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Title: Transcranial Magnetic Stimulation for Mal de Debarquement Syndrome

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Abstract
Mal de debarquement syndrome (MdDS) is a balance disorder in which patients develop a persistent internal sense of movement after a prolonged period of passive motion exposure. This is classically described as "land-sickness" occurring after boat rides. Patients describe a hallucination of movement such as "rocking" and "bobbing" even though they are not physically moving. This disorder is thought to be due to a primary problem of brain adaptation as testing of inner ear function and structural brain imaging is always normal. However, it is unknown which parts of the brain control this adaptation. Most cases of *mal de debarquement* only last a few hours, but there are many people who experience the symptoms for months or years, leading to significant morbidity. The term MdDS is generally reserved for patients who experience symptoms for at least one month.

Our preliminary data on imaging patients with MdDS with FDG PET and functional MRI has shown that there is abnormal metabolism in limbic structures that control spatial processing and emotional regulation in these individuals and that there are also differences in the functional connectivity between these limbic structures and the cortex. We are now working on modulating the perception of motion in MdDS with transcranial magnetic stimulation (TMS), which is a form of external neuromodulation using pulsatile magnetic fields on the surface of the head. Preliminary data shows that TMS can at least temporarily suppress the perception of rocking with short-term treatment. However, long-term studies are needed in order to determine whether the short-term suppression can translate into a remission.

A. Specific Aims

The goal of this study is to determine whether external neurmodulation using rTMS can reduce the perception of self-motion that is experienced by patients with MdDS. We will make correlations between functional MRI data, EEG, and specific clinical features to determine whether functional connectivity between particular hubs in the brain correlate with clinical improvement.

B. Background and Significance

Mal de debarquement syndrome (MdDS), the term for persistent feelings of motion occurring after exposure to passive motion, was reported over 200 years ago, but there is still no explanation for why some people experience such persistent feelings of rocking and swaying after being exposed to prolonged but relatively minor amplitudes of motion. The most common trigger for MdDS is sea travel with the quintessential patient being a middle-aged woman who develops sensations of rocking and swaying after disembarking from a cruise. Although brief periods of self-motion perception are common, some people experience the chronic rocking sensation for months or years with very few options for symptom relief. These patients can become totally disabled, often stopping work, developing strained relationships, and experiencing severely reduced quality of life. The probability of symptoms spontaneously stopping decreases dramatically with longer durations of symptoms. Thus, patients who have had MdDS for more than a year have a limited chance for recovery and almost no therapeutic recourse if one or two medication trials have failed them.

MdDS is currently a clinical diagnosis with no available biomarkers. It is unique among balance disorders in that re-exposure to passive motion decreases the internal motion perception rather than increasing feelings of motion sickness. Vestibular function testing, structural brain, and inner ear imaging

are non-diagnostic. Various theories have been proposed to explain MdDS ranging from abnormal weighting of somatosensory inputs, to de-afferentation of vestibular signals, to persistent internal models of external stimuli. However, one major barrier to progress in understanding the basis of self-motion perception has been the limitation of diagnostic and therapeutic tools. Functional neuroimaging tools, however, can add valuable information about brain physiology that cannot be captured with historical methods of measuring vestibular function.

More options are needed for treating patients with MdDS because they do not respond to the typical therapies given for inner ear disorders. Vestibular therapy and vestibular suppressants are not helpful and sometimes worsen symptoms. Benzodiazepines provide palliation only, and limited data on the use of selective serotonin reuptake inhibitors shows that, though they are helpful in some patients, are not effective in many others. The second hypothesis of this study is that external neuromodulation with transcranial magnetic stimulation can reduce the perception of motion. Expanding the study of MdDS by examining changes in resting state networks, functional connectivity, and response to neuromodulation will change concepts of how vestibular adaptation occurs and can be modified.

C. Preliminary Studies

Neuroimaging: Determination of metabolic activity and functional connectivity differences between individuals with MdDS and healthy controls

We subsequently imaged 20 individuals with MdDS and 20 healthy controls with resting state FDG-PET to show that the left entorhinal cortex/amygdala junction is hypermetabolic in MdDS individuals (**Figure 1**) while prefrontal and temporal cortex areas are hypometabolic (Cha et al PLoSOne 2012).

