Journal of Neuropsychology (2015)

The British Psychological Society

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Brief communication

Efficacy of neurostimulation to treat symptoms of Mal de Debarquement Syndrome. A preliminary study using repetitive transcranial magnetic stimulation

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Mal de debarquement syndrome (MdDS) is a rare and poorly understood condition of perceived continual motion. Using a multiple-case design (n = 13; 8 f; 63.5 ± 12.6 years), this study investigated the efficacy of eight 20-min sessions, over 4 weeks, of repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral pre-frontal cortex. Compared to sham, rTMS demonstrated improvement in balance and confidence in daily living activities. rTMS shows promise for the treatment of MdDS. However, larger trials with longer intervention periods are required.

First described in 1881, Mal de debarquement syndrome (MdDS) occurs when an individual habituates to unstable movement, failing to readapt upon return to stable conditions. MdDS, classified as an 'orphan disease' through a definition of limited prevalence, has generally been reported following a sea voyage. However, MdDS has also been reported following plane and motor vehicle travel (see review by Cha, 2009).

Individuals have characteristically described MdDS using descriptive terms such as 'rocking', 'bobbing', or 'walking on a trampoline', despite being on stable ground. In most cases, this perception disappears quickly as individuals readjust to stable surfaces. However, a small percentage of cases present with persistent MdDS, where symptoms persist for months and, in some cases, years (Cha, 2009; Pearce, Adair, & Tooley, 2013). Those reporting onset of persistent MdDS appear to be aged in their late 40s (Cha, 2009). Macke, LePorte, and Clark (2012) revealed that patients with persistent MdDS (n = 101; mean age 52 ± 10.9 years; duration 44 ± 45.3 months) had self-reported a poorer quality of life (QOL), with a mean composite QOL score of 59.26 ± 1.89 (of 100).

Although little is known about persistent MdDS, the disorder cannot be explained by structural brain or inner ear pathology (Cha, 2009; Cha, Chakrapani, Craig, & Baloh, 2012; Cha, Cui, & Baloh, 2013). For example, magnetic resonance imaging results are uniformly normal. Similarly, utricular and vestibular function testing and vestibular evoked myogenic potentials show no abnormalities (see review Cha, 2009). Conversely, MdDS has been suggested that the condition may be a neuroplastic maladaptation of the

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DOI:10.1111/jnp.12070

sensorimotor system (Clark & Quick, 2011; Clark *et al.*, 2012; Shou, Yuan, Urbano, Cha, & Ding, 2014) and/or altered brain metabolism and functional connectivity from the dorsolateral pre-frontal cortex (DLPFC) in areas that process and store spatial information. For example, Cha *et al.* (2012) showed that patients with MdDS had hypermetabolism in the left entorhinal cortex and amygdala, with hypometabolism in frontal regions, including the supplementary motor area and left DLPFC, compared with controls.

To address this working hypothesis, transcranial magnetic stimulation has been considered as a potential treatment for patients with persistent MdDS. Using the technique of repetitive transcranial magnetic stimulation (rTMS) delivered over the DLPFC, Cha *et al.* (2013) demonstrated transient reduction in rocking sensations, measured via a visual analogue scale, following a single session of 4-s trains at 10 Hz (40 pulses), with a 26-sec rest interval between each train, for a total of 45 trains (session total of 1800 pulses for 22.5 min). More recently Shou *et al.* (2014) showed reduction in rocking sensations and alterations in electroencephalography (EEG) activity following five consecutive days of rTMS. Collectively, these studies indicate rTMS holds promise as a therapeutic treatment for persistent MdDS. However, as acknowledged by the authors, further trials are required including multiple sessions of rTMS and the inclusion of a sham condition. This study, using a multiple-case study design, presents preliminary data comparing the efficacy of 4 weeks of real versus sham rTMS on balance confidence in activities of daily living and postural ability.

Methods

Fourteen participants (8 female, 63.5 $\pm$ 12.6 years, 12 right-handed; mean time since first report of MdDS 89.5 $\pm$ 56.2 months) started, with 13 completing the study. One participant (sham) expressed feeling uncomfortable with rTMS and withdrew after three of the eight sessions.

Inclusion for the study required diagnosis of MdDS and referral from their neurologist based upon the following criteria by Cha *et al.* (2013): (1) continued reporting of 'rocking', or 'bobbing', initiated following sea-, air-, or land-based travel; (2) self-reporting of symptoms of minimum 6 months; (3) normal peripheral inner ear function testing; (4) normal MRI brain structural imaging; and (5) neurologist determining no other cause for symptoms. Participants were instructed to cease all other potentially therapeutic activities (e.g., vestibular training exercises) during the study intervention period. All study methods were approved by the university ethics board and completed according to the Declaration of Helsinki guidelines. Following signed informed consent, participants were randomly divided into either an rTMS or an sham rTMS group via computer-generated random number program.

