Transcranial Magnetic Stimulation as Treatment for Mal de Debarquement Syndrome: Case Report and Literature Review

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Abstract: This manuscript presents the case of an adult, male patient with mal de debarquement syndrome (MdDS); results from his experimental treatment with repetitive transcranial magnetic stimulation (rTMS) are also provided. Additionally, we included a review of literature related to the neurophysiology of MdDS and its treatment with rTMS. A 41-year-old man had been experiencing symptoms of MdDS, which initially emerged following a car ride, for 11 to 12 years. Pharmacologic approaches had failed to provide symptom relief; thus, we investigated an intervention using low-frequency (1 Hz) rTMS unilaterally for 2 consecutive weeks. The outcome measures included a standardized, computerized dynamic posturography test to quantify the patient's balance and identify abnormalities in his use of the sensory systems contributing to postural control, as well as the Hospital Anxiety and Depression Scale (HADS) to measure his anxiety and depression. An rTMS treatment log was created to document any adverse events. Following rTMS, the patient's balance scores improved significantly; these improvements were mostly related to the patient's increased reliance on the visual and vestibular systems. Our patient's HADS Anxiety and Depression subscores also showed improvement post-rTMS. The presented case study provides preliminary evidence that rTMS may be a noninvasive treatment option for improving balance, specifically in individuals with MdDS. This evidence can be used to further therapeutic research on, and provide strategies for treating, MdDS.

Key Words: mal de debarquement syndrome, transcranial magnetic stimulation, Sensory Organization Test, Hospital Anxiety and Depression Scale

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cDLPFC = contralateral DLPFC. **DLPFC** = dorsolateral prefrontal cortex. **EQS** = equilibrium score. **HADS** = Hospital Anxiety and Depression Scale. **iDLPFC** = ipsilateral DLPFC. **MdDS** = mal de debarquement syndrome. **rTMS** = repetitive transcranial magnetic stimulation. **SOT** = Sensory Organization Test.

Mal de debarquement syndrome (MdDS) is a rare neurologic disorder that is characterized by a subjective perception of self-motion (ie, bobbing, swaying, and/or rocking) for 1 month or longer (Cha, 2009; Hain and Cherchi, 2016; Mucci et al, 2018b). The disorder is more common in females than males, especially in middle age (Hain et al, 1999). The onset of MdDS is predominantly preceded by exposure to passive motion, referred to as *motion-triggered MdDS* (Brown and Baloh, 1987). Triggers for MdDS, in increasing order of commonality, are land, air, and maritime (eg, boat or cruise) travel (Brown and Baloh, 1987; Cha et al, 2008, 2018a; Hain et al, 1999). However, some individuals develop *spontaneous-onset MdDS*, in which symptoms occur in the absence of a motion trigger (Mucci et al, 2018a). Despite the different causes of onset, spontaneous-onset and motion-triggered MdDS appear similar in their epidemiology and symptomology (Canceri et al, 2018; Cha, 2015; Mucci et al, 2018a).

Additional symptoms associated with MdDS include headache, migraine, visual motion intolerance, fatigue, and cognitive slowing (Cha et al, 2016a). Consequently, individuals with MdDS can experience a low quality of life, high rates of anxiety and depression, and significant social and economic burdens (Macke et al, 2012).

Because individuals with MdDS do not exhibit structural abnormalities (Cha et al, 2016a), some researchers have suggested that MdDS is a disorder of abnormal excitability in the sensory-processing areas (Cha, 2015; Mucci et al, 2018b). This abnormal excitability may be the result of entrainment to low-amplitude oscillating motion exposure, such as maritime travel (Cha, 2015). According to these researchers, the entorhinal cortex, which is located in the medial temporal lobe and is a brain area that is involved in spatial-information processing, is the proposed central neural oscillator involved in the persistence of MdDS symptoms (Cha et al, 2012). Other researchers have suggested that MdDS results from maladaptive readaptation of multiplanar information from the vestibulo-ocular reflex (Dai et al, 2014). Neuroimaging studies are essential to evaluate these competing theories and understand the pathophysiology of MdDS (Mucci et al, 2018b).