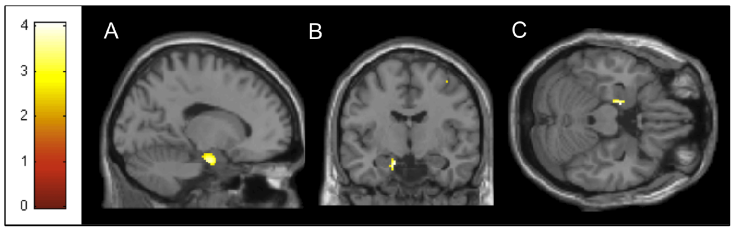


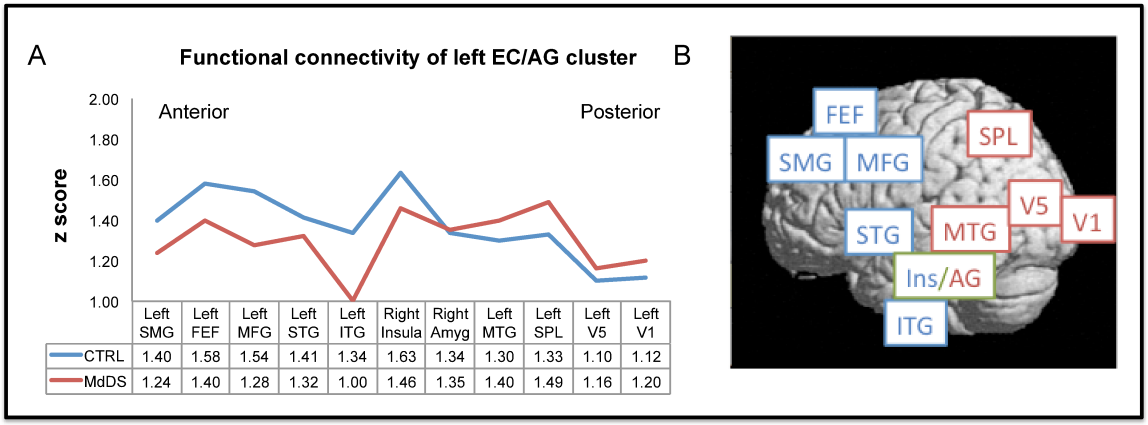
Figure 1: *Area of relative hypermetabolism in MdDS subjects compared to controls. Cluster with peak voxel z>3.3. for the MdDS>CTRL contrast (MNI coordinates -14, -8, -22) centered at the entorhinal cortex/amygdala transition shown in A) sagittal, B) coronal, C) axial planes. Image is presented at z=2.57 for better visualization.*
from Cha et. al. PLoSOne 2012.

The role of the entorhinal cortex in the processing of spatial information appeared to be a plausible factor in why people with MdDS experience spatial disorientation and increased visual motion sensitivity after illness onset. The metabolic differences seen in this study were found after regressing out the effect of high depression or anxiety scores determined through the Hospital Anxiety and Depression Scale (2). However, the decreased prefrontal activity along with amygdala activity may be a partial explanation for why anxiety tends to increase with the onset of symptoms of MdDS.

Using all of the areas of altered metabolism as regions of interest, as well as some other functionally determined landmarks through fMRI, e.g. area MT, frontal eye field, area V1, etc. we determined whether there were any differences in functional connectivity between these regions and the entorhinal cortex (EC).

We determined that functional connectivity between the EC and posterior sensory processing areas was increased in MdDS while it was decreased with prefrontal areas suggesting that perhaps the basis for the

symptoms of MdDS was enhanced connectivity with sensory processing areas with EC in the setting of decreased prefrontal control (**Figure 2**).



	Left SMG	Left FEF	Left MFG	Left STG	Left ITG	Right Insula	Right Amyg	Left MTG	Left SPL	Left V5	Left V1
CTRL	1.40	1.58	1.54	1.41	1.34	1.63	1.34	1.30	1.33	1.10	1.12
MdDS	1.24	1.40	1.28	1.32	1.00	1.46	1.35	1.40	1.49	1.16	1.20

Figure 2. *Functional connectivity differences in subjects with MdDS compared to controls. A) Functional connectivity between the left EC/AG hypermetabolic focus in MdDS and other landmarks: FEF, SPL, V5/MT, and V1. B) Foci are presented anterior to posterior anatomically. Blue line: Controls; Red line: MdDS. from Cha et. al. PLoSOne 2012*

The role of the entorhinal cortex

The EC is a brain region that processes both visual and vestibular information and acts a gatekeeper of spatial information entering the hippocampus . The medial EC contains "grid cells," that maintain a spatial map of the environment. Theta rhythms generated by EC neurons are critical for the generation of place cell fields in the hippocampus. Relevant to MdDS is that baseline EC activity can be "tuned" by the injection of periodic input leading to a stepwise rather than continuous (linear) change in resting state firing rates. Moreover, the junction of the EC and amygdala is an important functional area because concurrent amygdala activation enhances entorhinal cortex stimulation of the hippocampus. The EC also receives input from major hubs of the default mode network such as the medial prefrontal cortex and the posterior cingulate cortex. The potential involvement of the default mode network in MdDS is important and is supported by direct stimulation studies that indicate that electrical stimulation of the anterior cingulate cortex or the precuneus (hubs of the default mode network) can induce an oscillating motion perception which is distinct from stimulation of the temporal cortex which leads to illusions of tilting and spinning vertigo.

Neuromodulation and imaging biomarkers

A. Transcranial magnetic stimulation studies

One area of decreased metabolism was the left middle frontal gyrus in the region of the dorsolateral prefrontal cortex (DLPFC), which also had decreased connectivity with the EC. We postulated that stimulating over the DLPFC could reduce the rocking sensation of MdDS through its effects on EC. The other important factor in the choice of this target was that a desirable side-effect of DLPFC stimulation could be improvement in mood and anxiety. If the studies were successful, individuals with MdDS could potentially receive rTMS in the community since DLPFC stimulation is FDA approved for the treatment of depression.

We did not know, however, whether the metabolic changes were direct drivers of pathology or were compensatory changes. If they were directly related, then exciting the left DLPFC would probably help, but if they were compensatory, then exciting the left DLPFC would make symptoms worse. Therefore, we performed a balanced protocol of either excitatory (10Hz) or inhibitory (1Hz) stimulation of the left or right DLPFCs to measure the acute effects of stimulation. Each protocol was given one time with a separation of at least two days between each of the four combinations (left 10Hz, right 10Hz, left 1Hz, right 1Hz).