Assessment for balance and confidence in daily activities

Balance testing was performed at baseline and at completion of eight sessions of rTMS treatment. A modified form of the balance evaluation systems test (BESTest) known as the miniBEST (Franchignoni, Horak, Godi, Nardone, & Giordano, 2010), incorporated 14 items of dynamic balance across four subscales: (1) anticipatory postural adjustments, (2) postural responses, (3) sensory orientation, and (4) balance during gait. For details regarding testing protocols, please see Franchignoni *et al.* (2010).

Confidence in balance during activities of daily living was evaluated at baseline, after four sessions, and at the completion of the eight sessions using the Activities-specific Balance Confidence Scale (ABC) (Powell & Myers, 1995). The ABC includes 16 items, providing a composite score out of 100, according to how confident the participant is not losing their balance or becoming unsteady whilst performing certain daily activities. For further detail, please see Powell and Myers (1995).

Transcranial magnetic stimulation

Individualized stimulus intensities for the rTMS sessions were first determined using single-pulse TMS (Magstim, UK). For reliability of TMS stimulation, electromyography, and determination of motor threshold, please see Cha *et al.* (2013) and Pearce *et al.* (2013). Resting motor threshold was identified as the percentage of stimulator output that produced a motor-evoked potential in the first dorsal interosseous muscle of 50 μV amplitude in 50% of trials.

rTMS treatment was provided twice per week, by an independent operator for 4 weeks. A Rapid^2 stimulator delivered pulses using a 70-mm figure-of-eight air-film coil or identical sham coil (Magstim, UK) at 100% of resting motor threshold, at a frequency of 10 Hz in 45 trains of 40 pulses per train for a total number of 1800 pulses per session (Cha *et al.*, 2013). During each treatment session, participants wore a snugly fitted EEG cap (Easycap, Germany) with pre-marked sites based upon the international 10–20 system. DLPFC rTMS stimulation was delivered over either F3 or F4 area contralateral to the participant's dominant arm. As a neuronavigation system was not used, to ensure reliability of stimulation, the operator regularly checked the placement of the fitted cap with pre-marked sites with reference to the nasion–inion and interaural lines (Pearce *et al.*, 2013) between stimulation trains, to ensure consistency of the site of stimulation.

Data analyses

Data are presented as individual changes in pre/post balance performance and confidence of balance activities. Descriptive statistics (group means ± *SD*) and Cohen's *d* were calculated by quantifying the difference between two means divided by the mean of the standard deviation as follows:

$$d = \frac{M_1 - M_2}{SD_{\text{pooled}}}.$$

The difference between the before and after values for each group is described using the terms 'trivial' (<.2), 'small' (.21–.5), 'medium' (.5–.79), and 'large' (>.8). Correlations (Pearson's *r*) were undertaken between the change in miniBEST and ABC scale between each group.

Results

In the 13 who completed the intervention, no serious adverse effects were reported. Two participants described experiencing a mild transient headache after only one of the eight sessions.

Group comparisons revealed following real rTMS a large overall effect change (group miniBEST mean score before: 25.7 ± 1.7 vs. after: 28.2 ± 1.7 1.4; $d = 1.6$), whilst the

sham rTMS group showed a small effect change (group miniBEST mean score before: 24.2 ± 4.4 vs. after: 24.7 ± 5.6; $d = 0.1$). Individual miniBEST data are shown in Figure 1. Six of seven participants in the real rTMS demonstrated improvement in miniBEST scores. In the control group, two of the six demonstrated improvement in miniBEST scores, three remained unchanged, and one showed decline.

Group comparisons showed a large effect size change in confidence from before to middle (group ABC score 45.8 ± 10.9% vs middle 56.8 ± 12.2%; $d = 0.95$) and before to after (group ABC score 45.8 ± 10.9% vs after 58.9 ± 12.8%; $d = 1.11$) in the real rTMS group. Small effect sizes were found in the sham rTMS group (before 45.4 ± 5.1%, middle 46.3 ± 10.0%, after 48.2 ± 16.2%; $d = 0.12$ before–middle; $d = 0.26$ before–after). Figure 2 illustrates individual changes in ABC scores. The same six participants in the real rTMS group expressed improvement in ABC scores. However, the correlation between the change in ABC scale and the miniBEST was small ($r = .21$; $p = .69$). In the control group, one of the six communicated improvement, two remained unchanged and three conveyed decline in ABC scores ($r = .10$; $p = .69$).

Discussion

To date, this is the first randomized sham-controlled study presenting data investigating the efficacy of rTMS to treat symptoms of MdDS. Participants who received real rTMS in this study reported reduction in descriptive symptoms of 'rocking' and 'bobbing', with associated improvement in undertaking activities of daily living (revealed in the ABC scores) such as walking up and down stairs, reaching for objects above head height, and walking in crowded public spaces. Extending on the recent work by Cha *et al.* (2013) and Shou *et al.* (2014), data in this study support these findings suggesting further promise in utilizing rTMS in reducing symptoms of MdDS.

