number of MdDS respondents that attempted to identify a link between MdDS and gonadal hormones. From our results women affected by MdDS in particular participants from the MT group reported aggravation of symptoms in relation to menses and mid cycle hormonal fluctuations. We hypothesized that such aggravation may be the result of estrogen withdrawal, which is known to similarly aggravate migraineous symptoms [39]. In addition to this, we noted that a higher number of SO subjects seemed to suffer from irregular menses. The influence of the fluctuation of estrogen in MdDS may also lie within its estrogenic ability to affect the central nervous system function. Thus, we created a new hypothesis, where the homeostasis of one of the major neurotransmitter Gamma-Aminobutyric Acid (GABA) is hypothesised to be implicated in MdDS pathophysiology. Hormonal changes, such as changes in estrogen levels are known to influence the GABA turnover, as observed in animal studies [218], thus a similar hormonal fluctuation may influence several neurotransmitters in humans. In addition to this, within this study we also enquired about migraine and motion sickness susceptibility. This investigation reported a high prevalence of migraine associated with MdDS onset, and failed to support any significant relationship between motion sickness as a predisposing factor for MdDS. This suggests that the mechanism(s) involved in hormonally regulated migraine may be present, or relevant, for female MdDS patients.

Although we did not observe a higher rate of hormonal conditions in male respondents when compared to the general population, future studies should consider examining the possibility of hypogonadism. It could be that as observed in animal studies, that GABA turnover can be likely stimulated by testosterone in a manner similar to that of

estrogen in the female rat [218]. Thus that hypogonadism may be influencing or being a predisposition factor for developing MdDS in male subjects.

In conclusion, this research has provided novel insights into the potential hormonal influences within MdDS pathophysiology and peculiar differences related to onset types. These results require future testing, to further elucidate the role of hormones in MdDS, and in particular, call for more detailed clinical investigations to help elucidate the role they play in MdDS symptomatology, onset, as well as if hormonal intervention can have a therapeutic potential.

Another part of this research focused on MdDS female subjects who have experienced pregnancy. We hypothesised that similarly to what observed in migraine patients [39], during pregnancy MdDS patients would report a relief or alleviation of symptoms. To evaluate if this hypothesis was true, we performed a first pilot study on pregnant MdDS females. Despite preliminary, our results indicated an improvement of symptoms during the 9 months of pregnancy in MdD patients.

Respondents, regardless of their onset type (MT or SO), reported overall an improvement of symptoms during pregnancy compared to before pregnancy, suggesting a potential beneficial influence of higher estrogen and progesterone concentrations. Motherhood is one of the most complex periods of cross talk between hormones and the brain in adult life [118]. The hypothalamus is one of the main brain regions undergoing plastic neuronal and glial remodelling during motherhood [118]. These changes, are hormonally regulated and they could potentially modulate the GABAergic system [118]. These preliminary data may provide incentive for further investigation into the role of hormones in the symptom profile and pathophysiology of MdDS. Further research should be built on these observations and proposed theories.

Part of this research was also focusing on investigating the use of optokinetic (OKN) stimuli as a treatment for MdDS. With a clinical trial involving 25 MdDS patients from both onset groups, we obtained similar data to the one presented by Dai and colleagues in 2014 [53], where 24 MdDS patients reported an improvement in postural stability after the exposure for 5 consecutive days to OKN stimuli. This treatment was based on the theory that MdDS is the result of a maladaptation of the VOR, with a disrupt velocity storage. Our study has also demonstrated that the sham protocol performed on MdDS patients from both onset subtypes does not induce a placebo effect. If a placebo effect were to occur, we would expect a postural improvement after two days of sham sessions, this was not the case as no significant posturography changes were recorded after the exposure to the sham protocol. We also proved that the OKN treatment for MdDS can be easily implanted within a shorter time frame, three days instead than 5 days and that successfully reduce some of the patient's complaints especially in the MT group. It is possible that MT and SO shares abnormal brain functioning and physiology, although entering by different pathways or mechanisms [51], which may explain their different response to OKN intervention. However it is still unclear if MdDS onset subtypes differentiate in their pathophysiology, suggesting that more research is required.

Also in this group of patients a higher number of females was present, most of the patients in this study were perimenopausal, in line with what hypothesised in Chapter 4, (that estrogen level changes may be implicated in the pathophysiology of MdDS). In addition to this, most of the younger participants reported to be menstruating during the believed onset. One hypothesis to explain this could be that low levels of estrogen, as during the luteal phase, may have altered the brains adaptability to new environments. Aside from this, both genders from both onset types responded similarly to the treatment, despite the SO group overall had a lower success rate.

In both groups and gender, we have recognised that migraine and visual motion sensitivity remained after the OKN treatment, suggesting that the underlying pathophysiology of MdDS may not simply involve a disruption of the VOR or that the prolonged impact of the disorder on the patient's brain has led to generating other symptoms. Thus, future research should involve neuroimaging studies to underline the pathophysiology of MdDS and to fully elucidate potential differences in the two onset types.

On the other hand, to ease MdDS motion sensitivity we proposed to reproduce an intervention normally used for subjects affected by Visually Induced Dizziness (VID).

In Chapter 6 a pilot study on subjects affected by VID symptoms with different vestibular disorder is presented. This study aimed to assess which could be the best rehabilitation protocol to reduce visual dependency in vestibular patients, considering that most participants to the study already underwent other form of treatment including vestibular rehabilitation, with poor results. The protocol involved not only OKN stimuli, but also behavioural instructions and customised exercises for each VID patients, according to their primary vestibular disorder they were affected to.

Contrary to the OKN stimuli used for MdDS symptoms, the OKN protocol used for VID patients is based on sensory integration. For VID rehabilitation, the present mismatch is improved by inducing multisensory stimuli training (visual and proprioceptive), which are believed to induce plastic changes in the brain [32, 212]. Despite no concrete data having yet been published on a sample of MdDS patients, we suggested that a similar protocol could be used for MdDS patients reporting persistent VID symptoms after their self-motion complaints are treated.

Overall the studies reported suggested that MdDS has multiple faces and that the best approach to improve patient management should involve specialists with diverse expertise, for example involving psychiatrists and gynaecologists with otorhinolaryngologists. Many questions remain to be address such as if hormonal therapeutic intervention could ease or reduce MdDS symptoms as well as investigating if GABAergic modulation can induce symptoms changes in MdDS patients. Ultimately to improve the current therapeutic strategy more research needs to be put in to the underlying pathophysiology of MdDS.

8.CHAPTER 8 – LIMITATIONS, CHALLENGES, AND FUTURE

PERSPECTIVES:

- Limitations
- Challenges and Solutions
- Future perspective

Part of this chapter has been published on Frontiers of Neurology:

Perspective: Stepping Stones to Unravelling the Pathophysiology of Mal de Debarquement Syndrome with Neuroimaging

Mucci, Viviana, Cha Yoon-Hee, Wuyts Floris L., Van Ombergen Angelique. (2018) 1-6
doi: 10.3389/fneur.2018.00042

This chapter presents the main limitations (section number 8.1) encountered throughout the studies previously discussed, as well as challenges and potential solution (section number 8.2), based on the experience gained with this research.

In Addition to this, in section number 8.3 after reintroducing the two main theories about MdDS pathophysiology, few pending questions are presented (section number 8.4).

With regards to the pending questions, particularly emphasis is given to neuroimaging studies, which have not been explored in this thesis, but are here discussed to further encourage new research line by pointing out the remaining questions with respect to MdDS.

8.1 Limitations encountered in the studies presented

As previously described MdDS is currently considered a rare disorders, with a high prevalence of misdiagnosed patients. As a result, the greatest challenge and limitation to this research was to engaged MdDS patients. Access to patients was limited to those who came across our studies or those being assessed at Antwerp University Hospital. In Chapter 5, twenty-five patients were recruited over two years and half, demonstrating the difficulty in studying MdDS subjects. For the patients recruited for the online survey, a small number of respondents were self-diagnosed, although most patients received a diagnosis from a healthcare professional.

With regards to Chapter 3 and 4 we presented the largest survey of people with MdDS to our knowledge in the form of retrospective studies. Patients could complete the surveys fully anonymously, allowing respondents to be open and frank. However, we do acknowledge the surveys suffered from a high rate of non-response, especially the data regarding the hormonal section reported in Chapter 4. We had no satisfactory method for estimating response rates or response biased in this survey. In addition to this, the retrospective aspect could have introduced information bias, due to the inability of the patients to recall the exact information, particularly those connecting symptoms patterns to cycle phases of the menstrual cycle (e.g. ovulation).

Participant numbers for the SO group were limited in all studies, it remains unclear if this is due to being less common or simply due to a higher number of SO patients who are misdiagnosed and unaware of their condition.

The surveys questions were requiring information about events, which in some cases had a time lapse of several years and no specific strategies for reducing recall bias were implemented. In Chapter 4, in order to control for bias, when possible, we compared our sample against normative data, which suggested no major biases in the limited number of variables we examined. The studies presented in Chapter 3 and 4 involved questions, which were designed for the specific need of each surveys, thus they were not validated or tests. Furthermore, the subjects engaged in our studies in Chapter 3 and 4 represented a volunteer sample rather than a probabilistic sample, thus the validity of the statistical inference was undermined. As previously noted, especially for Chapter 4, all confidence intervals and pvalues should be therefore interpreted with caution. With regards to Chapter 4 for the hormonal questions, a great limitation to our survey was that patients were not screened for Pre Menstrual Syndrome (PMS), a condition that could trigger symptom aggravation around menses, as reported by the participants. The overlap with other hormonal conditions such as PMS should be closely evaluated in MdDS patients reporting aggravation of symptoms during menses, in order to elucidate the etiology of such aggravation.