The most effective treatment was 10Hz excitatory stimulation of the left DLPFC in right-handed individuals and right DLPFC stimulation in left-handed individuals. 1Hz right DLPFC stimulation was occasionally better than 10Hz left DLPFC stimulation in right-handers. This handedness has not been noted to be a factor in the treatment of depression (all patients are usually treated with left DLPFC stimulation), but it was a clear factor in our studies in terms of the rocking perception. Though DLPFC is not a part of the vestibular system, we postulated that perhaps functional connectivity between DLPFC and the more extended vestibular "circle" contributed to the lateralized effects, since vestibular cortex activation follows handedness (e.g. greater activation of the ipsilateral stimulated ear if also ipsilateral to the dominant hand) (14,15). Improvement after 10Hz stimulation of the DLPFC contralateral to the dominant hand was negatively related to symptoms duration, i.e. individuals with longer symptoms had relatively less improvement (**Figure 3**) (Cha et al Otol Neurotol 2013) (13).

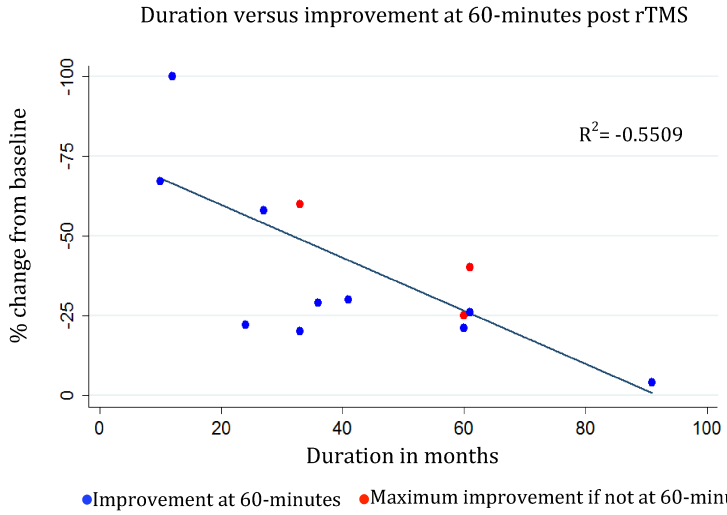


Figure 3. *Correlation between treatment effect at 60 minutes after 10Hz DLPFC stimulation and duration of illness. Blue circles= score at 60-minutes; red circles =cases in which the maximum change was not at 60-minutes.*

The next study was a double-blind sham-controlled study of five sessions of left DLPFC stimulation in eight women with MdDS.

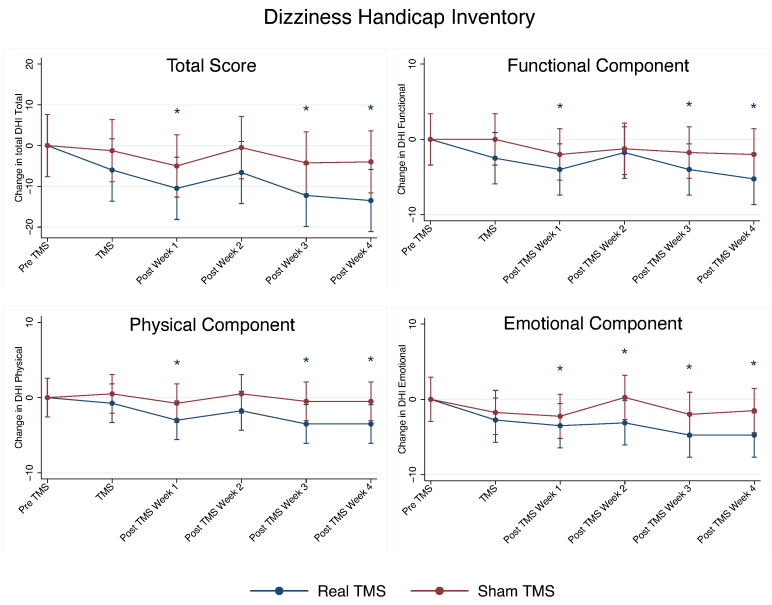


Figure 4. *Change in Dizziness Handicap Inventory from baseline, immediately after rTMS, and for four weeks post rTMS. Mixed effects repeated measures ANOVA was performed to account for both within subject and between subject variance.*

In this study (manuscript in progress) we found that Dizziness Handicap Inventory scores decreased significantly after real rTMS but not after sham rTMS at post TMS weeks 1, 3, and 4 with a trend for improvement at week 2 (**Figure 4**). From a functional standpoint, two of the eight women experienced significant reductions in rocking dizziness for about three months after receiving rTMS. They were able to return to almost all of their regular activities with only minimal symptoms. Two others noted some moderate improvement. Two had no change with either real or sham stimulation, and two were worsened by both kinds of stimulation likely due to the fact that they had to travel by plane to participate in the study. A second group in Australia has also provided evidence that rTMS over DLPFC can improve balance function in MdDS. However, our recent study was the first to show that long-term symptom relief could be achieved with rTMS with improvement that lasted well beyond the treatment period.

