Mal de Debarquement Syndrome – What do you need to know?

Imagine disembarking from a ship or a train and feeling that you are still in motion, when the motion has stopped [1]. Many of us have experienced this sensation at least once in our lifetime and it usually resolves within a few hours [2, 3]. Now, imagine having to live with these feelings of constant instability for the rest of your life. This is what happens to patients suffering from **Mal de Debarquement Syndrome (MdDS).** Mal de Debarquement (MdD) is French for "*sickness of disembarking"*.

MdDS is a complex neurological disorder where the perception of self-motion is accompanied by additional symptoms such as light sensitivities and fatigue. Patients are mostly Motion Triggered (MT) meaning that the symptoms occur after disembarking from a vehicle (cruise, car ride, plane, train etc). However, the same symptoms can also arise spontaneously, which is called Spontaneous Onset (SO) or non-Motion Triggered Onset. Like migraine, more women present with MdDS.
MdDS is under-recognized and poorly understood; patients have a high rate of misdiagnosis and are often poorly managed [4]. The difficulties in recognizing this disorder results in a significant socio-economic burden for patients and for healthcare systems. As a result treatments are limited.

One of the earliest reports of (temporal) 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 [2]. 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) [3, 5].

MdDS was recognised as a clinical condition only in 1987 [2], therefore, it can be considered an old condition, present since the old days, but which has only recently become a clinically recognised. Despite the growing interested in this topic in the past decades and the increase number of clinical research, 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 between 40 to 50 years of age [6, 7]. Additionally, an inexplicable female predominance has been reported in numerous studies [7, 8].

Pathophysiology-wise currently there are two main theories.

Theory 1 - Abnormal Functional Connectivity

One theory has been developed following neuroimaging and neuromodulation studies on MdDS patients pathophysiology [9, 10] 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 [11]. This central oscillator drives widespread cerebral connectivity and can toggle between high and low states [6]. These alterations are believed to be responsible for symptom fluctuations [6]. 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 [9, 12–14]. 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 [13].

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 [13]	n= 20	5 M; 15 F	43.4 (2.5)	*Association between resting state metabolic activity and functional connectivity between the entorhinal cortex and amygdala.*
Cha et al 2013 [15]	n=8	0 M; 8 F	47.5 (15.2)	*Neuromodulation- rTMS on DLPFC tolerated in subjects with MdDS- short-term symptoms improvement.*
Ding et al 2014 [14]	n= 10	0M; 10F	47.6 (10.7)	*Quantify the neural changes after the DLPFC rTMS stimulation, through rsEEG.*
Pearce et al 2015 [16]	n= 66	4M; 62F	52.1 (12.2)	*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.*
Cha et al 2015 [9]	n=28	5M; 24F	43.0 (10.2)	*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.*

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.

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 [17] by Dai and colleagues and it primarily derives from animal research in subhuman primates [18].
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 [17]	n=24	3M; 21 F	42.0 (8.8)	*OKN stimulation reduced MdDS symptoms in 70% of the participants*
Dai et al 2017 [19]	n=141	22M; 119F	49 (13)	*1-year follow up after patients being exposed to the same protocol performed in 2014, reduction of success rate from 70% to 42%.*
Cohen et al 2018 [20]	X	X	X	*Theory and review of the potential mechanism involved in the optokinetic treatment*

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 [21] and it is controlled by the velocity storage. This contextual VOR adaptation may be long lasting [22] and is the basis for suggesting VOR maladaptation as an underlying mechanism in MdDS [19]. 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 [23, 24], 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 [25, 26], 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 subjection to motion sickness stimuli [25]. 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 [17]. 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 [25].

Personal Experience and Studies on MdDS:

My name is Dr.Viviana Mucci and I am a postdoc researcher working in the field of neurotology. For the past four years I have been focusing on addressing some of the challenges of diagnosing as well as managing MdDS patients. What you just read was a summary prepared for my Ph.D. thesis on MdDS.

During my Ph.D. I was lucky to be able to create an international collaboration with the top experts in the field such as Dr. Dai and Dr. Yakushin (from Mount Sinai Hospital, Ichan School of Medicine), as well as with Dr.Cherylea Browne (from Western Sydney University). I enjoy the stimulation of sharing ideas across boarders, which is crucial when studying a rare condition, such as MdDS. I was also mentored by Dr.Cha and Prof.Van de Heyning, who were extremely helpful in guiding my next research steps.