8.2 Challenges and Solutions

Studying a poorly recognised and understood disorder, poses great challenges and difficulties. In this section are reported some of the many challenges encountered in this research and potential solutions and strategies to overcome them.

8.2.2 Sample size

As briefly commented in the limitation section (8.1), in Chapter 3, 4, and 5, patient recruitment was challenging in every single project performed on MdDS. Since MdDS is considered to be an uncommon disorder, acquiring sufficient sample sizes is difficult. Therefore, future research should continue to promote multi-center studies, as we did. The collaboration among experts and centres allowed us to gain meaningful data. In this research collaboration has enhance recruitment. Therefore this is further suggested for future studies. Additionally other channels for patient recruitment could be used, such as the MdDS Balance Disorder Foundation (MdDS Foundation; www.mddsfoundation.org). Moreover the scientific community should consider the creation of an international MdDS Consortium, which may facilitate collaboration in the future.

8.2.3 Intersubject variability

In Chapter 3 and 4 we collected epidemiological data to increase the current knowledge on the typical MdDS patients and symptoms. Patients reported high subject inter-variability in symptoms and onset types. To address and facilitate clinicians to consider the diversity of MdDS patients and the presence of different onsets, we developed new diagnostic guidelines (e.g. proposed in Chapter 3 [21]) including the Spontaneous / Other onset.

The typical long duration between the start of symptoms and the actual diagnosis (and thus, the inclusion in scientific studies) could be responsible to raise secondary and confounding factors, (e.g. the development of phobic behaviour, anxiety, and depression). This is a challenge in the study of any chronic disorder. However, with the diagnostic criteria proposed the improvement in timeliness and accuracy of diagnosis should be anticipated. In addition to this, for future research longitudinal studies should be considered. For example given the symptom fluctuation observed in female patients the implementation of longitudinal studies could help model MdDS symptom variation over time. Longitudinal studies should incorporate symptom severity scales as well as online diaries to control hormonal fluctuations and symptom changes. Such information could serve to identify triggers responsible for aggravating MdDS symptoms as well as to monitor potential therapeutic intervention.

8.2.4 Comorbidities

The relationship between MdDS, migraine and high visual dependency has been reconfirmed with our studies (see for details in Chapter 4, 5 and 6). A potential overlap between MdDS and migraine as co-morbidities has already been suggested [51]. Similarly from our findings (see Chapter 4) numerous MdDS patients reported migraineous symptoms, more so the SO group, thus this aspect should be further elucidated. Knowing more about potential co-morbidities could help to elucidate MdDS pathophysiology. We encourage, future prospective studies including MdDS (+) migraine and MdDS (-) migraine patients to develop a first insight.

As for increased visual dependency, quantifying visual reliance, e.g. by means of measuring the subjective visual vertical (SVV) or Visual Vertigo Analogue Scale (VVAS) could help evaluate the degree of visual dependency in MdDS patients; the

association of these results with brain alterations could be made before and after treatment.

As reported in Chapter 3 Persistent postural-perceptual dizziness (PPPD) [96] is not necessarily a comorbidity, but a differential diagnosis from MdDS. Although both entities share an overlap in similar features, they differ in one important feature: symptoms during re-exposure to motion. While MdDS patients experience symptom alleviation when re-exposed to motion [21], this can worsen symptoms for PPPD patients [96] (see Chapter 3 for details). The new diagnostic guidelines proposed, consider this element of temporary relief in passive motion as a distinguish factor for MdDS patients, which can help discriminate MdDS from other vestibular disorders and motion sickness [50].

When considering hormonal studies in MdDS female patients, it is important to screen patients for co-morbidities, as reported in Chapter 4. Patient's hormonal profile (e.g. affected by Hypothyroidism etc.) should be defined before to draw any conclusion.

8.2.5 Risk factors

Currently, it remains unclear why MdDS is developed within a specific time frame. More specifically, as discussed in Chapter 4 and 5, our studies suggested that a particular hormonal phase (e.g. menopause or perimenopause) or age could be considered as potential risk factors to develop MdDS. It has been shown that the cholinergic and serotonergic systems are biological mediators of hormonal influences on the brain [219], therefore it is possible to hypothesised that hormonal changes may be interrelated within MdDS pathophysiology. These findings suggest that a more precise analysis of the patient's hormonal status during onset should be considered. The menopausal hormonal changes can modulate neuronal activity and as such, contribute to age-related memory loss and the development of neuropsychological disorders [219]. For future studies, neuroimaging research aiming to investigate neurotransmitters could help to address such question.

8.3 Future perspective

8.3.1 Overview on MdDS pathophysiology

Theory 1

As presented in Chapter 2, one of the hypotheses regarding MdDS pathophysiology was developed through neuroimaging and neuromodulation studies on human subjects. According to theory 1, MdDS patients report abnormal functional connectivity driven by a central neural oscillator that becomes entrained during periodic motion exposure. Functional connectivity reductions in MdDS subjects, who have responded favourably to neuromodulation, indicate that MdDS may be a disorder of over-synchronization of brain networks (For more details please refer to Chapter 2).

Theory 2

Following another theory, MdDS is believed to be a consequence of maladaptive coupling of multiplanar information of the vestibular ocular reflex (VOR) [53]. As reported in chapter 2 and 5, this theory was developed through animal research in subhuman primates [78, 220]. Based on this theory, a treatment scheme involving the recalibration of the using optokinetic stimulation has been developed [53] (see Chapter 5 for details).

Ultimately, the two hypotheses presented may not be mutually exclusive. It is possible that if VOR coupling was a brainstem manifestation of MdDS, a cortical manifestation may be enhanced functional connectivity. This remains to be empirically shown, however. The current literature, which describes the clinical profile, potential treatments and initial results from imaging studies on MdDS, has raised several key questions that could be answered by future neuroimaging investigations. As such, we have presented some of the main questions that could be addressed with the use of neuroimaging techniques in future studies.

8.3.2 Questions that remain to be addressed

- Question 1 (Q1): "What brain alterations are associated with MdDS and what is the specific role of the EC/amygdala complex in motion perception and adaptation?"

MdDS patients reported an over-synchronization, which may have been driven by entrainment to background low-amplitude oscillating environments, such as experienced on water [49]. The substrate of the entrainment process has been proposed to be the entorhinal cortex (EC), a central hub of spatial information processing located in the medial temporal lobe which has been shown to exhibit entrainability, toggle between high and low states, and is positioned to drive large scale neural networks through its extensive connectivity. The left EC has been shown to be hypermetabolic in MdDS patients through fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging [23]. MdDS has thus been proposed as a condition of abnormally high long-range resting-state functional connectivity that is driven by this central oscillator. Specifically, this high resting-state functional connectivity occurs in sensory-processing areas, with associated MdDS symptoms attributed to the inability to desynchronize brain networks that have become abnormally yoked [49]. However, up

to date, it remains unclear whether the metabolism of these limbic regions changes as a function of symptom changes.

- Question 2 (Q2): "How are symptom variations over time and therapeutic effects related to the brain alterations seen in MdDS patients?"

A previous study has investigated functional connectivity measures that were related to changes in symptoms [66, 221]. By combining high-density EEG and fMRI, it has been revealed that specific regions in the posterior parietal and occipital cortices exhibited coupled changes with the changes in MdDS symptoms [221]. More recently, it has been shown that improvements in MdDS symptoms, treated with rTMS over the bilateral DLPFC, correlated most strongly with a post-treatment reduction in functional connectivity between the left EC and precuneus, the right inferior parietal lobule, and the contralateral EC, part of the posterior default mode network [67].

Additionally, individuals with MdDS report symptom fluctuations throughout the day, as well as improvement when being re-exposed to passive motion [47]. Symptom fluctuations with menses have also been shown (see Chapter 4). In line with RQ1, future studies might aim to further focus on this specific aspect, perhaps with real-time brain connectivity monitoring, since it can provide more insight into inter-subject variability in MdDS symptoms and in treatment response. Ultimately RQ1 and RQ2 should be united, ideally a series of neuroimaging studies should be performed prior or after an intervention, with a time of interval of 6 months. In this time frame real-time brain connectivity monitor could be used to assess potential changes weekly or monthly.

- Question 3 (Q3): “Can the VOR maladaptation theory induce neural changes (by affecting the velocity storage), which are detectable by neuroimaging studies?”

Over the last decade, neuroimaging studies that have included functional magnetic resonance imaging (fMRI) and Electroencephalography (EEG) have attempted to unravel the underlying neural basis of MdDS [23, 64, 221]. MdDS patients exhibit alterations in gray matter volume in visual-vestibular processing areas (e.g. V5/MT), in the default mode network (e.g. the cingulate cortex), in the somatosensory network brain regions (e.g. the postcentral gyrus), and the central executive network (dorsolateral prefrontal cortex; DLPFC) [64]. Resting-state fMRI (rsfMRI) studies have shown an increased functional connectivity between the left EC/amygdala and visual and vestibular processing areas in the setting of decreased connectivity in multiple prefrontal areas [23]. Future rsfMRI may be extended to assess whether these are cortical manifestations of successful treatment with VOR decoupling manoeuvre. Altered functional connectivity may potentially be related to the changes of the velocity storage since it is known that the velocity storage mechanism is modulated by the vestibulo-cerebellum interaction, specifically by the nodulus and the ventral uvula [22]. As a result, lesions of these structures result in an impaired ability to realign the eye velocity vector towards the gravito-inertial acceleration vector. Cerebellar influence on cerebral resting state networks may be impacted by vestibulo-cerebellar pathways.

- Question 4 (Q4): “What are the risk factors for developing MdDS?”