In order to determine what biomarkers may be different in responders versus non-responders to rTMS, new collaborators were cultivated in Oklahoma and the subsequent rTMS studies included both resting state fMRI and high-density EEG before and after five days of treatment with a combination of 10Hz left/1Hz right DLPFC rTMS (there was no access to a PET scanner in Tulsa). Our goal was to determine what functional connectivity changes were markers of symptom improvement, markers that could lead to the development of better subsequent targets.

Our initial analysis of 10 right-handed women treated with this protocol showed that five out of 10 achieved improvement with rTMS, with three experiencing quite significant improvement (30-50 point improvement on 0-100 visual analogue scale. Three participants worsened during the week, but only one of these appeared to be due to the rTMS itself (some extraneous stressors became relevant in the other two) (**Figure 5**).

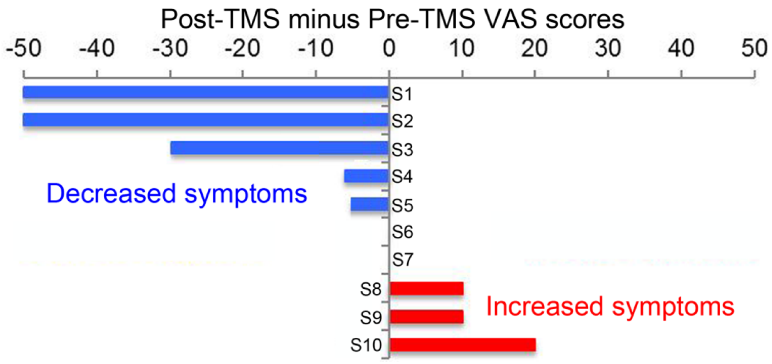


Figure 5. *Change in symptom severity based on a 0-100 point visual analogue scale in which "0" represents complete remission. Therefore, negative deflections represent improvement. from Ding et al, IEEE TBME, 2014*

B. Functional connectivity measured by resting state EEG

An independent component analysis was performed with EEG resting state data in the above participants. An ICA with a node in the left visual cortex showed that high alpha (11-13Hz) and beta power (14-30Hz) went *up* as symptoms improved. An ICA with a node in the middle posterior parietal lobe over the region of the precuneus showed that beta power went *down* as symptoms improved (Ding et. al. IEEE TBME 2014).

Alpha power is typically associated with resting or "idling" brain activity while beta power is associated with brain activation. We may extrapolate this to suggest that activating the left visual cortex or inhibiting the precuneus is associated with symptoms improvement. This hypothesis would need to be tested with direct targeting of those areas. The degree of phase coherence between the nodes was also determined. This is a measure of the degree of synchronization between the ICAs. We discovered that, as a function of symptom improvement, coherence between specific nodes in posterior parietal and occipital lobes *decreased* as symptoms improved. In addition, connectivity between the prefrontal cortex and a mid-parietal node also decreased with symptom improvement (**Figure 6**).

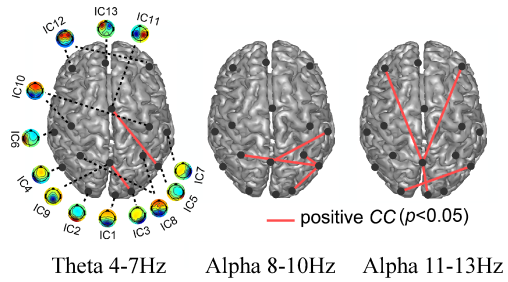


Figure 6: *Significant cross-subject correlations ($p<0.05$) between independent component phase coherence (ICPC) changes from the pre to post TMS sessions in theta, low alpha, and high alpha bands. from Ding et. al. IEEE TBME 2014*

In contrast, global coherence of brain activity, i.e. the degree of synchronization, increased when symptoms worsened (**Figure 7**).

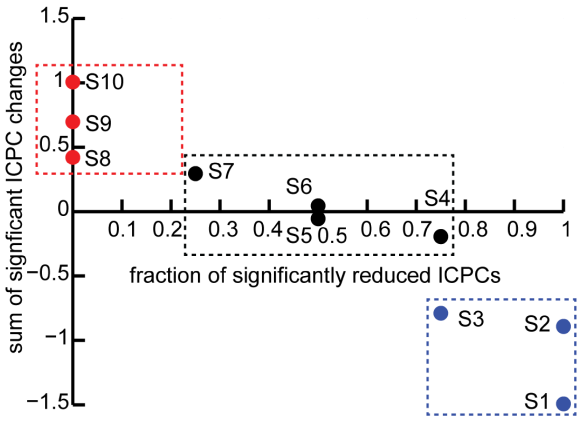


Figure 7: *Directions of ICPC changes in subjects who improved (blue dots), had no change (black dots), or were symptomatically worse (red dots) after rTMS. The two metrics were: 1) x axis= number of negative significant ICPC changes over the total number of significant ICPC changes and 2) y axis= sum of all significant ICPC changes.*
from Ding et. al. IEEE TBME 2014

Thus, it appeared that symptom improvement in MdDS is correlated with a decrease in electrical synchronization (at least in the frequency bands that were studied), and that symptom worsening is associated with an increase in synchronization.

As a function of symptom improvement, functional connectivity between the left EC and the ventral precuneus, the right inferior parietal lobule (IPL), and the right EC all decreased (**Figure 8**) (Yuan et al OHBM 2015).