Until recently, only partial palliative relief for the symptoms of MdDS was possible through medications such as benzodiazepines and selective serotonin reuptake inhibitors

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(Cha, 2009; Cha et al, 2008). Benzodiazepines enhance the activity of gamma-aminobutyric acid, which is a major inhibitory neurotransmitter, and improve one's sleep and balance. Whether these improvements are mediated through the regulation of abnormal excitability, shifting the power of limbic rhythms, or something else remains to be clarified. However, incomplete clinical response, serious side effects, and dependence are common risks of benzodiazepines, especially with long-term use (Guina and Merrill, 2018). Selective serotonin reuptake inhibitors increase the brain's extracellular levels of the neurotransmitter, serotonin. Although some selective adverse effects of serotonin reuptake inhibitors can be intolerable or troubling, except for serotonin syndrome, they are not life threatening (Ferguson, 2001). Selective serotonin reuptake inhibitors are often used as a baseline treatment for MdDS in conjunction with benzodiazepines.

Functional neuroimaging studies of individuals with MdDS have highlighted the presence of hypermetabolism in the left entorhinal cortex and amygdala, and hypometabolism in the left prefrontal and temporal cortex, compared with normal controls (Cha et al, 2012). External modulation may be an effective treatment to correct aberrant excitability in individuals with MdDS (Cha et al, 2013, 2018b; Chen et al, 2019; Ding et al, 2014). For instance, repetitive transcranial magnetic stimulation (rTMS) is a method of modulation in which an electromagnetic coil is placed over an individual's scalp in order to induce an electrical current in the underlying brain structures (Hallett, 2007). Based on the lower left prefrontal metabolism (Cha et al, 2012), previous studies have investigated the use of bilateral dorsolateral prefrontal cortex (DLPFC) rTMS to correct this metabolic imbalance (Cha, 2015) by using facilitatory high-frequency stimulation on the left DLPFC and inhibitory low-frequency stimulation on the right DLPFC.

Previous TMS studies have suggested that interactions between primary cortices are possibly mediated by a "sensory gating" mechanism, either via the thalamus or through callosal connections between the right and left DLPFC (Meehan et al, 2011). Therefore, we aimed to investigate whether long-term, unilateral, low-frequency right DLPFC rTMS may be an effective strategy to increase excitability of the left DLPFC via transcallosal pathways, thereby yielding sustained symptom improvements in individuals with MdDS. We hypothesized that low-frequency right DLPFC rTMS would improve our patient's balance and lessen his symptoms of anxiety and depression for at least 6 weeks.

CASE REPORT

In 2010, a 41-year-old, right-handed male with a medical history of dizziness and migraine headaches presented to the Denver Health Outpatient Clinic for evaluation of abnormal perception of motion while awake, which he described as "constant rocking." He was diagnosed with MdDS by a neurologist. The patient's MdDS symptoms had begun in 2005 following exposure to motion on an airplane. He complained of dizziness immediately following the ride, which ultimately worsened 2 months later after car travel to Las Vegas, Nevada. According to the patient, the symptoms were worse in the morning than in the afternoon and evening, and they became more severe with each episode, during which he reported difficulty walking, maintaining balance, thinking, and seeing. The patient reported that his symptoms temporarily subsided when he drove a car; thus, his ability to drive remained unaffected.

The patient had a prior history of migraine headaches that started in his late 20s, including pulsating headache attacks associated with photophobia and nausea. These episodes lasted several hours. He also reported episodes of monocular flashing lights, which lasted for 60 minutes. His family history was positive for similar migraine headaches on the maternal side. He also reported a history of anxiety and panic attacks but did not seek treatment for those.

Following his diagnosis, the patient was referred to physical therapy and was prescribed clorazepate 15 mg daily for MdDS and 10 mg olanzapine three times daily for mood and depression. In prior reports, serotonin reuptake inhibitors have been shown to reduce MdDS symptoms (Canceri et al, 2018), but it is certainly possible that decreased anxiety or other comorbid symptoms could have contributed to this effect. Our patient reported that when he started the clorazepate, it definitely helped his MdDS symptoms, and he noticed an increase in symptoms whenever he stopped or ran out of the medication; however, the patient also felt that the symptoms were not completely relieved by medication, hence his desire to try TMS-related interventions in 2016 during his regular care visit.