It is known from previous studies that MdDS affects more women than men [60]. As such, age and hormonal status should be taken into account and considered as potential risk factors for developing MdDS. As observed in Chapter 5, most of the MdDS patients examined were either menopausal or perimenopausal, suggesting a potential hormonal implication in the pathophysiology of MdDS. It could be possible that age or hormonal status may be more determinative in the development of MdDS than the actual conditions of the motion [49], which could explain why SO patients report the same symptoms without being exposed to a motion event. This argument is also supported by the fact that temporary land sickness is a common phenomenon in both men and women, while persistent MdDS is more common in women. Thus, individual variables that prevent the adaptation to motion from readapting, through a new adaptive process, when returning to stable conditions may be more relevant to the development of MdDS than the motion conditions themselves [49]. Future neuroimaging studies involving positron emission tomography (PET) could focus on hormonal receptors, e.g. estrogen receptors [222] in order to assess potential alterations in MdDS patients. Additionally studying neurotransmitter indirectly affected by hormones, such as for example GABA concentration [148], could lead to a greater insight of the overall function of the hormones on the brain. These data could be related to hormonal parameters and to symptom scales. Gaining information about whether hormonal levels correlate with brain alterations found in MdDS patients and, perhaps more practically, whether further treatment should consider these hormonal fluctuations on therapeutic choices may be of great relevance to ease MdDS symptoms and develop successful treatments.

- Question 5 (Q5): “What is the role of the associated features and comorbidities typically seen in MdDS?”

MdDS patients tend to develop kinesiophobia (i.e. the fear of movement) and fatigue [57]. Therefore, these aspects might be confounding variables in neuroimaging studies and should be taken into account. In addition, individuals with MdDS have high comorbidities with migraine, increased visual sensitivity, and mood disorders, e.g. depression and anxiety [21, 47]. Visual sensitivity and MdDS should be closely evaluated, as a similar underlying pathophysiology may be present.

In addition to this, a longitudinal investigation of 122 patients with Chronic Subjective Dizziness (CSD) (currently renamed as PPPD [96]) and anxiety demonstrated three possible patterns of correlations between oto-neurological illnesses and anxiety disorders [107]. As reported in Chapter 3 and 5, anxiety is highly prevalent among MdDS patients. High level of anxiety has been found to match with aberrant stress response. The association with stress following high levels of anxiety and living with a chronic condition should also be further investigated, since it is known that ultimately stress can exacerbate MdDS symptoms [21]. Often anxious patients report a high cerebrospinal fluid level of corticotrophin releasing hormone and serum cortisol and disproportionate amygdalar responses, thus anxiety and stress are interrelated.

An important mediator for the cognitive and emotional effects of stress is Corticotropin-Releasing Hormones (CRH). CRH is synthesized in the hypothalamus and regulates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which in turn is responsible for the release of adrenocortical steroids, initiating many of the autonomic, immunological and behavioural responses to stress. The amygdala is a major extra-hypothalamic source of CRH-containing neurons; amygdala neurons express both CRH type 1 and type 2 receptors [118]. CRH is released into the amygdala during stress, consequently activating the local CRH receptors. The activation of CRH in

the amygdala seem to be involved in modifications of affective behaviour, and also, in the synaptic plastic changes that occur in this brain region in response to stress [118]. Thus, if considering the amygdala has been described as a key area involved in MdDS pathophysiology [64], it is essential to assess how stress may influence the amygdala.

An easy tool to assess stress is thought the test of cortisol, the principal hormone product of the Hypothalamic Pituitary Adrenal Axis (HPA), a closed loop endocrine system [223]. Cortisol is secreted naturally following the circadian rhythm (basal cortisol) and it is also secreted periodically as a response to perceived stress. As a result, it is often used as a predictive value of HPA-axis dysfunction. Recent findings from Redfern et al [224] have shown that patients reporting anxiety are also prone to visual sensitivity and to respond differently to visual sensory conflict tasks. By taking this into account, defining the neuroendocrine profile of MdDS patients (e.g. through cortisol assessment) is a potential non-invasive method to investigate any aberrant stress responses in MdDS patients. We hypothesize that MdDS patients may have an aberrant stress system, which is particularly important since neuroendocrine parameters, such as cortisol, have been associated with functional connectivity [225]. Neuroendocrine data such as cortisol, could be related to MRI data.

- Question 6 (Q6): “Cognitive impairment in MdDS patients?”

In addition to self-motion as described in Chapter 2, MdDS patients report a myriad of other symptoms, such as mental fatigue, cognitive impairment and brain fog [47, 52]. Up to now, MdDS cognitive impairment has never been quantified. Future studies should consider to screen MdDS patients during high and low symptoms levels, for example using Addenbrooke's Cognitive Examination (ACE-R) or other screening test involving multiple key abilities [226]. Secondly, cognitive parameters could be related to volumetric MRI or PET studies, which are often performed to assess or monitor mild cognitive impairment [227]. Gaining more information about the cognitive status of patients can help in modulating effective treatment to support patients, as well as provide further insights on the effect of MdDS on the wellbeing of the patients.

8.3.3 What to consider when performing neuroimaging studies on MdDS

Neuroimaging Challenges:

Magnetic Vestibular Stimulation (MVS): An important aspect to mention when considering neuroimaging studies on vestibular patients is the magnetic vestibular stimulation (MVS) phenomenon. It is well known that strong magnetic fields like the one used during magnetic resonance imaging studies are able to induce vertigo sensations in humans [228]. MVS occurs due to Lorentz forces, which are the result of the interaction between the magnetic field itself and the natural occurring ionic currents in the labyrinthine endolymph fluid. A recent study showed that the endolymph could potentially induce nystagmus as a result of the MVS, as it delivers ionic current and fluid pressure, affecting the cupula [228]. The trend to use stronger magnetic fields may worsen the effect of stronger Lorentz forces. Neuroimaging studies performed on MdDS patients have not reported MVS among the subjects tested. Eye tracking with an external camera was performed during an fMRI study at 3T [23] but no nystagmus was reported. Whether nystagmus could have been present with eyes open in the dark, monitored with a scleral coil, which is possible, remains a theoretical issue. Data on over-synchronization as a function of MdDS symptoms has mostly been based on EEG, however, which has been consistent with fMRI indicating that MVS is not the major driver of fMRI findings in MdDS [54, 221].

Case-control matching:

Ideally, a patient and control group should be matched for as many variables as possible. Age, gender, and handedness should be considered the absolute minimum in neuroimaging studies. However, for MdDS specifically, depression and anxiety levels should also be matched (e.g. by means of the Hospital Anxiety and Depression Scale, HADS [229] or the Beck Depression Inventory [230]), as it is known that there is a high depression/anxiety comorbidity in MdDS patients [47]. In addition, the Panic Disorder Severity Scale (PDSS) [231] could be implemented. Furthermore, fatigue should be matched for when possible, as previous studies have already shown that chronic illnesses and MdDS specifically can lead to increased levels of fatigue [57]. This could be done, for example with the Fatigue subscale of the Functional Assessment of Chronic Illness Therapy questionnaire [232].

For neuroimaging and neuroendocrine studies, it may also be relevant to match the level of physical activity in control and patient groups. It is known that MdDS patients, and neurological and vestibular patients in general, tend to develop kinesiophobia [57]. As such, this might induce non-disease specific differences in structural and functional properties of the brain, which similarly may be differently affecting the release of neuroendocrine hormones. This is especially true for MdDS patients, as there is often a long time interval between symptom start and diagnosis [21]. A possible tool to quantify activity level would be the Global Physical Activity Questionnaire (GPAQ) [233] and the Tampa Scale for Kinesiophobia (TSK) [234].

Conclusion:

Overall several questions remain to be addressed, the integration of new techniques such as neuroimaging or real-time brain connectivity monitoring hold great promise for the study of MdDS. Although progress can be impeded by particular challenges posed when studying these patients. By summarizing some of the key questions to be addressed and the related challenges, we hope to enhance and guide future studies and particularly neuroimaging studies, which were not conducted in this research, but should be explored further to disentangle the pathophysiology of MdDS. Despite considerable challenges, neuroimaging offers the prospect of a greater understanding of MdDS as a central nervous system disorder, as well as a platform for the further extension and improvement of therapeutic strategies to treat MdDS symptoms.

9. CHAPTER 9 SUMMARY & CONCLUSION:

- Summary
- Conclusion

9.1 Summary:

Chapter 1

In Chapter 1 an overview of the vestibular system is provided. The vestibular system contributes to our sense of orientation and movement in space, via the integration of vision (ocular reflexes), proprioceptors and inner ear inputs. The vestibular organs located in the inner ear are presented as well as the main reflexes such as the vestibular ocular reflex (VOR). In addition to this, the integration of multiple signals in the central nervous system is also described. An overview of the most relevant central regions for vestibular processing is provided.

In addition to this, for the specific purpose of this thesis, Chapter 1 provides also a brief summary on female gonadal hormones and ovarian cycle. This section aims to provide more insights about female hormonal fluctuations to the reader, as female hormones are widely discussed in the thesis.

Chapter 2

In Chapter 2 Mal de Debarquement Syndrome (MdDS) is introduced.

We presented Mal de Debarquement, a temporal form of “sickness from disembarkment”, with a brief history overview of when these symptoms were first described. After that, the main features of Mal de Debarquement Syndrome, such as the self-motion chronically perceived by the patients and the associated symptoms like migraine, brain fog and visual sensitivity are reported. Two different onsets (Motion Triggered /MT; Spontaneous /SO) types are also discussed in this section.

Lastly, in this chapter a brief introduction to the current theories regarding MdDS pathophysiology and following treatment options are presented.

Chapter 3

The aim of Chapter 3 was to increase the current understanding of the main features of MdDS, current diagnostic procedures, secondary mood disorders and the effect of stress on patients. To gain a large number of respondents, we created a multicentre international survey, which run across USA, Europe and Australia. The results collected represented the largest dataset ever recorded on MdDS patients.