In the past years we have accomplished to publish an updated version of the diagnostic guidelines previously created by my colleague Dr.Van Ombergen in 2016 [8]. Our diagnostic guidelines were taking into account a series of data that we collected from the largest ever survey done on MdDS patients. We aimed to evaluate different types of onsets. We ended up observing that some MdDS patients may have an atypical onset, despite reporting the same symptoms as a typically motion triggered MdDS' one. Thus we proposed two more comprehensive diagnostic guidelines, one for MT and one for SO.

DIAGNOSTIC GUIDELINES:

New proposed MdDS diagnostic guidelines for patients with MT onset, adding new elements to Van Ombergen's 2016 guidelines.

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

New proposed MdDS diagnostic guidelines for patients with SO onset.

1. Chronic perception of 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

The key distinguish feature that we identified was that symptomatic relief during passive motion was similarly reported for the MT and SO groups. This specific feature can clearly help distinguish MdDS patients from Persistent Postural Perceptual Dizziness (PPPD) (previously described as Chronic Subjective Dizziness [9, 18], Phobic Postural Vertigo).
We hope that these guidelines will allow more physicians to identify this disorder and to reduce the number of misdiagnosed patients.

HORMONAL RESEARCH

Another focus of my research was on hormones. 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 [29]. From our findings, it was clearly reported that symptoms were aggravated during menstruation and around the mid cycle in female MT subjects. This triggered us to proposed a new theory where symptoms in female MdDS patients may be aggravated by estrogen withdrawal, similarly to what happen to migranienous patients.
We also ran for the first time a study specifically designed study for pregnant MdDS subjects [30]. From the data collected, most participants reported an improvement of symptoms during the 9 months of pregnancy (especially in the first two trimesters). This is potentially the result of the absence of estrogen withdrawal and high levels of estrogen and progesterone, which may alleviate MdDS symptoms. Despite being preliminary these research will further push more studies into the gonadal influence on vestibular symptoms and MdDS. For more info on another potential theory please check this other publication [31], where we proposed how future studies should focus on the hormonal influences on neurotransmitters (e.g. GABA) and on the trial of CGRP antagonist drugs for the treatment of MdDS patients.

TREATMENTS

Treatment Currently Available

Treatment wise, at this stage, there are no clear established treatment options for MdDS sufferers of either onset group. However experimental treatment options have been investigated in recent years.

Treatment Based on Theory 1 – NEUROMODULATION

Neuroimaging studies have led to the implementation of non-invasive brain stimulation as a therapeutic strategy for MdDS [12]. Specifically, repetitive transcranial magnetic stimulation (rTMS) over the left prefrontal cortex (DLPFC) [10]. Transcranial magnetic stimulation (TMS) has proven to be an important neural stimulation tool in investigating the pathophysiological bases of neurological and psychiatric conditions [10]. In several cases MdDS is used to modulate cortical excitability, using facilitator high- frequency stimulation (to excite) ($\geq$5 Hz) or inhibitory low-frequencies ($\leq$1 Hz) [12]. TMS effects results in not only

affecting the specific areas stimulated, but also in inducing anatomically and or functional connected site changes [12]. 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 [12]. Thus this technique was chosen as a potential treatment tool for MdDS patients. Particularly rTMS were performed on the DLPFC area [11]. 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 [14, 16, 32].
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 [6, 10]. 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 [6].
However, this treatment is currently being trialled by a relatively small number of patients worldwide [33]. More research and possibly multicentre studies are needed to fully understand this type of intervention.

Treatment Based on Theory 2 – OPTOKINETIC
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 [17]. Optokinetic stimuli are known to have an effect on the VOR, by inducing an optokinetic response, which indirectly modulates the VOR [19]. 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 [17]. The subjects' heads is rolled ±20° at their rocking frequency by the researcher [17]. 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 [17]. 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 [17]. In 2017 the same group published the follow up data, where a larger sample of patients were assessed [19]. 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% [19]. The same researchers also reported a higher success rate among the patients from the MT group, when compared with the SO onset subtype.

Similar findings were obtained in my most recent study, where we performed a sham study on MdDS patients (MT and SO) [34].

FUTURE
MdDS patients are still unable to access these types of treatment and often they are left with poor managements for years. In my next research step I am committed to developing more effective treatments for people challenged by this rare, complex and debilitating neurological disorder.
I hope in the future more centers worldwide will be able to effectively manage these patients' symptoms. My wish is that the work presented in this blog 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.

If you are keen to receive more info please reach out at: viviana.mucci@usz.ch

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