INTERVENTION AND OUTCOME MEASURES

rTMS Intervention

We performed rTMS on our patient using an air-cooled Magstim SuperRapid2 (Magstim Co) figure-of-eight-coil and a Magstim SuperRapid stimulation unit. Following standard skin preparation procedures, we attached bipolar surface EMG electrodes over our patient's right first dorsal interosseous muscle, 2 cm apart. EMG signals were band-pass filtered (5–1000 Hz) and amplified (×2000) using a Biopac EMG system (BN-EMG2, Biopac Systems Inc). The resting motor threshold was determined by finding the lowest amplitude that elicited an EMG response from the first dorsal interosseous muscle at rest, following five of 10 pulses delivered over the hand-knob area of the motor cortex (M1). We applied rTMS to the right DLPFC (5.5 cm anterior of M1) using 1 Hz at 110% resting motor threshold for 1800 pulses/day (30 minutes) for 2 weeks, for a total of 10 treatments (5 consecutive days/week). These specific rTMS parameters, which have previously been adopted in MdDS research protocols, are generally accepted as safe and are considered to be low risk for side effects (Chen et al, 1997; Rossi et al, 2009; Wassermann, 1998).

Outcome Measures

To address the full symptomatic spectrum of this disorder, we chose to assess our patient's balance function, anxiety, and depression using an experimental reversal design (baseline-intervention-baseline). The outcome measures we selected were the Sensory Organization Test (SOT; Nashner and Peters, 1990), a quantitative method for assessing upright and in-place balance, and the Hospital Anxiety and Depression

Scale (HADS; Snaith, 2003), a standardized scale for assessing potential improvements in anxiety and depressive symptoms.

Sensory Organization Testing

The SOT is a standardized, computerized dynamic posturography test that measures an individual's ability to use information from the visual, vestibular, and somatosensory systems to control his or her balance (Nashner and Peters, 1990). The SOT provides the opportunity to change the interplay of visual, vestibular, and somatosensory inputs during testing, which in turn provides information regarding each system's importance in maintaining one's balance (Nachum et al, 2004).

The SOT consists of six test conditions, with three trials per condition and each trial lasting 20 seconds. According to Shim et al (2018, p. 917), there are six SOT test conditions: "(1) eyes open with fixed surroundings and platform (SOT 1); (2) eyes closed with a fixed platform (SOT 2); (3) sway-referenced surroundings with a fixed platform (SOT 3); (4) eyes open with fixed surroundings and a sway-referenced platform (SOT 4); (5) eyes closed with a sway-referenced platform (SOT 5); (6) sway-referenced surroundings and a platform (SOT 6)." The results provide an equilibrium score (EQS) for each of the six conditions, an EQS composite score, four ratios of sensory analysis, and a strategy analysis report.

EQSs ranging from 0% to 100%, with 100% indicating perfect stability and 0% indicating a fall, were calculated for each trial. The EQS for each condition is the average of the three trials (Vanicek et al, 2013). Because individuals with MdDS have notable disturbances in their equillibrium (Nachum et al, 2004), a composite EQS change of ≥ 8 points is considered a clinically significant change (Wrisley et al, 2007).

There are four ratios of sensory analysis: somatosensory, visual, vestibular, and visual preference. The scores for each somatosensory, visual, and vestibular ratio reflect the individual's ability to use each sensory system to maintain balance. According to the NeuroCom Balance Manager 2016 SOT protocol (www.natus.com), the scores for the visual preference ratio reflect the degree to which an individual relies on visual information to maintain balance, even when that information may be incorrect.

The strategy analysis is a report that quantifies the relative movement about the ankles (ankle strategy) and about the hips (hip strategy) that an individual uses during each trial to maintain balance. Normally, when a surface is stable, individuals move primarily about the ankles; when a surface begins to lose its stability, individuals shift their movements to their hips. A strategy analysis score change of ≥ 10 points is considered a clinically significant change (Wrisley et al, 2007).

We used Version 8 of the SMART Balance Master Equitest software (NeuroCom) to conduct the SOT. To our knowledge, our study is the first study to use a standardized balance-specific test as the primary measure of treatment efficacy for MdDS. Previous studies have used the SOT only to demonstrate balance differences in individuals with and without MdDS (Nachum et al, 2004). Our patient took the SOT on four occasions: a practice session, pre-rTMS, post-rTMS, and 6 weeks post-rTMS. The practice session was provided in order to familiarize the patient with the SOT procedure and eliminate a potential learning effect of the test prior to actual testing. We excluded the practice test data from our analysis.