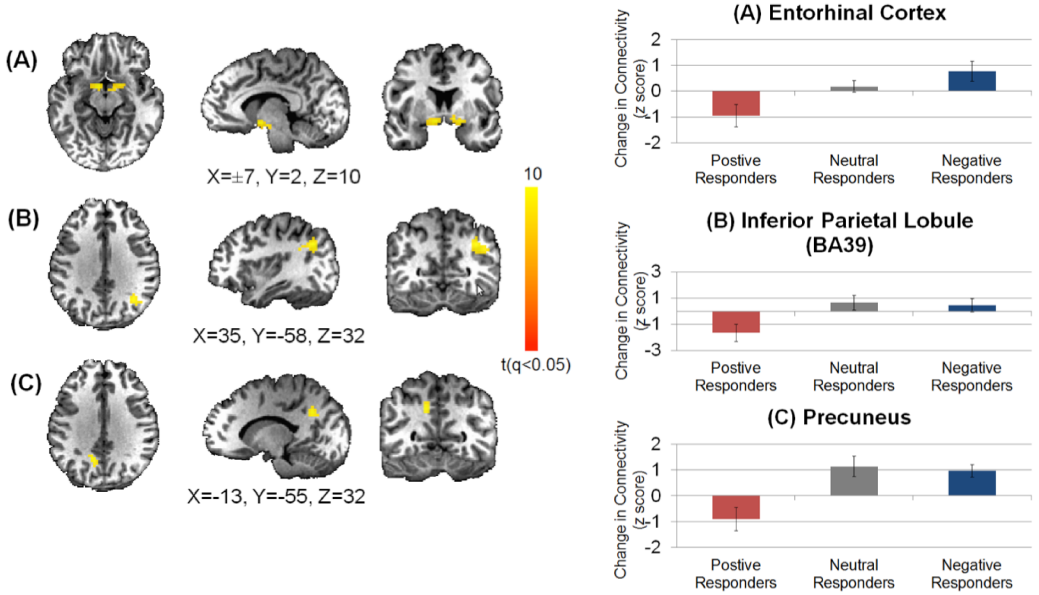


Figure 8. *Conjunction analysis found areas where changes in connectivity with left EC co-varied with changes in VAS scores (Talairach coordinates listed). Positive responses represented by a decrease in symptom rating are associated with decreased connectivity with the left entorhinal cortex.*

The EC is part of the default mode network, as are the ventral precuneus and the IPL, specifically in the area of connectivity change that we determined (angular gyrus). The default mode network is a resting state network that increases in activity at "rest" and is thus deactivated during the execution of specific tasks. It is associated with resting activities such as daydreaming and introspection. Thus, it appeared that decreases in the posterior portion of the default mode network were associated with decreases in MdDS symptoms. This decrease in resting state functional connectivity in major nodes of the default network measured by BOLD was consistent with the decrease in phase coherence between the posterior parietal ICA node and other nodes (EEG looks at surface activity so the connectivity with EC itself could not be determined). These analyses are now being extended to a total of 24 participants with MdDS who have undergone the same protocol.

Finally, we have recently studied differences in grey matter volume between individuals with MdDS and healthy controls using voxel-based morphometry and have found decreases in grey matter volume in the anterior cingulate cortex (ACC) even after correcting for concurrent depression scores. ACC volume decreases further as a function of duration of illness (manuscript in review). Cerebellar volume increases in bilateral hemispheric lobules VIII and IX were concurrently observed. Both the ACC and the cerebellar lobule IX are functionally part of the default mode network. Though lobule VIII is primarily functionally connected to the premotor cortex, it is also anti-correlated with every portion of the precuneus, suggesting that it may also have some impact on the default mode and other resting state networks of which the precuneus is a part.

We are now using the functional connectivity information from our pilot participants to determine whether there may be other more optimal rTMS targets in terms of causing this desynchronization. For example, since there is evidence for a role of the default mode network, direct stimulation over one of the nodes of the default mode is one of our next plans. The second is to use a target that is functionally connected to the EC in order to more precisely target the region of the DLPFC. This requires using individualized targets that are determined by a functional connectivity map.

D. Research Design and Methods

Screening: All potential subjects will be screened by the PI to determine whether they meet any exclusion criteria (see attached screening script) such as major medical or psychiatric illness or any personal or family history of seizures. All screening will occur prior to participation and will be either in person or on the phone. They will complete an MRI safety screen if they qualify for the TMS portion of the study.

Consent: The purpose, content, duration, and expected risks and benefits of the study will be reviewed with each participant by the PI. If they pass the screening interview, written consent will also be obtained before subjects can participate in either the MRI or TMS portions of the study. Subjects will be encouraged to be open with the investigators about any questions or concerns they have either before, during, or after the study.

Enrollment: All subjects will undergo a directed interview and a screening neurological exam by one of the investigators. A subset of the questionnaires will be completed by the participants depending on the participant's symptoms:

ABC Scale,Beck Depression Short Form, Cognitive Assessment Questionnaire, Dizziness Handicap Inventory, Edinburgh Handedness Scale, Functional Activities Questionnaire, Hospital Depression Anxiety Scale, Mal de Debarquement Rating Scale, Multidimensional Fatigue Scale, MIDAS Migraine Disability Scale (if applicable), Motion Sensitivity Questionnaire, MSSQ, Memory Questionnaire, SF-36 (quality of life scale), Tinnitus Handicap Inventory (if applicable), an Empathy Scale (40 point), Body

Awareness Questionnaire, a generalized anxiety scale (GAD7), and Overall Anxiety Severity and Impairment Scale (OASIS), a Self-Efficacy Scale, and a and a Visual Analogue Scale.