In this chapter we identified a common feature for both onset groups: the temporal relief of symptoms when re-exposed to passive motion. This unique feature was integrated in two new diagnostic guidelines that included both onset groups. Additionally we reconfirmed the great impact that MdDS has on patient's lifestyle, as previously observed in other studies. We also reported that anxiety among MdDS subjects developed after onset and that stress was perceived as a trigger to aggravated MdDS symptoms. Thus, new theories between the implications of the stress system and MdDS were formulated.

Chapter 4

We investigated whether gonadal hormones influence MdDS pathophysiology and/or symptomatology. We presented the data collected through a retrospective online survey on male and female patients from both MT and SO onset groups. From our findings, it was clearly reported that symptoms were aggravated during menstruation and around the mid cycle in female MT subjects. We proposed a new theory where symptoms in female MdDS patients may be aggravated by estrogen withdrawal, observed at these specific period of the menstrual cycle, similarly to what described for migraineous patients. In addition to this our main findings suggested that a higher number of SO respondents reported to have irregular menses compared to MT participants. Patients were also asked about migraine, and it resulted that migraine was more prevalent after MdDS onset. Similarly participants were enquired about motion sickness and most participants were not significantly affected by motion sickness prior to their MdDS onset. This suggests that migraine and motion sickness may not be predisposing factors for developing MdDS.

In the second section of Chapter 4, we ran for the first time a study specifically designed for pregnant MdDS subjects. From the data collected, most participants reported an improvement of symptoms during the 9 months of pregnancy. This is potentially the result of the absence of estrogen withdrawal and high levels of estrogen and progesterone, which may alleviate MdDS symptoms.

Chapter 5

In Chapter 5 a clinical trial to assess one of the few treatments available for MdDS subjects is described. The treatment considered was based on optokinetic stimuli (OKN) in combination with head roll (rolled at customised frequency), and it was performed for five consecutive days. This treatment protocol was first assessed in 2014 by Dai and colleagues and for the first time we reproduced it and further evaluate its validity.

Additionally, we assessed if patients were subjected to a placebo effect and if the standardization of the protocol could lead to the same beneficial effects previously described. We were able to prove that 48% of the patients benefitted from the treatment, with a decrease or complete remission of self-motion symptoms (e.g. rocking, swaying), the majority were MT subjects. More research is needed to assess if a potential pathophysiological difference may be present between MT and SO, which could explain why SO patients responded differently to this treatment. No placebo effect was recorded in this setting and a standardization of the procedure (fixed head frequency at 0.165Hz) did not influence the treatment outcome. Our main findings were that the positive effects of the exposure to OKN stimuli in combination with head roll appeared within the first three days of treatment, suggesting that a shorter treatment protocol is possible. When examining patients after a three months follow-up, migraine and visual heightened sensitivity were reported in most of the patients, indicating that the OKN treatment may be able to ease only some of the symptoms. Similarly to what was reported in Chapter 4, also in this trial we encountered a female preponderance. Most of the patients reported to be in menopause or perimenopause, in line with previous findings.

Additionally, from the younger female patients, it was highlighted that onset occurred while menstruating, also perimenopausal subjects described being on their last menstrual period when travelling, suggesting the implication of hormonal fluctuation while travelling as a potential risk factor for developing MdDS. We believe that our investigation will encourage other clinics to implement a similar non-invasive and short protocol, even if it can only partially ease MdDS complaints. Our research will also stimulate clinicians to further consider the hormonal changes in women affected by MdDS.

Chapter 6

We evaluated vestibular patients that similarly to MdDS sufferers reported visual motion sensitivity, also named Visually Induced Dizziness (VID) in Chapter 6. We proposed a combination of optokinetic stimuli (in the form of a rotating disk) in combination with customized exercises and behavioural/lifestyle changes. Most of the VID subjects engaged in this study had trialled other vestibular rehabilitations or pharmacological therapies with no real success.

Most patients, despite developing VID symptoms after different primary vestibular insults or disorders, (e.g. vestibular neuritis, vestibular migraine), reported a reduction in the heightened visual dependency after our intervention.

Similarly to what reported for MdDS in Chapter 4, a great female predominance was also observed in the VID group. Most women were in their reproductive years and reported an aggravation of symptoms during menses. The underlying hormonal interaction equally affecting VID and MdDS patients, may suggest a hormonal implication across different vestibular disorders.

With regards to the OKN protocol, we hypothesised that a similar protocol could be successfully implemented to ease secondary symptoms in those MdDS patients that have cured their self-motion symptoms but retained visual motion sensitivity.

Chapter 7

In Chapter 7 a brief discussion of the main findings of each study was reported. The study aims and main key findings were summaries in this Chapter. Moreover, the most relevant aspects that made these results clinically relevant were discussed.

Chapter 8

Limitations and difficulties encountered throughout the different studies were reported and discussed in Chapter 8. A summary of the main challenges in performing studies on MdDS patients and potential solutions were also described. The last section of this chapter reported future potential studies and questions that remained to be addressed, strengthening the need for more studies also focusing on neuroimaging research.

9.2 Conclusion:

This dissertation focused on addressing four main research questions and to provide guidance for future studies on Mal de Debarquement Syndrome (MdDS).

Our first purpose was to increase the knowledge on MdDS clinical features: to evaluate associated mood disorders, diagnostic procedures and common misdiagnoses. We also aimed to define similarities and differences between the two onset subtypes.

Via an international collaboration we were able to gain the largest dataset ever collected on MdDS subjects using a series of retrospective questionnaires. Our results were in line with the literature by reporting a high level of anxiety among MdDS patients and high levels of frustration, with associated mood disorders. In addition to this, an aggravation of symptom in response to stress was also reported in our study, as often observed in other chronic disorders. In this survey, both onset groups reported a temporary relief of symptoms when re-exposed to passive motion. We highlighted that this factor should be considered a key component in distinguishing MdDS patients from those with other chronic vestibular conditions. Thus, we proposed new comprehensive guidelines that include both MdDS onsets (MT and SO), as well as a new theory on the potential effect of stress on MdDS patient symptomatology.

The second purpose of this thesis was to assess a potential gonadal hormonal influence on MdDS onset and symptomatology. MdDS is known to be more prevalent in female patients, yet there were no investigations into the influence of gonadal hormones on MdDS symptomatology and pathophysiology. With the retrospective surveys performed in this study, we were able to show an interrelation between hormonal fluctuations and symptom changes in female MdDS patients, particularly in the MT group. These results are novel and have not been demonstrated before. MT patients reported symptom

aggravation during menses and mid cycle. Thus, we described a potential hypothesis, which requires further evaluation. We hypothesized that the estrogen withdrawal, occurring during menses, may trigger an increase in MdDS symptoms. We also gained valuable information about female MdDS patients, for example that onset age should be further evaluated as a risk factor, matching with menopausal and perimenopausal phases. In addition to this, for the first time we also collected data from MdDS women, who had been pregnant or were currently pregnant while having MdDS symptoms. The study was performed by means of a retrospective questionnaire. During the 9 months of pregnancy a great number of women affected by MdDS reported an improvement in symptoms. In support of the estrogen withdrawal theory during pregnancy, the absence of cyclic hormonal fluctuations and the high level of estrogen and progesterone were hypothesised to influence the reduction of MdDS symptoms. The retrospective aspect of these questionnaires posed a limitation to our studies. Consequently, our data should be considered novel but also preliminary. Nevertheless, these studies provide a base where future research can be built upon.

The third aim of this research project was to evaluate a potential treatment. Given the lack of understanding of the pathophysiology of MdDS, treatment options are currently limited. We explored one of the few treatments currently proposed, based on optokinetic (OKN) stimulation in combination with head roll. From the clinical trial performed, we proved that the OKN treatment based on moving stripes and head roll at a fixed frequency of 0.165Hz can ease MdDS symptoms and improve postural stability in MdDS patients. This makes the OKN treatment easier to be replicated, as more standardised. MT patients, in line with previous research, responded better to this intervention. The different response, of SO and MT patients to the OKN treatment, suggests a potential difference in the pathophysiology between MT and SO MdDS

subtypes. Further research is encouraged. Within this clinical trial, similarly to what was reported in Chapter 4 a female predominance was also recorded, and most women were menopausal or perimenopausal. This data supports the hormonal theory described in Chapter 4, where hormone levels in female subjects may be a potential risk factor for developing MdDS.

In addition to this, following the OKN treatment, additional secondary symptoms were identified such as associated migraine and visual motion sensitivity, also in patients who reported an improvement of MdDS self-motion symptoms. This could underlie the complex nature of MdDS, where not only self-motion complaints should be considered.

The fourth aim of this thesis was to report a potential treatment for helping MdDS patients with visual motion sensitivity also named as Visually Induced Dizziness (VID).

We assessed a rehabilitation protocol based on desensitizing patients through OKN stimulation, customized vestibular rehabilitation and behavioural changes. This protocol proved to be beneficial for vestibular patients (with diverse primary vestibular disorders) reporting VID symptoms. As a result, we hypothesised that a similar protocol may ease MdDS patients who retained visual motion sensitivity. Additionally, for the first time, female VID patients were enquired about symptom fluctuations throughout their menstrual cycle. Most of the VID subjects reported symptom aggravation during menses, similarly to the MdDS subjects. Thus, the hormonal changes observed throughout the monthly cycle may affect equally both MdDS and other vestibular disorders with VID symptoms.

Lastly, this thesis evaluated the current limitation encountered within the various research project described. A series of main challenges were also described with potential solutions based on problem solving strategies explored throughout the years of research, such as patient recruitment, sample size and considering patient co-morbidities. In the final part of this thesis the next stepping-stones to address some of the pending questions related to MdDS pathophysiology are reported, with a strong focus on neuroimaging. Among the numerous questions remaining to be addressed, some to consider are: *the role of the entorhinal cortex (EC) in the relief of symptoms during motion re-exposure, and if metabolism of limbic brain regions modulate according to patients symptom fluctuations.*

Additionally, if considering MdDS as a maladaptation of the VOR, it would be essential in order to prove this theory further, to assess if changes in the VOR and velocity storage are detectable by neuroimaging.

