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Mal de debarquement syndrome: new insights

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Abstract

Mal de debarquement syndrome (MdDS) is an enigmatic neurotological disorder with high morbidity, psychosocial burden, and few treatment options. Fortunately, there has been recent growth in scientific interest in understanding the biological basis of and in treating MdDS. Recent studies using functional neuroimaging have shown increased glucose metabolism in the left entorhinal cortex and amygdala in the setting of decreased prefrontal and temporal cortex metabolism in subjects with persistent MdDS. The entorhinal cortex is a key player in processing and gating spatial information to be stored in the hippocampus and is a major driver of brain oscillations. A limbic focus may also be key to spontaneous MdDS-like symptoms occurring in individuals with a history of anxiety or chronic stress. Treatment with repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex can decrease the rocking dizziness of MdDS, with successful responses associated with decreases in the coherence between brain networks with nodes in the parietal and occipital lobes. A new theory of MdDS is proposed as pathology secondary to entrainment of intrinsic brain networks driven by oscillatory motion exposure coupled with an inability to subsequently desynchronize the activity of these nodes. Future treatment strategies may be directed toward unyoking these networks.

Keywords

mal de debarquement syndrome; entrainment; fMRI; rTMS; neuromodulation

Introduction

The modern scientific study of mal de debarquement syndrome (MdDS) started with a case series of six patients published by Brown and Baloh in 1987.[1] Though MdDS is still considered to be an uncommon disorder, it is emerging from obscurity and is recognized for the core clinical features that were well described by this short but informative paper—the motion-triggered onset of chronic rocking dizziness, the female predominance, the lack of peripheral vestibular abnormalities, and the improvement of symptoms with re-exposure to passive motion. Many other clinical features, such as chronic fatigue, cognitive slowing,

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Conflicts of interest

The authors declare no conflicts of interest.

visual-motion sensitivity, hypersensitivity to environmental stimuli, headache, and anxiety, have since become recognized as part of MdDS.[2]

Recent interest in investigating the pathophysiology and treatment of MdDS is evidenced by the observation that over two-thirds of all scientific publications on MdDS have been published within the last 10 years. Part of this growth has been due to the recruitment of more researchers contributing theories, practical advice, and potential treatments for MdDS. Many of these studies would not have been practical or even possible without the growth of the Internet, which has facilitated the creation of patient groups that advocate for increasing education and research into MdDS. Investigations are still in their early stages, but compared to just 5 years ago, when the literature was mostly comprised of case reports, there are now more active areas of research that attempt to delve into the biological underpinnings of MdDS.

Psychosocial aspects and burden of illness

To date, MdDS remains an intractable illness with a progressively lower likelihood of remission as time passes. Individuals with MdDS expend significant time, energy, and money in an effort to be diagnosed and treated. One study showed that MdDS patients made an average of 19 healthcare visits before being correctly diagnosed.[3] Lack of general recognition of the disorder is a problem, but even among practitioners who recognize MdDS, there are some who try to dissuade patients from the diagnosis because of the chronicity. Patients are told that they could not have MdDS because their symptoms lasted too long. MdDS sufferers subsequently experience high levels of depression and anxiety attributable to both the intrusiveness of their symptoms into their daily lives and the social stigma of having a disorder that is not easily understood or validated by the medical community.[4,5] Patients with MdDS experience low quality of life in both the physical and emotional realms, comparable to patients who have multiple sclerosis, with an annual economic burden almost twice as high as migraine.[3] In addition to more scientific investigations of MdDS, increasing general awareness of MdDS as a neurological disorder is an important goal in reducing the morbidity attributable to this disorder.