Hospital Anxiety and Depression Scale

The HADS is a well-validated self-rating scale that is used to assess symptom severity and determine clinically significant anxiety and depression (Bjelland et al, 2002). The HADS is divided into an Anxiety subscale and a Depression subscale; each consists of seven items rated on a 4-point scale from 0 to 3 (Zigmond and Snaith, 1983). The classification descriptors for scaled scores on the HADS are as follows: 0 to 7 is considered normal, 8 to 10 is considered borderline, and ≥ 11 indicates potentially clinically relevant anxiety or depressive symptoms, respectively. A HADS subscale score change that results in a different classification descriptor is considered a clinically significant change (Snaith, 2003).

RESULTS

Analysis of the SOT

The EQS and strategy analysis score from our patient's SOT are summarized in Table 1. The patient's results showed

TABLE 1. Equilibrium Score (EQS) and Strategy Analysis Score for Each Condition, as Well as the EQS Composite Score, on the Sensory Organization Test

	Pre-rTMS		Post-rTMS		6 Weeks Post-rTMS	
Test Condition	**EQS**	**Strategy**	**EQS**	**Strategy**	**EQS**	**Strategy**
1	87.33	85.33	92.00	93.67	93.33	95.67†
2	70.33	73.00	88.33	90.00†	83.33	87.67†
3	75.00	75.00	87.33	89.33†	83.33	86.00†
4	59.33	32.00	79.00	69.67†	85.33	84.00†
5	38.33	0.00	52.33	62.33†	59.33	66.00†
6	26.00	4.00	53.67	69.67†	62.67	67.00†
EQS Composite Score	54.00		71.00†		75.00†	

Data are reported as M.

†A composite EQS change of ≥ 8 points, and a strategy analysis score change of ≥ 10 points, from pre-rTMS to post-rTMS and at 6 weeks post-rTMS, is an indication of clinically significant change.

rTMS = repetitive transcranial magnetic stimulation.

improvements in EQSs and strategy analysis scores in all but one condition after rTMS treatment. The EQS change from pre-rTMS to post-rTMS in all SOT conditions except for SOT 1 was > 8 points, indicating a clinically significant change post-rTMS, which was maintained 6 weeks post-rTMS. There was also a strategy analysis score change of ≥10 points from pre-rTMS to post-rTMS and at 6 weeks post-rTMS in all SOT conditions except for SOT 1 post-rTMS, indicating a clinically significant change. The EQS composite score changed from 54 pre-rTMS to 71 post-rTMS, a 17-point change, indicating a clinically significant change.

Our patient's reliance on each sensory input (somatosensory, visual, vestibular, visual preference) to maintain balance is represented in Figure 1. After rTMS, our patient improved on every sensory input, and these improvements were maintained at 6 weeks, except for somatosensory input.

On a stable surface (fixed support; SOT 1–3), our patient relied on ankle movements to maintain his balance pre-rTMS, as expected in a normal individual, and rTMS increased our patient's use of this strategy post-rTMS and at 6 weeks post-rTMS. In contrast, on a less stable surface (sway-referenced support, SOT 4–6), our patient relied on hip movements to maintain his balance pre-rTMS, as expected in a normal individual, but rTMS changed this strategy by decreasing his reliance on hip movements to favor ankle movements post-rTMS and at 6 weeks post-rTMS (Figure 2).

Analysis of the HADS

Our patient's anxiety and depression decreased, as expressed in lower HADS subscores, after the rTMS intervention, and this was sustained for 6 weeks post-rTMS (Figure 3). On the Anxiety subscale, the sum decreased by 2 points post-rTMS and by 3 points at 6 weeks post-rTMS, compared with pre-rTMS. These scores were considered abnormal on each test occasion. However, on the Depression subscale, the sum decreased by 7 points post-rTMS and by 6 points at 6 weeks post-rTMS, compared with pre-rTMS. These scores were considered abnormal pre-rTMS and borderline post-rTMS and at 6 weeks post-rTMS. Therefore, in terms of a classification descriptor, our patient moved from abnormal to borderline on the Depression subscale, which is a clinically significant change.