MRI procedure:
All MRI scanning in this protocol will be non-invasive (i.e. NO intravenous or other forms of external contrast agents will be used) and participants will be provided with earplugs as protection from scanner sounds. Participants will be placed in the magnet with the investigator ensuring that the subject is comfortable, able to easily manipulate any required response apparatus and trained to use the scanners emergency call button. The emergency call button is a response apparatus the patient can press to indicate that he/she needs immediate attention. A series of MRI localizer scans will then be obtained in order to prescribe the study-relevant anatomical scans. Before the anatomical scans, participants will be instructed as to the type of scan being performed and asked to stay as still as possible by remaining relaxed. These scans typically take 45-90 minutes to complete.

EEG procedure:
Subjects will undergo EEGs using either the standard electrode-paste leads with between 32 and 128 leads, or a wireless EEG system with 14 leads that is designed to allow the subject to move. The EEG set-up may take 1-2 hours depending on how much hair the subject has. These studies will be performed before and after the block of TMS or during the TMS sessions. In each EEG session, they may receive either or both the wireless or standard EEG leads. They will be told beforehand which will be used, or both. The wireless EEG system uses saline soaked sponges which can be applied within about 5-minutes. Therefore, these will be applied first then removed before standard EEG leads are placed.

TMS procedure:
TMS: Determining motor threshold (for MdDS subjects and controls)
The first step in the procedure is to determine individual subject's motor threshold in order to select the appropriate intensity of stimulation to use in the study. This is done by eliciting motor evoked potentials (MEPs) in the first dorsal interosseus muscle of the dominant hand. Surface electrodes will be attached to the skin over the muscle using electrode paste and tape. Subjects will wear insert earplugs or earphones to attenuate the sound that the magnetic coil makes during stimulation. Ear protection is recommended to prevent temporary increases in the auditory threshold during studies involving TMS at frequencies greater than 1 Hz. Subjects will sit in a chair. Frameless stereotaxy will be used to position the TMS coil over the subject's head. This procedure uses computer software to co-register the location of the subject's head in real space with his/her head on the MRI scan. Motor threshold is commonly defined as the minimum amount of stimulation needed to evoke a MEP in a hand muscle after a single pulse over M1. As such, single TMS pulses will be delivered at multiple locations around the motor cortex contralateral to the dominant hand. The intensity of the stimulation will be gradually lowered until reaching a level of stimulator output at which 5 out of 10 motor evoked potentials (MEP's) in a hand muscle have an amplitude of at least 50 microvolts. This intensity is considered to represent motor threshold. The duration of this procedure usually takes about 20 to 30 minutes.

rTMS session (for MdDS subjects only)
After determination of motor threshold, the TMS coil will be positioned at predetermined locations over the cortex using frameless stereotaxy as described above. Surface electrodes will be kept over hand muscles on both hands for the purpose of continuous monitoring of the safety of the procedure. We will also use theta bursting TMS (TBS) at inhibitory settings (continuous TBS-cTBS).

Theta burst TMS will be limited to established protocols using 600 pulses per session (40 seconds for cTBS). The first TMS session could last as short as 2 hours and as long as 3 hours with multiple sessions of TBS administered with a break of 30-minutes in between sessions.

Daily rTMS sessions (for MdDS subjects only)
Participants with MdDS will receive one sessions each of 3 different targets: occipital cortex, cerebellar vermis, lateral cerebellar hemisphere. The order in which these sessions will be administered will be randomized between participants. All test sessions will be done on Day 2 (Day 1 will involve baseline fMRI and EEG measurements). The treatment choice will depend a combination of the participant's assessment of which target was a the most effective in reducing the vertigo. If they are not sure, then balance assessment with the SWAY balance app will be used to determine which protocol improved their balance the most.

We plan an enrollment of 24 participants which would provide 4 groups of each of 6 possible orders of stimulation. Participants will be asked to rate the intensity of their rocking vertigo. The goal is to provide up to 12 sessions of rTMS over 3 days with 30-minutes of break in between. The end of the final day of stimulation will include fMRI and EEG.

E. Statistical Methods
This is a pilot study so there are no set power calculations. The goal is to determine which if any of three rTMS targets are most effective in reducing oscillating vertigo. Pre-stimulation baseline scores will include weekly assessments of the DHI, MBRS, and the HADS divided into the Anxiety and Depression subscores. The median of 4 weekly prestimulation scores will be used as the baseline. The participants will be making immediate post assessments of each of these scores and weekly thereafter for 6 weeks. The differences between these weekly scores and the prestimulation baseline will be calculated. Baseline clinical features that determine target selection will be placed in a **o**ne-way ANOVA with one factor and three levels for response groups (occipital target, vermis target, lateral cerebellar target) with post hoc Bonferroni correction to determine which targets showed different responses.

F. Gender/Minority/Pediatric Inclusion for Research
Women and minorities will be included in the study. Prior research indicates that MdDS predominantly affects females, without any predilection for any racial or ethnic groups. It is a disorder of adults, however, as the average age of a first episode is near 40 years old.