Moreover, as proven from our studies, MdDS pathophysiology and/or symptomatology seems to be partially influenced by hormonal changes, thus future studies should focus on the hormonal influences on neurotransmitters (e.g. GABA) and how to correlate them to MdDS symptoms. Following these studies, hormonal therapeutic strategies should be assessed in female MdDS patients.

As a result, to fully understand the impact of MdDS on patient's social and working life, future studies should assess cognitive impairment, which has been reported by MdDS subjects. Knowing more about the real consequences of MdDS on the cognitive performances of patients could help to develop effective countermeasures.

The work presented in this thesis, despite being preliminary, has helped us gain more insights into such a new disorder. The difficulties faced by patients affected by what is considered to be a rare disorder has been presented and supported with these studies, such as high level of anxiety, drastic changes in lifestyle and secondary mood disorders. We hope that this work will lead to a reduction in the number of MdDS patients currently misdiagnosed and overall to better patient management. Based on the findings presented and discussed in this dissertation, from a diagnostic perspective, it can be generally concluded that MdDS is a complex disorder, and thus, multiple aspects should be considered to improve patient care. MdDS should be approached with a broad spectrum and the collaboration from different healthcare professionals is essential. Ideally a team with different expertise, such as gynaecologists, physiotherapists, neurologists and otorhinolaryngologists should follow MdDS patients.

With regards to hormonal assessment, our investigations on hormonal fluctuations with MdDS symptomatology and pathophysiology may pave the way for new research and treatment strategies for female MdDS patients. Female patients should have access to gynaecologists, in order to evaluate their hormonal profile and if a correlation between hormonal changes and symptoms aggravation is present.

In Chapter 5, we presented our clinical trial on one of the few treatment options available, based on OKN exposure and head roll. By demonstrating that the OKN treatment for MdDS patient can be shortened and standardized, we hope more centres will adopt such technique for treating MdDS patients in clinical settings.

We concluded that this treatment is more effective for MT patients and that other symptoms like visual sensitivity remained also when the self-motion sensations were solved. Many questions have been raised from these studies; as a result the research on this topic should continue, especially involving neuroimaging techniques and larger samples of patients.

MdDS is currently considered a rare disease, however travelling is becoming a significant part of societies daily existence and being exposed to passive motion is a major trigger for MdDS patients; thus MdDS may not be as rare in the years to come. As it is predicted that the number of patients being diagnosed with MdDS rises, in line with the travel habits, it is essential to further research what causes MdDS. More efforts should be placed to understand its pathophysiology, as well as how to prevent MdDS in the first place and to how improve patient's care. Exploring MdDS further will be insightful in the understanding of other of conditions.

There is a common meme amongst rare conditions patients that we should 'treasure the exceptions' since what is learned from rare conditions brings added knowledge to more common disorders.

"MdDS is a good example of this, since it is the natural result of the human brain adapting to environmental motion and thus the quintessential neurological disorder (Quote from Dr. Cha)."

I hope that the work presented in this thesis will provide further ideas and data to build a new research line, for helping MdDS patients and that what is found out about MdDS will increase human knowledge about both balance and sensory processing conditions.

Figures used in Chapter 1 (Figure 1; 2; 4; 7) were made by Jeroen De Coninck and belong to the Ph.D. thesis of Angelique Van Ombergen. These figures are used with permission.

ANNEXES:

Annex 1 Chapter 3:

Supplementary Material

Questions analysed and discussed in this Chapter 3.

Motion Triggered (MT) Questionnaire

1. BASIC INFORMATION

1.2: Country/State/City:

1.3: Sex:

Male

Female

1.4: Date of Birth:

2. MDDS DIAGNOSIS

2.1: Who initially diagnosed you with MdDS:

Neurologist

Otolaryngologist

Physiotherapist

Self-diagnosed

Other [Free text box]

2.2: Who diagnosed you with MdDS after your initial diagnosis: (e.g. if you were self-diagnosed initially and received an official diagnosis subsequently) and was the specialist/health care professional confident in the diagnosis?

Neurologist

Otolaryngologist

Physiotherapist

- Other [Free text box]
- N/A as initial diagnosis was the only diagnosis
- N/A as self-diagnosed is the only diagnosis

2.3: How long did it take to get the diagnosis of MdDS from the onset of your symptoms?

- 1– 2 months
- 3 – 6 months
- 7–12 months
- 1– 2 years
- 2+ years
- 5+ years
- N/A Self diagnosed

2.4: If you have been diagnosed by a medical professional, provide an estimate of how many medical appointments you attended before your MdDS diagnosis (for example if you were sent to a physiotherapist, radiologist, etc.).

- 1
- 2-5
- 6-10
- 10-20
- 20-40
- 40+

2.5: If you are self-diagnosed, provide an estimate of how many medical appointments you have attended in the quest for an official diagnosis (for example if you were sent to a physiotherapist, radiologist, etc.).

- 1
- 2-5

6-10

10-20

20-40

40+

2.6: Prior to being diagnosed with MdDS, what other diagnoses have you received in response to your symptoms? Select all answers that apply:

Labyrinthitis

Inner ear infection

Depression

Anxiety

Posterior canal dehiscence

Brain tumour

Meniere's disease

Vestibular dysfunction

Vestibular migraine

Vertigo

Psychogenic vertigo

Persistent postural-perceptual dizziness (PPPD)

Benign paroxysmal positional vertigo (BPPV)

Other [Free text box]

2.7: Is there anything you would like to add about your MdDS diagnosis or any experience that you feel is appropriate to this section? [Free text box]

3. MDDS ONSET AND SYMPTOMS

3.1: To the best of your knowledge, what was the motion event that induced your MdDS? Select one answer:

Short cruise (less than a day)

- Long cruise (more than a day)
- Short airplane flight (<3 hours)
- Long airplane flight (>3 hours)
- Short Train ride (<3 hours)
- Long Train ride (>3 hours)
- Short Car ride (<3 hours)
- Long Car ride (>3 hours)
- Short Bus ride (<3 hours)
- Long Bus ride (>3 hours)
- Short Tram ride (<3 hours)
- Long Tram ride (>3 hours)
- Fairground/theme park ride
- Other [Free text box]

3.14: Are you prone to getting anxious or having depressive episodes?

- Before and after MdDS onset
- Before MdDS only
- After MdDS onset only
- No

3.15: Have you been diagnosed with depression?

- Yes, before MdDS onset
- Yes, after MdDS onset
- No

3.16: Have you been diagnosed with an anxiety disorder?

- Yes, before MdDS onset
- Yes, after MdDS onset
- No

3.17: Do you consider that your depressive or anxiety symptoms are a consequence of your MdDS?

Yes

No

4. SYMPTOM TRIGGERS

4.1: What are the triggering factors that would make your symptoms worse?

For each please select either (not a trigger / sometimes a trigger (producing moderate symptoms) / sometimes a trigger (producing severe symptoms) / always a trigger (producing moderate symptoms) / always a trigger (producing severe symptoms) for all triggers below: *the manuscript only discusses the STRESS responses

4.2: Do you feel that you have made lifestyle changes to avoid your triggers?

Yes, I feel like my lifestyle has significantly changed because of this condition

Yes, I feel like my lifestyle has somewhat changed because of this condition

No, I continue to live my life as per usual

No, this condition has little effect on my lifestyle

Spontaneous/Other Onset (SO) Questionnaire

1. BASIC INFORMATION

1.2: Country/State/City:

Annex 1

1.3: Sex:

Male

Female

1.4: Date of Birth:

2. MDDS DIAGNOSIS

2.1: Who initially diagnosed you with MdDS:

- Neurologist
- Otolaryngologist
- Physiotherapist
- Self-diagnosed
- Other [Free text box]

2.2: Who diagnosed you with MdDS after your initial diagnosis: (e.g. if you were self-diagnosed initially and received an official diagnosis subsequently) and was the specialist/health care professional confident in the diagnosis?

- Neurologist
- Otolaryngologist
- Physiotherapist
- Other [Free text box]
- N/A as initial diagnosis was the only diagnosis
- N/A as self-diagnosed is the only diagnosis

2.3: How long did it take to get the diagnosis of MdDS from the onset of your symptoms?

- 1–2 months
- 3–6 months
- 7–12 months
- 1–2 years
- 2+ years
- 5+ years
- N/A Self diagnosed

2.4: If you have been diagnosed by a medical professional, provide an estimate of how many medical appointments you attended before MdDS was diagnosed (for example if you were sent to a physiotherapist, radiologist, etc.).

1

2-5

6-10

10-20

20-40

40+

2.5: If you are self-diagnosed, provide an estimate of how many medical appointments you have attended in the quest for an official diagnosis (for example if you were sent to a physiotherapist, radiologist, etc.).

1

2-5

6-10

10-20

20-40

40+

2.6: Prior to being diagnosed with MdDS, what other diagnoses have you received in response to your symptoms? Select all answers that apply:

Labyrinthitis

Inner ear infection

Depression

Anxiety

Superior / Posterior canal dehiscence

Brain tumour

- Meniere's disease
- Vestibular dysfunction
- Vestibular migraine
- Vertigo
- Psychogenic vertigo
- Persistent postural-perceptual dizziness (PPPD)
- Benign paroxysmal positional vertigo (BPPV)
- Other [Free text box]

2.7: Is there anything you would like to add about your MdDS diagnosis or any experience that you feel is appropriate to this section? [Free text box]

3. MDDS ONSET AND SYMPTOMS

3.1: Do you think your MdDS was triggered by an event, which was not motion, for example: trauma, concussion, childbirth, strong emotion (other onset); or did the onset of your MdDS seem to have no obvious cause (spontaneous onset)? Your answer will direct to you specific 'other' or 'spontaneous' onset questions.