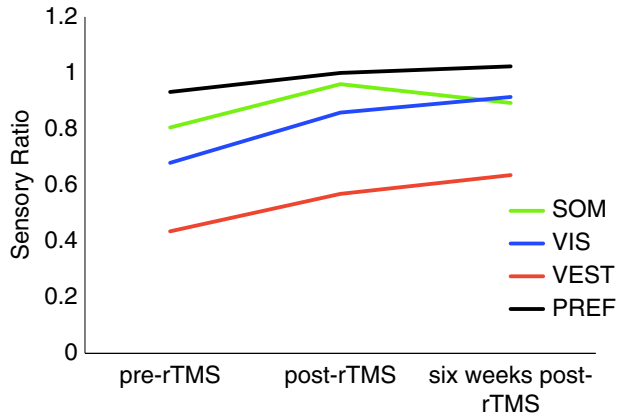

FIGURE 1. Our patient's strategy of sensory systems' use for postural control. The somatosensory (SOM), visual (VIS), and vestibular (VEST) ratios reflect our patient's ability to use each sensory system to maintain balance. The preference (PREF) ratio reflects the degree to which our patient relies on visual information to maintain balance, even when the information may be incorrect. **rTMS** = repetitive transcranial magnetic stimulation.

LITERATURE REVIEW

We conducted an online literature search for studies concerning MdDS and rTMS using English-language health databases (ie, PubMed, Google Scholar, and PsycInfo). Articles dating until June 18, 2019 were included. Keywords searched included "rTMS," "MdDS," and "theta burst stimulation." All articles included in the literature review were qualitatively analyzed for their rTMS protocol, outcome, and adverse events.

We discovered that experimental rTMS protocols have been used to treat individuals with MdDS in 12 studies (including this one), with one research group largely contributing to the total participant sample in the literature (Table 2).

rTMS Protocols and Outcomes

In a pilot study, Cha et al (2013) investigated the feasibility and tolerability of rTMS for 10 individuals with MdDS, as well as different stimulation parameters using DLPFC as the anatomical target. The DLPFC, a well-studied target for other functional brain disorders, was chosen based on the lower prefrontal metabolism in individuals with MdDS (Cha et al, 2012), the DLPFC's role in attention to spatial information (Diwadkar et al, 2000; Grimault et al, 2009), and its common use as a target in the treatment of anxiety and depression. One session of high-frequency (10 Hz) rTMS over the contralateral DLPFC (cDLPFC), with respect to the dominant hand, or low-frequency (1 Hz) rTMS over the ipsilateral DLPFC (iDLPFC), reduced self-reported symptoms of the study participants' rocking perceptions. In right-handed patients, the observed effectiveness of the high-frequency cDLPFC was potentially explained by decreased metabolism in the cDLPFC in individuals with MdDS, based on resting-state fMRI and fluorodeoxyglucose-PET (Cha et al, 2012). The observed effectiveness of the low-frequency iDLPFC in those same patients was potentially explained by decreased interhemispheric inhibition of the cDLPFC (Cha et al, 2013).

In a later publication, high-frequency cDLPFC for five consecutive sessions was investigated, whereby symptoms of MdDS were reduced; specifically, the self-reported impact of dizziness on daily life and the HADS Anxiety and Depression subscores (Cha et al, 2016a). Subsequent studies used a combination of these two protocols: low-frequency iDLPFC followed by high-frequency cDLPFC for five consecutive sessions, whereby self-reported symptom reduction was observed in select individuals (Chen et al, 2017; Ding et al, 2014; Shou et al, 2014, 2016; Yuan et al, 2017). Pearce et al (2015) applied a different rTMS protocol, consisting of high-frequency cDLPFC twice per week for 4 weeks. This protocol showed improvements in