G. Human Participants
We plan to enroll 24 subjects with MdDS and 20 healthy controls over a span of 5 years.

Inclusion criteria for controls:
1. Age ≥18 years old
2. Willing and capable of interacting with the informed consent process
3. No history of dizziness or balance disorder.

Inclusion criteria for MdDS subjects:
1. Age ≥18 years old
2. Willing and capable of interacting with the informed consent process
3. Primary disorder being a persistent perception of motion with no other cause determined after a careful interview.

Exclusion criteria for both:
1. Subjects who cannot comply with study conditions.
2. Active psychiatric condition such as mania or psychosis
3. Unstable medical condition
4. Implanted metal anywhere in the body (infusion pumps, pacemakers, metal or shrapnel in the body, deep brain stimulators, aneurysm clips, metal prostheses, joints, rods or plates). Dental fillings are acceptable.

5. Personal history of seizures or a first-degree relative with uncontrolled epilepsy
6. Medications known to lower seizure threshold: typical (high-potency) neuroleptics and tricyclic antidepressants: Subjects who take one or a combination of the following drugs will be excluded: imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine. clozapine, foscarnet, ganciclovir, ritonavir, amphetamines, cocaine (including MDMA, ecstasy), phencyclidine (PCP, angel's dust), ketamine, gamma-hydroxybutyrate (GHB), theophylline, haloperidol, fluphenazine, bupropion.
7. Pregnancy

Eligibility will be determined by the PIs through history and neurological examination. Dr. Cha is a Board certified neurologist who has expertise in the evaluation of patients with motion perception disorders, auditory symptoms, movement disorders, pain, and stroke. Control subjects who are recruited by advertisement will undergo a screening interview to determine whether they have had any problems with motion perception in the past. This includes various kinds of motion sickness or vertigo and a history of migraine.

H. Recruitment and Consent Procedure

Subjects will be recruited from advertisements Flyers/Information Sheet/Internet Postings.

Screening will be conducted by study personnel in person or over the phone. A screening script will be used to ensure uniformity in the screening process. We will need to obtain their name and contact information should they pass the phone screening and still remain interested. If the subject is qualified by the initial phone screen, they will be invited to the first visit with the PI in order go through the consent process and undergo a neurological exam. They will be mailed the consent form prior to the first visit in order for them to have adequate time to review and think of questions.

The informed consent process will include interactive assurances that participation in this study is voluntary, that there is no consequence to refusing to participate, that participating or not will not affect any ongoing or future care, and that the subject is free to withdraw at any time with no consequence to their ongoing or future care.

I. Subject Risks

MRI: Risks and general protection against risk

Possible mild side effects include mild muscle stiffness or discomfort from prolonged immobility in the MRI scanner. This side effect will be monitored and logged on the investigators scanning log. Participants are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Participants will be screened for these conditions prior to the study, and if they have any, they will not receive an MRI scan. Women who are pregnant may not undergo a research MRI. Therefore, all women of childbearing potential will be excluded if they are unsure of their pregnancy status. Individuals with fear of confined spaces may become anxious during an MRI.

Side effects that occur during MRI could include temporary contractions or twitching of muscles during the MRI scan. It is described as a creeping sensation along the back, twitching of the nose, or electric shocks, which may be almost imperceptible or mildly painful. Some individuals experience nausea and/or dizziness during the MRI scan.

Participants that are taking medications during the screening process will not be discontinued from their current treatment for the MRI procedures.

EEG: Risks and general protection against risk
An EEG is minimal risk procedure that is performed widely for clinical purposes. In this study, there are potentially more leads being placed than a standard EEG, which will increase the set-up time. We will initially start with only 32-leads, similar to a standard clinical EEG, but over time we may need up to 128 leads in order to attain better localization. The placement of the leads themselves is not uncomfortable, but the subject may find cleaning the scalp with alcohol pads to be irritating. The conductive gel used in the studies will require that the subject wash their hair afterwards, which may be a hassle. It is possible, though highly unlikely that the subject would be allergic to the conductive gel. There are no limitations on who can receive an EEG since it is a non-invasive procedure that only involves recording. The subject may discontinue the set-up at any time if they are uncomfortable.

TMS: Risks and general protections against risk
One person who is certified to administer TMS will be present at every TMS session. In general, this will either be one of the PIs or a technician. In addition, all rTMS studies will be performed with a physician skilled in seizure management present on-site.

Subjects will be fully informed about the foreseeable risks and discomforts associated with participation in this study. The consent forms describe these risks and discomforts clearly. Patients must know that they have the option to withdraw from TMS studies at any time. Withdrawal from this study can be done without consequence. The investigators may also choose to terminate a participant from this study, if they suffer a severe adverse event, do not follow study requirements, or feel that continued participation will put the person at a greater risk than indicated.

Specific protections against risk
1. Headaches or neck aches. Headaches and neck aches routinely respond to acetaminophen ibuprofen. Headaches are no different that usual headaches that patients may get. Efforts to minimize TMS intensity to avoid sensitive areas of scalp muscles or nerves will be done.

2. Use of earplugs. In order to prevent transient hearing threshold shifts due to TMS, subjects and investigators will be offered earplugs during TMS.

3. Fainting. All investigators must know and will be trained on how to manage fainting in the laboratory.

4. Inadvertent seizure. Screening and enrollment procedures will exclude subjects for whom rTMS is contraindicated or who are at increased risk of seizure or for whom the potential consequences of a seizure are increased. The informed consent process will note the potential risk of seizures with rTMS and should mention possible medical and social consequences. There is no evidence that a rTMS induced seizure increases the risk of having a second seizure in an otherwise healthy individual.