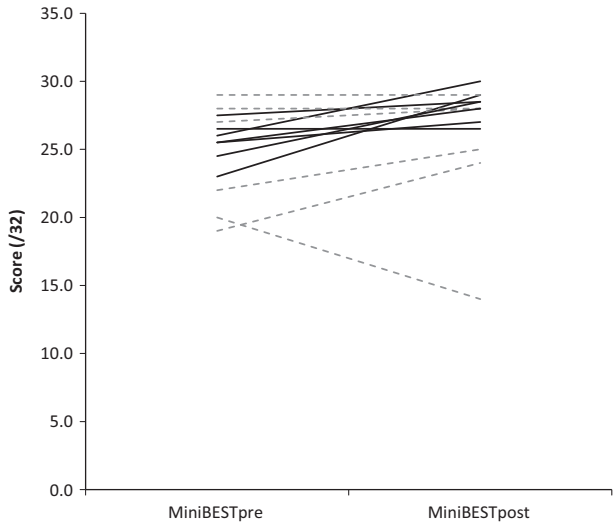

Figure 1. Individual responses to balance testing (miniBEST) scores before (pre) and after (post) eight sessions of repetitive transcranial magnetic stimulation (rTMS). Dark lines represent each participant who received real rTMS ($n = 7$), whilst the light broken lines represent sham rTMS ($n = 6$).

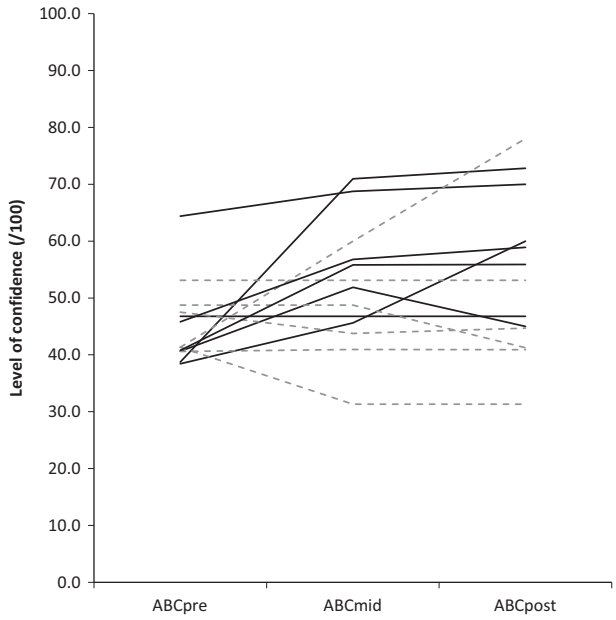

Figure 2. Individual responses in Activities-specific Balance Confidence Scale (ABC) before (pre), after four sessions of repetitive transcranial magnetic stimulation (rTMS) (mid) and after (post) eight sessions of rTMS. Dark lines represent each participant who received real rTMS ($n = 7$), whilst the light broken lines represent sham rTMS ($n = 6$).

However, the preliminary nature of the study and the rarity of this orphan condition limited the ability to recruit a larger sample. The small sample studied would contribute to the variance in the spread of the data, demonstrated by the large group standard deviations. Similarly, it is not possible to explain the observed larger increase in the ABC scores over the first 2 weeks of the intervention (Figure 2). Finally, the mean age of the participants recruited for this study is relatively high, compared to the usual age reported in the literature (see review Cha, 2009). Taken together, this limits capacity for clinical interpretation of the findings. Caution, therefore, should be taken when generalizing the present study outcomes to the wider MdDS population.

Although the exact mechanisms are yet to be elucidated, there is accumulating evidence that multiple bouts of high frequency rTMS, inducing long-term potentiation and modulating intracortical activity, over DLPFC are helpful for a range of behavioural and cognitive conditions. With its high connectivity to other regions of the brain, Shou *et al.* (2014) demonstrated EEG modulation, not only in the site of stimulation but also in functionally connected regions including the visual cortex, supplementary motor area, and pre-frontal cortex that were associated with improvements in MdDS symptoms.

In this group, the present study showed that multiple bouts of rTMS were well tolerated in 13 participants who completed the intervention. Further, participants did not anecdotally report fatigue, mood, or cognitive changes between stimulation sessions (other than improvement in symptoms in the rTMS group). This differs to some of the side effects reported by Cha *et al.* (2013) but may be explained by the differences in methodologies. For example, Cha *et al.* (2013) compared differences in low (1 Hz)- and high (10 Hz)-frequency stimulation over two areas (left and right DLPFC) with testing

separated between 2 and 7 days. Conversely, this study had fixed rTMS protocols and days of treatment (Mondays/Thursdays).

Despite these differences, the growing data to date on using rTMS show promise for those with persistent MdDS. Further studies are required to explore the efficacy of individualized rTMS treatments (such as frequency rate of stimulation and number of trains prescribed per session) as well as determining the optimal interval between treatment sessions, as well as the total number of sessions for treatment.

Acknowledgements

No financial assistance was provided for this study.

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Received 12 January 2015; revised version received 16 February 2015