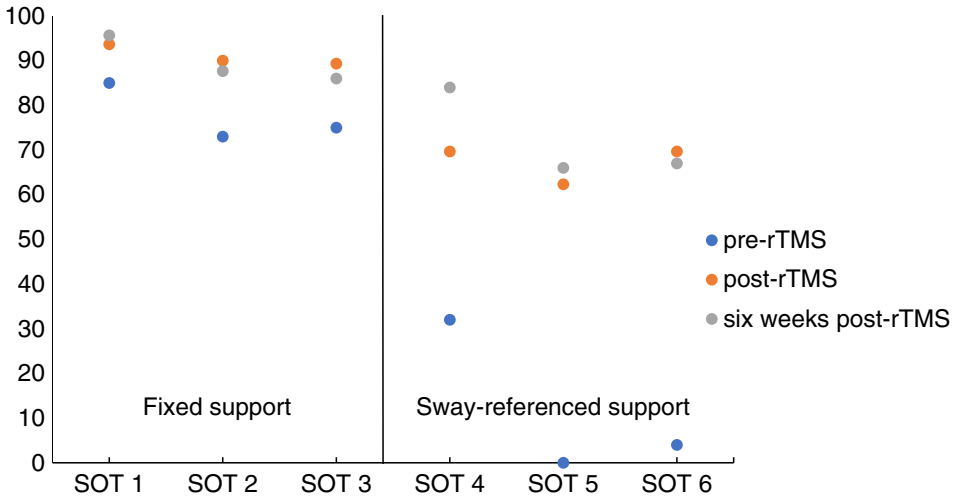

FIGURE 2. Our patient's strategy of ankle versus hip movements' use for postural control. A score near 100 indicates a full ankle strategy; a score near 0 indicates a full hip strategy. SOTs 1 to 3 are fixed support; SOTs 4 to 6 are sway-referenced support. Normal individuals move primarily around the ankle joints when the surface is stable and shift to hip movements when the surface becomes less stable. rTMS increased use of the ankle strategy on stable surfaces and decreased use of the hip strategy on unstable surfaces. **rTMS** = repetitive transcranial magnetic stimulation. **SOT** = Sensory Organizaton Test.

balance, and confidence in balance, during activities of daily living.

Neurophysiologic Mechanisms of Clinical Benefit

A variety of neuroimaging techniques have been used to evaluate the neuromodulatory effects of rTMS protocols and optimize their effectiveness, including EEG and fMRI (Ding et al, 2014; Shou et al, 2014, 2016; Yuan et al, 2017). Ding and colleagues (2014) developed a simultaneous TMS-EEG protocol to investigate the effect of rTMS on neural activity and connectivity in individuals with MdDS. This study used a 5-day consecutive bilateral rTMS protocol in conjunction with a novel resting-state EEG analysis framework, resulting in a significant correlation between resting-state EEG connectivity in the parietal and occipital areas and symptoms pre- to post-TMS sessions—such that spectral power changes in high alpha and beta were negatively correlated with visual analog scale score changes. By combining EEG neural synchrony measures and fMRI resting-state functional connectivity measures in another study, Chen et al (2017) observed a significant negative correlation between spectra frequency shifts of EEG and connectivity change in fMRI in the parietal cortex, temporal cortex, visual/parietal area, and DLPFC. Similarly, in another study, Cha et al (2018b) found that intrinsic functional connectivity changes correlated with MdDS symptom improvement.

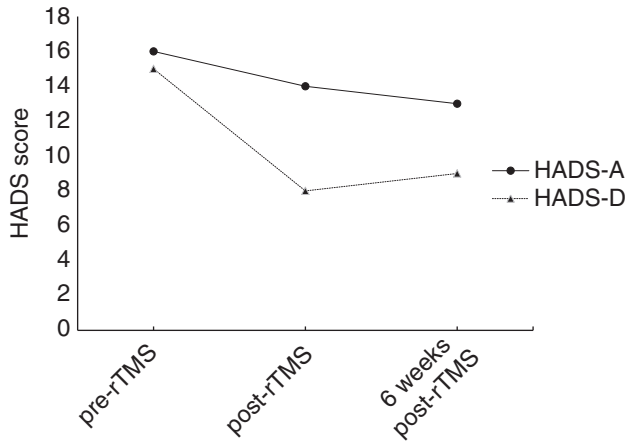

FIGURE 3. Our patient's scores on the Anxiety subscale (HADS–A) and Depression subscale (HADS–D) on the Hospital Anxiety and Depression Scale (HADS) decreased from pre-rTMS to post-rTMS and at 6 weeks post-rTMS, indicating a reduction in anxiety and depression symptoms. **rTMS** = repetitive transcranial magnetic stimulation.