I think that my MdDS onset was triggered by an event which is not considered passive motion. ('other')

I think that I had a spontaneous MdDS onset, as I cannot recall a specific event. (spontaneous)

FOR SUBJECTS ANSWERING 'OTHER':

OTHER event 3.2: To the best of your knowledge, what was the event that induced your MdDS?

- Concussion
- Trauma (physical or psychological)
- Childbirth
- Pregnancy

Strong Emotion

Other [Free text box]

OTHER event 3.5: Were you under a lot of stress when symptoms first appeared?

Yes

No

Not sure

OTHER event 3.6: Were you depressed when symptoms first appeared?

Yes

No

Not sure

OTHER event 3.23: Are you prone to getting anxious or having depressive episodes?

Before and after MdDS onset

Before MdDS only

After MdDS onset only

No

OTHER event 3.24: Have you been diagnosed with depression?

Yes, before MdDS onset

Yes, after MdDS onset

No

OTHER event 3.25: Have you been diagnosed with an anxiety disorder?

Yes, before MdDS onset

Yes, after MdDS onset

No

OTHER event 3.26: Do you consider that your depressive or anxiety symptoms are a consequence of your MdDS?

Yes

No

FOR SUBJECTS ANSWERING 'SPONTANEOUS':

SPONTANEOUS 3.4: Were you under a lot of stress when symptoms first appeared?

Yes

No

Not sure

SPONTANEOUS 3.5: Were you depressed when symptoms first appeared?

Yes

No

Not sure

SPONTANEOUS 3.17: Do you feel better or normal when you are riding in a car?

Yes

No

SPONTANEOUS 3.21: Are you prone to getting anxious or having depressive episodes?

Before and after MdDS onset

Before MdDS only

After MdDS onset only

No

SPONTANEOUS 3.22: Have you been diagnosed with depression?

Yes, before MdDS onset

Yes, after MdDS onset

No

SPONTANEOUS 3.23: Have you been diagnosed with an anxiety disorder?

Yes, before MdDS onset

Yes, after MdDS onset

No

SPONTANEOUS 3.24: Do you consider that your depressive or anxiety symptoms are a consequence of your MdDS?

Yes

No

4. SYMPTOM TRIGGERS

BOTH SPONTANEOUS AND OTHER:

4.1: What are the triggering factors that would make your symptoms worse?

For each please select either (not a trigger / sometimes a trigger (producing moderate symptoms) / sometimes a trigger (producing severe symptoms) / always a trigger (producing moderate symptoms) / always a trigger (producing severe symptoms) for all triggers below: *the manuscript only discusses the STRESS responses

4.2: Do you feel that you have made lifestyle changes to avoid your triggers?

Yes, I feel like my lifestyle has significantly changed because of this condition

Yes, I feel like my lifestyle has somewhat changed because of this condition

No, I continue to live my life as per usual

No, this condition has little effect on my lifestyle

Annex 2 Chapter 4.1:

Questions analysed and discussed in Chapter 4.1

Motion Triggered (MT) Questionnaire

1. BASIC INFORMATION

1.2: Country/State/City:

1.3: Sex:

Male

Female

1.4: Date of Birth:

5. HORMONAL INFLUENCES

FEMALE Q:

5.1: Have you gone through menopause?

Yes

No

If yes to menopause

5.2: Are you on Hormone Replacement Therapy (HRT)?

Yes, combined HRT

Yes, oestrogen-only HRT

No

Other [free text box]

If no to menopause

5.3: To the best of your knowledge, were you menstruating during the motion event that you believe initiated your MdDS?

Yes

No

Not sure

If no to menopause

5.4: Do you feel that your symptoms are worse in the days surrounding menstruation and ovulation (which is usually ~ 2 weeks before your period)?

Yes

No

Not sure

If no to menopause

5.5: Do you feel more sensitive to your triggers in the days surrounding menstruation and ovulation (which is usually ~ 2 weeks before your period)?

Select one answer:

Yes

No

Not sure

If no to menopause

5.6: Are your periods usually regular?

Yes

No

If no to menopause

5.7: Are you on any form of hormonal contraception? I.e. Oral contraceptive pill, nuvaring, hormonal patches, implanon)

Yes, combined Oestrogen + Progesterone hormonal contraception

Yes, Progesterone only hormonal contraception

No

If no to menopause

5.8: Were you on any form of hormonal contraception during the motion event that you believe caused your MdDS? I.e. Oral contraceptive pill, nuvaring, hormonal patches, implanon)

Yes, combined Oestrogen + Progesterone hormonal contraception

Yes, Progesterone only hormonal contraception

Yes, but was taking the placebo/sugar pill at that time

No

Not sure

5.9: Do you have Polycystic Ovarian Syndrome (PCOS)?

Yes

No

5.10: Do you have any hormonal imbalances or conditions?

Yes, low testosterone

Yes, high testosterone

Yes, high oestrogen and progesterone

yes, high oestrogen only

yes, high progesterone only

Hypothyroidism

Hyperthyroidism

No

Not sure

If yes to a condition

5.11: Are you on any medications for your hormonal imbalances or conditions?

Yes, please specify [free text box]

No

5.12: Are you pregnant or have you been pregnant whilst having MdDS?

Yes

No

MALE Q:

5.13: Do you have any hormonal imbalances or conditions?

Yes, low testosterone

Yes, high testosterone

Yes, high oestrogen and progesterone

yes, high oestrogen only

yes, high progesterone only

- Hypothyroidism
- Hyperthyroidism
- No
- Not sure

If yes to a condition

5.14: Are you on any medications for your hormonal imbalances or conditions?

- Yes, testosterone only HRT
- No
- Other [free text box]

FEMALE AND MALE Q:

5.15: Is there anything you would like to add about hormonal influences on your MdDS symptoms or any experience that you feel is appropriate to this section? [free text box]

Spontaneous / Other (SO) Questionnaire

1. BASIC INFORMATION

1.2: Country/State/City:

1.3: Sex:

- Male
- Female

1.4: Date of Birth:

HORMONAL INFLUENCES

Female and Male subjects will be re-directed to different questions. Female subjects will also be directed to different questions according to whether they are on a hormonal contraceptive or not.

5. HORMONAL INFLUENCES

FEMALE Q:

5.1: Have you gone through menopause?

- Yes
- No

If yes to menopause

5.2: Are you on Hormone Replacement Therapy (HRT)?

- Yes, combined HRT
- Yes, oestrogen-only HRT
- No
- Other [free text box]

If no to menopause

5.3: To the best of your knowledge, were you menstruating during the motion event that you believe initiated your MdDS?

Annex 2

- Yes
- No
- Not sure

If no to menopause

5.4: To the best of your knowledge, were you ovulating (~ 2 weeks prior to period) during the time your MdDS symptoms started?

- Yes
- No
- Not sure

5.5: Do you have Polycystic Ovarian Syndrome (PCOS)?

- Yes
- No

5.6: Do you have any hormonal imbalances or conditions?

- Yes, low testosterone
- Yes, high testosterone
- Yes, high estrogen and progesterone
- Yes, high estrogen only
- Yes, high progesterone only
- Hypothyroidism
- Hyperthyroidism
- Hypocortisol
- Hypercortisol
- No
- Not sure

5.7: Are you on any medications for your hormonal imbalances or conditions?

- Yes, please specify [free text box]
- No

5.8: Are you pregnant or have you been pregnant whilst having MdDS?

- Yes
- No

5.9: Do you take any hormonal contraceptive? If yes, please specify which one

- Yes [Free text box]
- No

(According to this answer the female subject will be re-directed to two different sections, one for those under hormonal contraceptive and one for those free from hormonal contraceptive).

FEMALE FREE FROM CONTRACEPTIVE:

5.9: Do you feel that your symptoms are worse in the days surrounding menstruation (3 to 4 days before your menstrual cycle)?

- Yes
- No
- Not sure

5.10: Do you feel that your symptoms are worse in the days surrounding ovulation (which is usually ~ 2 weeks before your period)?

- Yes
- No
- Not sure

5.11: Do you feel more sensitive to your triggers in the days surrounding menstruation and ovulation (which is usually ~ 2 weeks before your period)? Specify if worse during ovulation or menstruation

- Select one answer:

Menstruation:

Yes

No

Not sure

Ovulation:

Yes

No

Not sure

5.12: Are your periods usually regular?

Yes

No

5.13: Is there anything you would like to add about hormonal influences on your MdDS symptoms or any experience that you feel is appropriate to this section? [free text box]

FEMALE UNDER CONTRACEPTIVE:

5.14: Specify which hormonal contraceptive you are currently taking? (I.e. Oral contraceptive pill, nuvaring, hormonal patches, implanon)

Yes, combined Oestrogen + Progesterone hormonal contraception

Yes, Progesterone only hormonal contraception

Specify the brand and/or name ... [free text box]

5.15: Were you on any form of hormonal contraception during the time your MdDS symptoms started? I.e. Oral contraceptive pill, nuvaring, hormonal patches, implanton)

Yes, combined Oestrogen + Progesterone hormonal contraception

Yes, Progesterone only hormonal contraception

Yes, but was taking the placebo/sugar pill during the suspension/break week at that time

No

Not sure

5.16: Do you feel that your symptoms are worse during the days of suspension of the pill?

Yes

No

Not sure

5.17: Do you feel more sensitive to your triggers when off the contraceptive pill?