There have been no seizures reported after theta burst TMS to date. Both medical and psychological support will be provided to patients and normal subjects who have TMS-induced seizures. Subjects who experience a TMS-induced seizure will be informed of the fact that an induced seizure does not place them at greater risk for further seizures than before. The seizure event does become documented in the subject's medical record. None of the subjects who have been described as having TMS-induced seizures has suffered lasting physical sequelae. Electroencephalographic and neuropsychological measures had returned to normal within 1-2 days. Furthermore, there is no evidence to suggest that a TMS induced seizure makes another seizure more likely in an otherwise healthy individual. Documentary support of a healthy subject's claim that a provoked seizure carries no adverse prognosis will be provided in cases where the report of the seizure in the subject's medical record could be misinterpreted or deliberately used

as a pretext for the denial of employment or medical insurance. Prospective subjects will be informed of this potential consequence.

5. Neuropsychological and motor effects. rTMS can disrupt cognition during the period of stimulation. Monitoring for adverse events should be done with tasks based on regions stimulated, e.g. verbal fluency task after left prefrontal stimulation, perceptual task after right parietal stimulation.

6. Potential for unforeseeable adverse events. All subjects will be informed of this point.

J. Benefits versus Risks

In accordance to the principle of beneficence, research should maintain a favorable balance of benefit to risk. The proposed rTMS parameters in MdDS patients in this protocol fall within a Class II classification of benefit-risk ratio. That is, rTMS as used here is of potential, but unproven benefit. In comparison, use of TMS in normal subjects is a Class III classification of benefit-to-risk: providing no expected benefit, but will advance general understanding. As such, all TMS studies on normal subjects are done with a higher ethical guideline than studies on patients with neurological disorders as there may be a potential for benefit to those with a neurological disorder that does not exist in neurologically normal subjects. Given our experience, the recent FDA approval at more intense parameters, and experience of other TMS laboratories, to date, the rTMS parameters used in this protocol are safe and constitute a 'minimal risk' application.

K. Data and Safety Monitoring Plan

The risk for adverse events is minimal. No medication, therapeutic decision or investigational device is made based on the results of these studies. Participants may experience some discomfort upon discussing their symptoms with staff and receiving unanticipated information about diagnosis. Participants may find it difficult to participate in detailed ratings. Any reportable adverse events will be reported to the IRB of record and Laureate Institute for Brain Research Human Protection Administrator at (918) 502-5155 or via email at hpa@laureateinstitute.org.

Each subject is given a unique identifier with a code that depends on their primary vestibular disorder. For example, patients with *mal de debarquement* have a code starting with "MdDS" followed by their initials or a number code if initials overlap. Controls are labeled as "CTRL." The code key that links the unique identifier to the subjects' names is kept in a separate file. All psychophysics and imaging data are linked to this unique identifier. All data analysis is performed on de-identified data.

De-identified imaging, EEG, and TMS outcome data may be shared with other investigators at the Laureate or with collaborators outside of the Laureate. Other than the principal investigator, there is no need for personally identifying information to be known to other investigators.

Data will be coded on two levels. Each subject will be given a unique code according to their primary assignment. When data is entered, it is entered in numerical form, eg (Yes=1, No=2). The data code is kept separate from the data, which would make the raw data uninterpretable otherwise.

Data that is entered through the online diaries through either SurveyMonkey or REDCap will be entered with the subject's code, not their real name. No personally identifying information will be ascertained on the questionnaires. SurveyMonkey procedures allow for creation of a study specific research.net URL that only subjects within the study can ascertain. REDCap is an online electronic data capture program (project-redcap.org) used by over 600 institutions for anonymous data capture. As the study grows in scope, either one of these sites may be used. No personally identifying information is stored on either of these sites. The link to access the sites are, however, sent to the subject via their email address. If the

subject does not consent to use of electronic datacapture, they will always be give the option of entering all data on a paper document.

The link to the patient identifications as well as to the encoded data is stored on a password-protected computer on a separate spreadsheet in a locked room. Only Dr. Cha will have access to the link. Anonymized data can be requested in writing to the PI. However, there would be no need for any personally identifying information to be revealed to other investigators.

If Dr. Cha leaves LIBR, and agreement will be made between LIBR and Dr. Cha's new institution to transfer the data so that the study can continue. If another investigator at LIBR becomes a co-investigator of the study, their name will be added to the list of investigators and they will become responsible for maintaining data security at LIBR.

Study information will be made available to the subjects when there has been sufficient recruitment to make reasonable aggregate assessments. We can share general study characteristics (how many people were recruited, age, primary disorder etc.) early in the process but we do not share study results with subjects until the quality of the data is close to publication level.

L. Confidentiality

Records of the participant's participation in this study will be held confidential except as disclosure is required by law or as described in the informed consent document (under "Confidentiality"). The study doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and the Institutional Review Board (IRB) will be able to inspect and copy confidential study-related records which identify the subject by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subject will not be identified.

Paper copies of consents, other forms, testing results or papers containing Personally Identifiable Information (PII) will be stored in a secured medical records room with access granted only to authorized personnel.

Online datacapture will only not include any personally identifying information. These data will only be captured by the subjects research code.

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