Shou et al (2016) used EEG functional connectivity and neural synchrony measures to evaluate the bilateral rTMS protocol and develop a novel rTMS protocol designed to be subject specific, in which continuous theta-burst stimulation targeted either the cerebellar vermis or the occipital lobe. Interestingly, the authors found that self-reported symptoms of rocking perception were reduced to a greater degree after the cerebellum/occipital rTMS protocol rather than after the DLPFC protocol. However, no quantifiable measures were included. Since then, the Cha laboratory personnel have explored rTMS in MdDS as a way to normalize hyperconnectivity in occipital networks, and EEG as a complementary modality in predicting treatment responses (Chen et al, 2019).

DISCUSSION

We hypothesized that low-frequency right DLPFC rTMS would improve our patient's balance and lessen his symptoms of anxiety and depression for at least 6 weeks. Our results confirm this hypothesis. To our knowledge, this is the first report of the short-term use of low-

TABLE 2. Reported Cases of Repetitive Transcranial Magnetic Stimulation (rTMS) in Individuals with Mal de Debarquement Syndrome

Reference	N	rTMS Protocol	Outcome	Adverse Event
Cha et al (2013)	10	One session each of left 10-Hz, left 1-Hz, right 10-Hz, and right 1-Hz rTMS over the dorsolateral prefrontal cortex (DLPFC)	With respect to the dominant hand, 10-Hz contralateral DLPFC (cDLPFC) or 1-Hz ipsilateral DLFPC (iDLPFC) reduced self-reported symptoms of rocking perception Symptom improvement was sustained for at least 60 minutes Negative correlation ($R^2 = -0.5509$) between the duration of illness and the percent change in self-reported symptoms of rocking perception	Mild, site-of-stimulation headache; severe headache; post-rTMS fatigue; negative cognitive effects
Ding et al (2014)	10	Five sessions of 1-Hz iDLPFC followed by 10-Hz cDLPFC (hereinafter referred to as bilateral rTMS)	Negative correlations in high alpha and beta bands from independent component 2 (left occipital topography) and self-reported symptom change Positive correlations in beta band from independent component 9 (parietal topography) and self-reported symptom change	None noted
Shou et al (2014)	10 (same sample as Ding et al, 2014)	Five sessions of bilateral rTMS	Bilateral rTMS reduced self-reported symptoms of rocking perception in five out of 10 participants The resting-state electroencephalography (rsEEG) analysis suggested that spectral powers in low-frequency bands increased over occipital, parietal, motor, and prefrontal cortices post-bilateral rTMS There was a significant correlation between rsEEG and self-reported symptoms of rocking perception in the high-frequency bands over posterior parietal and left visual areas	None noted
Pearce et al (2015)	13	Eight sessions of 10-Hz cDLPFC	Score improvement in Mini-Balance Evaluation Systems Test (miniBEST) and Activities-specific Balance Confidence Scale	Mild headache
Cha et al (2016a)	8	Five sessions 10-Hz cDLPFC and sham rTMS	Group-level reduction in Dizziness Handicap Inventory score 1, 3, and 4 weeks post-rTMS Group-level reduction in Anxiety and Depression subscores on the Hospital Anxiety and Depression Scale (HADS) starting week 2 and 3, respectively	Head discomfort; mild, site of stimulation head tenderness; lightheadedness
Cha et al (2016b)	23 (includes Ding et al, 2014 sample)	Five sessions of bilateral rTMS; 20 sessions of transcranial direct current stimulation (tDCS) and sham tDCS	Bilateral rTMS followed by tDCS improved symptoms of rocking perception, as measured by the MdDS Balance Rating Scale (MBRS), and symptoms of anxiety, as measured by the HADS	Mild side effects, such as tingling, itching, redness, headache, tiredness, confusion, and nausea
Shou et al (2016)	36	Five sessions of bilateral rTMS; cerebellar theta-burst stimulation (cTBS) over the cerebellar vermis, lateral cerebellar hemisphere, or occipital lobe	cTBS led to a greater reduction in visual analog scale scores as compared to bilateral rTMS	None noted
Chen et al (2017)	10 (same sample as Ding et al, 2014)	Five sessions of bilateral rTMS	Three with reduced self-reported symptoms, three with increased reduced self-reported symptoms, four neutral	None noted