Yes

No

Not sure

5.18: Is there anything you would like to add about hormonal influences on your MdDS symptoms or any experience that you feel is appropriate to this section? [free text box]

MALE Q:

5.19: Do you have any hormonal imbalances? Select one answer:

- Yes, low testosterone
- Yes, high testosterone
- Yes, high estrogen and progesterone
- Yes, high estrogen only
- Yes, high progesterone only
- Yes, high prolactin
- Hypocortisol
- Hypercortisol
- Andropause
- Hypothyroidism
- Hyperthyroidism
- No
- Not sure

If yes to a condition

5.20: Are you on any medications for your hormonal imbalances or conditions?

- Yes, testosterone only HRT
- No
- Other [free text box]

5.21: Is there anything you would like to add about hormonal influences on your MdDS symptoms or any experience that you feel is appropriate to this section? [free text box]

Annex 3 Chapter 4.2:

Questions analysed and discussed in Chapter 4.2

1. BASIC INFORMATION

1.2: Country/State/City:

1.3: Sex:

Male

Female

**If Male subjects were automatically excluded.

1.4: Date of Birth:

1.7 Are you pregnant?

No

Yes

1.8 Do you have MdDS?

No

Yes

Symptoms:

2.1 Did you have MdDS prior your pregnancy?

No

Yes

2.2 When your symptoms started?

First two weeks you knew you were pregnant

3rd month of pregnancy

4th month of pregnancy

5th month of pregnancy

6th month of pregnancy

7th month of pregnancy

8th month of pregnancy

9th month of pregnancy

2.3 Are your symptoms better or worse or the same during the pregnancy?

No changes

<50% Better

>50% Better

<50% Worse

>50% Worse

2.4 Are your symptoms changing through out the months of pregnancy?

No

Yes

2.5 Is your mood influencing the symptoms?

No

Yes

2.6 When are you most dizzy during the day?

As soon as you wake up (6-9am)

Mid morning (11am)

Lunch time (12-2pm)

After lunch (2pm)

Mid Afternoon (4pm)

Before dinner (6pm)

After dinner (8-9pm)

Before to go to bed (9-11pm)

Gynecologist:

3.1 Did you speak about MdDS with your gynecologist?

No

Yes

If yes:

3.2 What did she/ he suggested?

Open Answer:

3.3. Were you undergoing a contraceptive hormonal therapy prior your pregnancy (meaning: contraceptive pill)?

No

Yes

If yes for how long:

Open-end Comments:

Annex 4 Chapter 5:

General Intake Information

1. Name:
2. Gender:
3. Age:
4. When have you been diagnosed with MdDS?

MdDS Symptoms

1. To the best of your knowledge, what was the motion event that induced your MdDS (e.g., cruising, boating, air flight, train)? *(Please specify onset date and if MdDS occurred spontaneously).*
2. Are your symptoms persistent or do your symptoms changes according to different days? *(Describe the fluctuations and if the changes are related to particular events: stress, menstrual cycle)*
3. Have you ever suffered from migraine?
4. Do you experience finnitus (ringing in the ears)?
5. Do you experience headaches? *(Please specify - frequent headaches, etc.)*
6. Have you noticed any triggering factor/s that makes your symptoms worse? *(Select: car ride, coffee or alcohol/ particular drinks, working on a computer, store lines in big shops, watching movies, weather changes, stress, busy days, etc.)*
7. Have you been diagnosed with depression? Yes/ No *(If yes, please specify when and treatment suggested)*
8. Do you feel more anxious since your MdDS appeared? Yes / No
9. Have you undergone Vestibular Rehabilitation for MdDS? Yes / No *(If Yes, please specify)*

10. Did you suffer from motion sickness before MdDS? (e.g.: Nausea, sweating, headache)

Questionnaires used from: Bos JE, MacKinnon SN PA (2005) Motion sickness symptoms in a ship motion simulator: effects of inside, outside, and no view. *Med, Aviat Space Environ*

Lifestyle:

1. Does your MdDS affect your employment? Yes / No
2. How much does MdDS impair your lifestyle? (Mention something you were able to do and now you have stopped or have difficulties in doing now)

Medications to ease MdDS Symptoms

1. List your current medications, why you take them, date you started them, response, and side effects (if any). Please specify what you have been given for MdDS symptoms.
2. List any past medications you were given for MdDS

Misery Scale Questionnaire from: Bos 2005.

Visual Analogue Scale:

How would you describe your symptoms?

no complaints

significant complaints

Hormonal questions:

Are you in Menopause? Yes/No (If yes please state since when:.....)

Are you in Perimenopause (entering menopause)? Yes/No (If yes please state since when:.....)

If you in your reproductive active years please state the last day of the last menstrual period (best estimate):

If taking contraceptive please state name of contraceptive used and since when:

Is your period regular?

Onset – medication / or menstruation while travelling:

Do you remember if during the “motion event” that triggered MdDS, you were under medications or where you having your menstrual cycle?

Annex 5 Chapter 6:

Intake VID questionnaire:

Name:

Gender:

Age:

- 1) Who diagnosed you with Visually Induced Dizziness (Neurologist, Otolaryngologist, PT, self)
- 2) Do you suffer from other balance or hearing symptoms (Meniere's Syndrome, Vertigo or Dizziness, Otosclerosis, Hearing loss, Balance Problems, Tinnitus..)?
- 3) Do you suffer from any additional pathological conditions or are you under any specific medication we should be aware of? (If under contraceptive please specify the type and duration)
- 4) Do you get dizzy by watching busy visual input (eg: Supermarket, Movie, Busy Places,)?
- 5) Do you get dizzy while watching at busy round about or if staring at traffic?
- 6) Have you noticed any trigger factor that makes your symptoms worst? (For example: car ride, coffee or alcohol/ particular drinks, working on a computer, store lines in big shops, watching movies, weather changes, stress etc)
- 7) Have you ever suffered from motion sickness? (eg: Nausea, sweating, headache)
- 8) Do you have migraine?
- 9) Have you ever suffered from migraine? (If so, which type: Vestibular Migraine, Menstrual Migraine, and Migraine)
- 10) Have you ever suffered from Sleep Disorders? (Please mention if you have ever been diagnosed with Obstructive – Central Sleep Apnea)
- 11) Do you feel ease while asleep?
- 12) How many hours do you sleep per night?
- 13) Do you feel anxious when getting dizzy by Visual Inputs? (Describe your mood and feelings in few words)
- 14) Have you undergone physical therapy for your condition? (eg: Vestibular Rehab)

Gynecological history:

Are you in menopause or perimenopause? (If yes specify from when:.....)

Is your period regular?

Do you report aggravation of symptoms during menses?

Visual Analogue Scale:

How would you describe your symptoms?

no complaints

significant complaints

Follow up symptoms:

Please state how your symptoms have been changing (good or bad) since the treatment?

Since the treatment, are you feeling dizzy when watching busy traffic intersections, scrolling your phone, walking in a supermarket?

Do you have brain fog since the treatment?

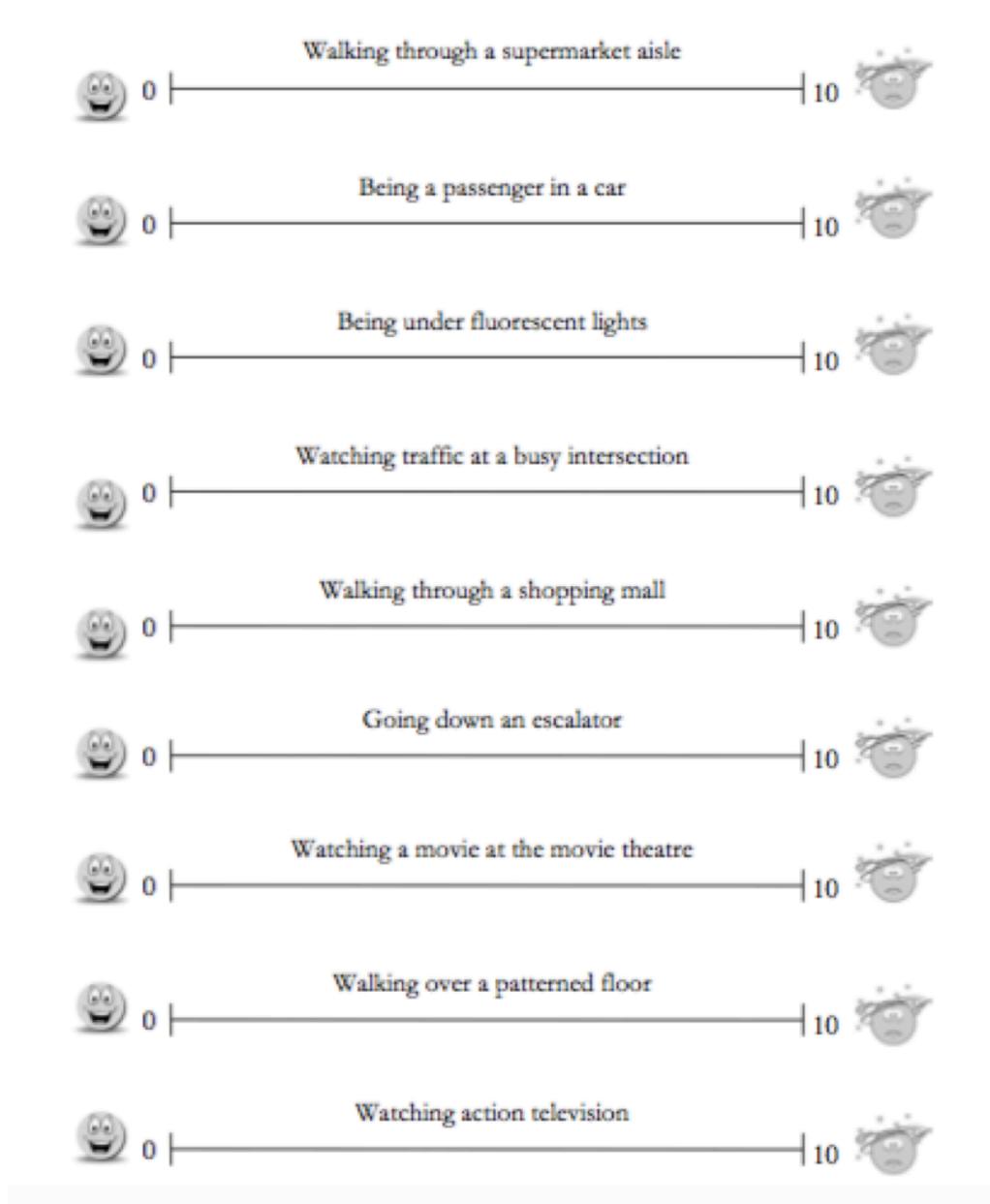
Do you have headaches since the treatment?