Epidemiology

The prevalence of MdDS in the general population is unknown, but in a well-established neurotology clinic at a major university, it was diagnosed in 1.3% of patients during a period before interest in MdDS starting rapidly increasing.[2] It is possible, however, that many cases of MdDS are being misdiagnosed as other disorders, particularly as vestibular migraine, especially because the relevant clinical history of the motion trigger is often not sought explicitly. A female predominance has been noted since the first reported case series, with the exact number varying from 75% to > 95%. Age of onset is typically in the 40s to 50s and appears to be consistent in both men and women.[1,6]

Related disorders

Spontaneous MdDS

A phenomenon very similar to motion-triggered MdDS is unofficially known as *spontaneous MdDS*. In this disorder, individuals develop the subacute onset of chronic rocking dizziness generally over the course of several days or weeks. Occasionally, the phenomenon can occur abruptly. Symptomatically, people with spontaneous MdDS are almost identical to those with motion-triggered MdDS, in the sense that they experience a chronic unrelenting perception of rocking self-motion that usually improves with passive motion. They are similarly plagued by fatigue, cognitive slowing, hypersensitivity to physical stimuli, and intolerance to visual motion.[2] In some cases, a spontaneous episode of chronic rocking dizziness can occur after a motion-triggered episode of MdDS has resolved. A personal history of migraine headaches is more common in people who develop spontaneous MdDS after a motion-triggered episode.[7] The term “spontaneous” is not entirely accurate, however, because recurrences are usually triggered by periods of stress or hormonal change. Chronic rocking dizziness is also noted in a disorder termed chronic subjective dizziness (CSD). Symptoms worsen with motion in CSD, however, and, as opposed to people with spontaneous MdDS, individuals with CSD do not appear to have any higher prevalence of migraine than population baseline.[8]

Migraine

A recent study investigated the relationship between migraine headache and spontaneous versus motion-triggered episodes of chronic rocking dizziness. After the onset of chronic rocking dizziness, both spontaneous and motion-triggered patient groups had a similar prevalence of headache that met criteria for migraine (41% in motion-triggered and 46% in spontaneous MdDS).[9] However, individuals with spontaneous onset of MdDS were much more likely to have had pre-existing migraine headache than those with motion-triggered MdDS. Individuals with motion-triggered MdDS showed a bimodal distribution of migraine headache onset with one mode between 20 and 29 years and the other between 40 and 49 years. The second peak correlated with the onset of the chronic rocking dizziness. Because of the chronic nature, MdDS does not meet the accepted definition of vestibular migraine, which is defined as an episodic disorder.[10] However, in most individuals, the onset of chronic rocking dizziness correlates with either the onset of migraine headache or an increase in migraine frequency, suggesting that MdDS and migraine have some pathophysiological overlap.[9]

Motion sickness

One prevailing theory about MdDS is that it is a disorder of poor adaptation to stable conditions after a period of adaptation to motion. Therefore, several studies have investigated the correlation between the development of seasickness and the subsequent development of MdDS. Positive correlations are reported, but the associations are not direct. Susceptibility to seasickness and the tendency to develop postsailing dizziness have both been shown to correlate with lack of experience at sea.[11,12] Motion sickness at sea was shown to correlate with body sway on land, whereas the tendency for postsailing dizziness

was shown to correlate with body sway on a boat but not on land.[13] Therefore, there may be an association but not a clear physiological connection .

There are two important qualifications to the research correlating seasickness to MdDS. Research subjects in studies that have investigated these correlations are usually around 20 years old and are heavily represented by males, whereas the typical demographic that suffers from the clinically relevant persistent disorder of MdDS that lasts for months or years is middle-aged women.[6,12–14] Second, studies on postsailing MdDS only evaluate short-term postmotion rocking dizziness, which appears to be quite common, being reported in 59–72% of subjects.[11–13] Persistent MdDS is, however, an uncommon disorder.

In a retrospective analysis of associated symptoms of MdDS, only seven of 21 respondents who had developed MdDS after a cruise had used motion sickness–preventive medication on the cruise.[15] It seems that motion sickness was not the main factor that contributed to persistent MdDS. Therefore, it is not clear that steps to reduce motion sickness during the exposure would have had much of an impact on reducing the incidence of persistent MdDS.

An argument might be made for an inverse correlation between motion sickness and MdDS, as persistent MdDS occurs later in life, when motion sickness–tendencies decrease.[16] If motion sickness were due to a failure of adaption to sea conditions, it would be more logical that people who do not adapt to the motion condition would have fewer problems readapting to land. Because of the commonness of temporary landsickness but the rarity of real MdDS, what appears to be relevant are not the conditions that create short-term periods of postmotion rocking dizziness, but rather the individual factors that prevent it from shutting off. Therefore, it may be more useful to look at the biological state of individuals who appear to be the most susceptible to developing persistent MdDS, such as factors related to physiological and functional brain changes due to age and hormonal status. Given the age of onset and female predominance of MdDS, brain physiology that changes with the perimenopausal or postmenopausal state would be relevant to understanding susceptibility to external entrainment.