Yuan et al (2017)	20 (same sample as Cha et al, 2016b)	Five sessions of bilateral rTMS	Symptom improvement was correlated with a post-rTMS reduction in functional connectivity in the posterior default mode network	Mild headache
Cha et al (2018b)	20 (same sample as Cha et al, 2016b)	Five sessions of bilateral rTMS	Post-rTMS symptom improvement was correlated with an increase in low alpha band intrinsic functional connectivity (IFC), a decrease in other IFC bands, and high baseline IFC in the high alpha and beta bands	None noted
Chen et al (2019)	20 (same sample as Cha et al, 2016b)	Five sessions of bilateral rTMS	EEG and functional MRI measures can be biomarkers used to optimize the treatment effect of rTMS	None noted
Present article	1	10 sessions of 1-Hz iDLPFC	The participant showed improvement in balance function, as measured by the Sensory Organization Test, and in symptoms of anxiety and depression, as measured by the HADS after rTMS	None noted

frequency iDLPFC rTMS to treat individuals with MdDS while also using a standardized and quantifiable outcome measure related to balance. The SOT has been used previously to investigate disorders that result in impairments and activity restrictions of balance and mobility, including multiple sclerosis (Horn et al, 2018) and mild traumatic brain injury (Walker et al, 2018). Cha et al (2013) concluded that one session of 1-Hz cDLPFC rTMS was not as effective as one session of 10-Hz cDLPFC or 1-Hz iDLPFC rTMS at reducing symptoms of rocking perceptions on a self-reported scale. However, our patient showed a significant and sustained improvement in balance function as measured by the SOT after a 2-week session of 1-Hz iDLPFC rTMS. Specifically, a composite change of >8 points, indicating a significant clinical change due to rTMS intervention, was achieved post-rTMS and was maintained for 6 weeks post-rTMS.

The SOT also provides information regarding the role played by each sensory system in maintaining balance (Nachum et al, 2004). Individuals with MdDS show brain volume differences in visual-vestibular processing areas and default mode network structures (Cha and Chakrapani, 2015). Interestingly, the rTMS intervention benefitted each of the six sensory inputs, and this benefit was maintained at 6 weeks post-rTMS (except for the somatosensory system).

A high anxiety/depression comorbidity exists in individuals with MdDS (Cha, 2009; Hain et al, 1999). Cha et al (2016a) observed statistically and clinically significant decreases in Anxiety subscores starting 2 weeks post-rTMS and in Depression subscores starting 3 weeks post-rTMS (five sessions of 10-Hz cDLPFC). Our study used 10 sessions of 1-Hz iDLPFC which, to our knowledge, is the greatest number of sessions used for the treatment of MdDS. Nevertheless, 10 sessions of rTMS is less than the standard 20 to 30 sessions for the treatment of depression (Trevizol and Blumberger, 2019). Still, our patient displayed a clinically significant change on the Depression subscore post-rTMS and at 6 weeks post-rTMS.

Investigations using neuroimaging methods have improved our specificity of stimulation targets using neuroimaging-based navigation strategies and have expanded our knowledge of the pathophysiology of MdDS. However, our fundamental understanding of MdDS and its treatment is still limited. It may turn out that a combination of several rehabilitation techniques will be more effective than one technique alone at improving symptoms in individuals with MdDS. For instance, Cha et al (2016b) showed that patients who received transcranial direct current stimulation after rTMS experienced significant improvements in their degree of rocking perception. Alternatively, as proposed by Chen et al (2019), MdDS may be a network-modifying disease for which transcranial direct current stimulation may be a better therapeutic strategy than rTMS because it targets distributed brain networks more adequately (To et al, 2018).

Study Limitations

The single-case experimental design of a novel treatment outcome in a single patient has limited utility in

terms of generalizability to the larger MdDS population. Though it seems unlikely that our patient's improvement was unrelated to the rTMS, given his long duration of symptoms, we cannot rule out this possibility. Moreover, although our patient improved on most outcome measures, the placebo effect cannot be excluded. It is possible that multiple sessions of rTMS itself may have affected our patient's balance, anxiety, and depression. Although the results suggest clinically significant change, according to Wrisley et al (2007), a single case study does not present sufficient statistical power for statistical analysis.

CONCLUSION

Our case study provides novel, preliminary evidence of the potential benefit of rTMS (based on the administered protocol) as a noninvasive treatment option for improving the major symptoms of MdDS—balance function, anxiety, and depression. Our patient showed an important and sustained improvement in all three after rTMS. Therefore, this study provides further support for the safe and effective clinical use of rTMS for individuals with MdDS, without significant side effects.

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