Do you suffer from migraine since the treatment?

Diagnostic:

VID patients were asked to complete the following questionnaires:

Visual Vertigo Analogue Scale



Hospital Anxiety, Depression Scale [235], **MISC** [84].

We follow the **Mallison questionnaire** [206] to diagnose VID patients in combination with the fitting of the inclusion criteria [42].

Exercises for VID patients:

The patient will be asked to report an average of the following questions:

At the end of every day when the protocol is conducted answer those questions:

Date:

Day of treatment:

Week number:

How much time did you spend doing the exercises?

Which activity/exercise was the most difficult?

Did you sweat or feel nausea?

From 2nd week onwards write down any improvements or if you feel anything is getting easier:

Acknowledgment

I would like to thank all the **patients** that participated to the various research projects conducted in the past years and the **ACTION for MdDS UK** for helping me to connect with other researchers. Your work is amazing and you are a true help for those who struggle with MdDS. Your support has made this research possible.

Thank you to the **Belgian Science Policy** (*Prodex Programme*) for supporting this work and **Western Sydney University** for funding some of the studies conducted.

A very special gratitude goes to my promoters: **Prof. Dr. Van de Heyning**, for being extremely supportive, for believing in me and for being very encouraging especially in the past months, when I most needed it.

An enormous thank you goes to **Dr. Cherylea Browne**, for being a wonderful mentor and an inspiration, for guiding me through each step of this journey and to be my support system. Working with you has been an amazing experience. I hope we will continue to collaborate in the future.

Thank you also to **Prof. Wuyts** for introducing me to this field and for giving me the chance to work on this topic, without your encouragement I would have never been in this field.

Thank you also to my co-promoters for your help and proactive guidance provided throughout the years.

Dr. Van Ombergen, you have been not just co-promoter but also a friend and I thank you for everything you have taught me in the past years. I know one thing you have made me realise is that we will have the skills and determination to achieve anything we want. I am sure you will have a great success as a postdoc and able to achieve even more than you think.

Prof. Jacquemyn thanks for your help and support with all the hormonal projects, without your guidance I would have never explored this line of research. Your kindness and support has been inspiring.

Prof. Van Rompaey I thank you for your clinical support and for guiding me by patiently reviewing my work.

Prof. Maes, I thank you for listening to me when I most needed it. It was great to get to know you in the past years and to learn from your dedication to your students.

I would also like to thank **Prof. Van de Eede**, your knowledge and guidance has been extremely valuable in setting up the VID project. Thank you also to **Prof. Vereeck** for help me in setting up the VID rehab protocol and always being willing to support my initiatives. I would like to thank **Prof. Sijbers** for being always available and supportive in the past months.

I am very grateful to my husband **Nikolaos**, who provided me through moral and emotional support in my life. Despite having neglected you in the past year, I am grateful you stood next to me.

A special thank you goes to all my **family** members and friends who have believed in me, and patiently supported me in those years. Thank you to my parents to always be there for me. A special mention to my friend **Dr. Choi Deblieck**, for challenging me and pushing me into research, you are an amazing powerful woman and source of inspiration for me.

Thank you to my colleague and friend **Steven Jillings** and **Dmitry Glukhikh** for being supportive and present for me whenever I needed it. Steven, your Ph.D. journey has not always been easy and straightforward but I am sure you will get it. Dimitry you are so close to the end, don't give up!

Thank you to **Josphine Canceri, Dr. Laura Celis, Dr. Berina Ihtijarevic, Dr. Emma Hallgren, Dr. Annick Gilles, Laure Jacquemin and Dr. Sarah Michiels** for being an inspiration and wonderful colleagues and friends to work with. Huge good luck to my friend **Dr. Kastoer Chloe**, who is also about to complete her Ph.D. journey. A big thank to **Tyché Perkisas** for all your technical help and friendship in the past years. Thank you to the engineer who has built the optokinetic stimuli, **Deblauwe William**.

An enormous thank you also to all the collaborators, **Dr. Dai** and **Dr. Yakushing** from Mount Sinai Hospital, New York, for patiently teaching me how to implement the OKN treatment and for guiding me in every step. You have been great mentors and inspiring researchers.

Thank you to **Dr. Watson, Dr. Brown, Prof. Topsakal**, for your help and support.

A special note goes to **Dr. Cha**, who has been guiding me into MdDS research from year one and always provided me feedback and answers when needed it. It has been my pleasure to get to know more about you and your work. You have been a great source of inspiration.

Lastly I would like to express my gratitude to the internal jury members, **Prof. Steven Staelens** and **Prof. Paul Parizel** for taking the time to read my work and the two external jury members, **Dr. Bertolini** and **Prof. dr. Bamiou** for agreeing in being part of this Ph.D. committee and for dedicating their time to this.

Thank you for reading this!

Per aspera ad astra

Viviana Mucci

Publications

2018

V. Mucci, J.M. Canceri, R. Brown, M. Dai, S.B. Yakushin, S. Watson, A. Van Ombergen, Y. Jacquemyn, P. Fahey, P.H. Van de Heyning, F. Wuyts and C.J. Browne. 'Mal de Debarquement Syndrome: A Retrospective Online Questionnaire on the Influences of Gonadal Hormones in Relation to Onset and Symptom Fluctuation.' March 2018. *Frontiers of Neurology*. DOI: 10.3389/fneur.2018.00362

V. Mucci, J. M. Canceri, R. Brown, M. Dai, S.B. Yakushin, S. Watson, A. Van Ombergen, V. Topsakal, P. H. Van de Heyning, F. L. Wuyts, and C. J. Browne, 'Mal de Debarquement Syndrome: a survey on subtypes, misdiagnoses, onset and associated psychological features', *Journal of Neurology*, pp. 1–14, 2018

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2017

A. Van Ombergen, L. Heine, S. Jillings, R. E. Roberts, B. Jeurissen, V. Van Rompaey, V. **Mucci**, S. Vanhecke, J. Sijbers, F. Vanhevel, S. Sunaert, M. Ali, P. M. Parizel, P. H. Van De Heyning, S. Laureys, and F. L. Wuyts, 'NeuroImage : Clinical Altered functional brain connectivity in patients with visually induced dizziness', 2017 *NeuroImage: Clinical*, vol. 14, pp. 538–545, 2017.

Papers currently under review

V. Mucci, T. Perkisas, S. Jillings, V. Van Rompaey, E. Fransen, L. Vereeck, F.L. Wuyts, P.H. Van de Heyning, C.J. Browne, and A.Van Ombergen, 'Sham-controlled study of optokinetic stimuli as treatment for Mal de Debarquement Syndrome.' March 2018

V. Mucci, J.M. Canceri, Y. Jacquemyn, A. Van Ombergen, L.K. Maes, P.H. Van de Heyning, C.J. Browne. 'Pilot Study on Mal de Debarquement Syndrome Patients during Pregnancy'. April 201

Extra

European Health Parliament: http://ehma.org/wordpress/wp-content/uploads/2016/07/European-Health-Parliament-Closing-Session_29.06.2016.pdf

We proposed policy recommendations to Members of the European Parliament to implement new policies related to the different healthcare systems in Europe.

Most Relevant Academic Presentations and Lectures:

- Barany Society 2018, Uppsala, Oral Presentation and poster presentation: "Mal de Debarquement Syndrome", June, 2018.
- Presentation on Mal de Debarquement Syndrome and on Visually Induced Dizziness on the 28th Ocular Motor meeting, Zürich-München-Tübingen, January 26-27, 2018, Department of Neurology, University Hospital Zürich.
- Presentation of Mal de Debarquement features. 2017 annual meeting of the Dutch Society for Ear-Nose-Throat Surgery of the Head and Neck Area.
- Visually Induced Dizziness and Mal de Debarquement Syndrome presentation Symposium Audiology Alumni 2017 Gent University.
- 26th Oculomotor Meeting ULM University, ULM, Germany
- KBV ORL – ENT association Belgium, Brussels, Belgium.
- Belgian, Dutch Vestibular Society, Antwerp, Belgium.
- Joint Life Sciences Symposium" (ESA / ISGP / CNES) Toulouse, France. I was part of the authors of the abstract from the Austrian Space Forum.
- Belgrade, Serbia, 19th and 20th April 2016 EMBalance
Discussing the finalising project of EMBalance and how to diagnose vestibular disorders
- Mati, Greece, 29 June, 1st July 2016 EMBalance Meeting. Discussing the Exploitation plans for the DSS system.
- London, UK 26th 27th January 2017. EMBalance meeting. Next business strategies and how to increase the management of vestibular disorders.
- Twente, Netherlands. 15th Sept 2016. EMBalance DSS system, rare vestibular disorders.
- Lectures in Space Physiology and extreme physiology and vestibular adaptations. 1st International Summer School in Extreme Sport Medicine, Politecnico of Milan (1 week).
- Lectures in Space Physiology and extreme physiology, Audiology MSc student, Ghent University, Ghent University Hospital, Ghent, Belgium

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