Functional neuroimaging

Clinically obtainable diagnostic imaging with brain computed tomography (CT) and magnetic resonance imaging (MRI) are normal in MdDS, and the first functional brain-imaging study on MdDS was only published in 2012.[5,6] In this study, 20 individuals with persistent MdDS underwent an ^{18}F-fludeoxyglucose positron-emission tomography (^{18}F-FDG–PET) scan looking for baseline changes in brain glucose metabolism that were distinct from age- and sex-matched controls. Hypermetabolism in the left entorhinal cortex (EC) and amygdala was found in the MdDS subjects only. Hypometabolism was predominantly found in the left prefrontal and temporal cortex, along with the right amygdala.[5] These findings did not correlate with measurements of depression or anxiety. In light of the extensive neocortical connections of the EC, functional connectivity measurements were made between the EC and other cortical structures. MdDS subjects showed increased connectivity between the EC and sensory processing areas located in the parietal and occipital lobes (V1, V5, superior parietal lobule), whereas connectivity with the prefrontal/premotor cortex was

reduced (frontal eye field, middle frontal gyrus). MdDS subjects also exhibited reduced connectivity between homologous structures in the prefrontal cortex.[5]

The medial EC plays a key role in mapping of the spatial surround and is particularly notable for the presence of spatially tuned grid cells.[17] Grid cells are active when an organism is in a particular location within its spatial environment. They can be remapped in new environments while maintaining their general hexagonal shape.[18] Navigation in a virtual-reality environment when moving in a hexagonal grid will activate the medial EC in humans.[19] Baseline EC activity can be tuned externally, both increasing and decreasing in a graded manner depending on the periodic input.[20] Notably, EC neurons play an essential role in keeping the hippocampus active during sleep, when the rest of the neocortex has shut down, giving it an important role in the process of memory consolidation during sleep.[21] It is postulated that this role may be relevant to why MdDS symptoms frequently do not start immediately after the travel exposure has ended but rather start the following morning after a night of sleep. A role for the hippocampus in MdDS was previously postulated, and this neuroimaging finding pointed to the gatekeeper of spatial information entering the hippocampus as being potentially relevant to MdDS pathology.[6]

Neuromodulation

The rationale for attempting external neuromodulation with repetitive transcranial magnetic stimulation (rTMS) was based on these functional neuroimaging findings, which correlated with the general symptoms of MdDS. The aim of the first attempt at rTMS for MdDS was to determine the stimulation parameters. Based on the lower prefrontal metabolism in the setting of enhanced limbic activity, the initial stimulation target of the dorsolateral prefrontal cortex (DLPFC) was chosen. The added benefits were that the DLPFC is a well-studied rTMS target for a variety of functional brain disorders and the target of choice in the treatment of depression and anxiety, which are comorbid with MdDS. For MdDS, it was particularly relevant for its role in modulating attention to spatial information.[22,23]

In this pilot study, 10 subjects with classical motion-triggered MdDS were given one session each of high- and low-frequency rTMS to the right and left DLPFC (i.e., four conditions).[24] In the right-handed subjects, high-frequency (10 Hz) stimulation of the left DLPFC was most beneficial. In some subjects, low-frequency (1Hz) stimulation of the right DLPFC was most beneficial. Intriguingly, in the three left-handed subjects, high-frequency right-sided stimulation was the most beneficial.

All subjective reports of either positive or negative phenomena lasted less than 1 day, except in one case in which one session of high-frequency left-DLPFC stimulation in a right-handed female participant who had had MdDS for 12 months induced 2 ½ days of complete rocking suppression. This suggested that, perhaps, stacking the stimulation sessions might provide more benefit.[24]

This study was followed up with a double-blind randomized trial of 5 days of 10-Hz rTMS to the left DLPFC in eight right-handed subjects. The subjects were randomly assigned to receive either real or sham stimulation first and were given a wash-out period of 2–4 months between treatment weeks (manuscript in process). Of these eight subjects, two experienced

substantial improvement in the intensity of the rocking dizziness, to the point that they were able to actively re-engage in their social and professional activities. Symptom improvement lasted for several months. Two additional subjects noted improvement in rocking to a milder degree. Sham effects were low. Future studies of neuromodulation in MdDS are investigating home-based therapies to address the wearing-off effect.

Functional connectivity as a biomarker

In order to determine which functional-connectivity measures are related to the change in symptoms, a current study is using high-density electroencephalography (EEG) and functional MRI (fMRI) to measure both connectivity related to entorhinal cortex changes, as well as an independent component analysis (ICA). A methods paper on the initial 10 right-handed subjects of a currently running trial has been published.[25] This study employed a dual sequential-rTMS paradigm in which right-sided low-frequency rTMS to the DLPFC was followed by left-sided high-frequency rTMS. Symptom change from day 1 to day 5 was used as a categorical variable in separating responders from non-responders. Power changes in the delta, theta, alpha, and beta bands that changed as a function of symptom changes were calculated. In addition, the degree of coherence between independent components (IC) was measured.[25]

In the 10 subjects, three achieved significant symptom improvement, four showed no change, and three were worse off on the last day compared to the first day, one case of which was directly due to rTMS. Power in the left visual ICA in both the alpha and beta bands had a positive correlation with symptom improvement, meaning that symptom improvement was correlated with an increased power change. Conversely, increased power in the beta band over a posterior parietal ICA was associated with symptom worsening.

The degree of coherence decreased between eight pairs of ICs in the responders, whereas it increased in the subjects who had worsened. In each of these eight pairs, one of the IC nodes was located in a sensory-processing area in the occipital or parietal lobes in addition to one node in the prefrontal cortex. Worsening symptoms correlated with an increase in global synchronization of brain activity, while improvement of symptoms was associated with a decrease in synchronization of brain networks.[25] Further support for the phenomenon of “unyoking” related to symptom improvement was seen by the disappearance of vertical nystagmus induced during head roll with a specific vestibular-ocular reflex (VOR) uncoupling procedure introduced by Dai *et al*.[26] The theory behind this procedure is that periodic motion exposure couples VOR in different planes, which can be explicitly uncoupled with a head-rocking maneuver during optokinetic stimulation.

A working theory

These findings suggested that MdDS maybe a disorder of over-synchronization of brain networks caused by entrainment to the background low-amplitude–oscillating environments typical of the triggers of MdDS. In an enlightening presentation on the process of brain entrainment, Thut and Gross explained the process of how external periodic forces can entrain intrinsic brain networks driving out-of-phase networks to oscillate in phase.[27] A requirement of efficient entrainers is that they exist outside of perception, since cognitive

interference can desynchronize the process of entrainment. It is relevant, therefore, that triggers of MdDS are typically those involving low-amplitude oscillatory exposure, such as voyages on cruises or airplanes, in which the motion stimulation is usually outside of conscience awareness.[7, 15] MdDS is proposed as a condition of abnormally high resting-state functional connectivity in sensory-processing areas where persistent symptoms are due to the inability to desynchronize brain networks that have become yoked together.

Future directions

Two studies, one with fMRI and one with EEG, have now shown that increased functional connectivity between posterior sensory processing areas and the EC and as a high degree of synchronization within these networks are markers of MdDS.[5,25] The understanding of these network-connectivity measurements and their patterns may lead to further insights into some of the clinical features of MdDS, such as the paradoxical phenomenon of suppressed symptoms during self-motion in MdDS, fatigue, and visual-motion sensitivity.

Studies that show the organic nature of MdDS and that reveal functional brain changes associated with symptom change will hopefully validate MdDS as a neurotological disorder with a central basis. Careful dissection of the symptoms of and risk factors for MdDS may help link MdDS with other functional brain disorders and delineate the pathways that are relevant to brain entrainment and motion perception. Excellent descriptions of clinical phenomena such as those provided in the initial case series by Brown and Baloh have opened doors to new investigations and understanding of brain function. The history of research into MdDS shows that modern imaging tools can provide a deeper understanding of symptoms that have no diagnostic correlate, but that progress still relies on excellent clinical assessment.

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