Changes of Symptom and EEG in Mal de Debarquement Syndrome Patients after Repetitive Transcranial Magnetic Stimulation over Bilateral Prefrontal Cortex: A Pilot Study

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Abstract— **Mal de debarquement syndrome (MdDS) is a chronic disorder of imbalance characterized by a feeling of rocking and swaying. The medical treatment for MdDS is still limited. Motivated by our previous pilot study that demonstrates the promising clinical efficacy of repetitive transcranial stimulation (rTMS) in MdDS patients, a novel rTMS paradigm, i.e., 1 Hz stimulation over ipsilateral dorsal lateral prefrontal cortex (DLPFC) with respect to the dominant hand followed by 10 Hz stimulation over contralateral DLPFC, was proposed and conducted in MdDS in the present study. To evaluate the potential efficacy, we examined the changes before and after rTMS in both subjective reported symptom using visual analogue scale (VAS) and direct brain activity in resting state electroencephalography (rsEEG). To disentangle activity from distinct brain substrates and/or local networks in rsEEG signals, a group-wise independent component analysis was employed and the corresponding spectral power changes were examined in the identified components. In general, reduction in rocking sensation was reported in five of ten subjects (with dramatic reductions (changes > 30) in three subjects) after rTMS using the present paradigm, while no changes and slight increases in rocking sensation were reported in the remaining subjects. In rsEEG, significant elevated spectral powers in low frequency bands (i.e., theta and alpha) over broad areas of occipital, parietal, motor, and prefrontal cortices were induced by rTMS, reflecting the enhancement of cortical inhibition over these areas. Meanwhile, the significant correlations between changes in rsEEG and VAS scores were detected in the high frequency bands (i.e., high alpha and beta) over posterior parietal and left visual areas, reflecting the suppression of spatial information processing. Therefore, the present findings demonstrate the promising clinical efficacy of a new rTMS paradigm for MdDS, and suggest its merit for further studies in more patients.**

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I. Introduction

Normally, the common phenomenon of rocking dizziness that occurs after one disembarks from a boat or plane, ceases within two days of returning to land [1]. However, in some rare individuals, this rocking dizziness lasts for months or years, and becomes a chronic disorder known as mal de debarquement syndrome (MdDS) [2]. While no impairments are observed in inner ear function testing and structural brain imaging in MdDS patients [2], the likelihood of remission is low when the symptoms persist beyond 6 months; therapy for persistent MdDS remains limited [3].

MdDS has been postulated to be a disorder of maladaptive neuroplasticity since it is usually triggered by passive oscillating motion, such from a boat or plane [2]. External brain modulation, such as by repetitive transcranial magnetic stimulation (rTMS) [4], was expected to be able to generate effective treatment responses in MdDS since it can modulate neuronal excitability and may change an underlying oscillating brain rhythm that had become entrained to the passive motion trigger. A recent study on MdDS patients using four different protocols of rTMS over dorsal lateral prefrontal cortex (DLPFC) demonstrated good subject tolerance and promising short-term symptom improvement after one session of rTMS [5]. High frequency (10 Hz) rTMS performed over contralateral DLPFC (cDLPFC) with respect to the dominant hand or low frequency (1 Hz) stimulation performed over ipsilateral DLPFC (iDLPFC) were the most effective. Using another neuromodulation technology, low-level transcranial direct current stimulation (tDCS), a recent study also provided preliminary evidence that neuromodulation is a safe treatment for use with MdDS patients [6]. Moreover, a recent study has shown that combining two rTMS protocols is more efficient than unilateral stimulation in terms of number of pulses required and duration of sessions [7].

Motivated by these results, a novel rTMS protocol, i.e., 1 Hz stimulation over iDLPFC followed by 10 Hz stimulation over cDLPFC, was proposed in the present study. Theoretically, reduced iDLPFC tone and enhanced cDLPFC tone would be achieved as the net effect of this rTMS protocol, considering that strong interhemispheric inhibition between symmetric cerebral hemispheres have been reported [8]. To evaluate the long lasting modulation effects of rTMS for MdDS, the proposed rTMS protocol was performed on subjects for five consecutive days. It has been reported that MdDS patients have hypermetabolism in the left entorhinal

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cortex and amygdala and hypometabolism in prefrontal cortex as compared with healthy controls in the setting of altered functional connectivity between entorhinal cortex/amygdala and other neocortex [9]. Thus, resting state electroencephalography (rsEEG) recorded before and after 5 days of rTMS treatment was used to investigate induced resting-state brain activity changes by rTMS. The efficacy of the present rTMS paradigm for MdDS was evaluated by examining subjective reported symptom changes using visual analogue scale (VAS) and EEG spectral power changes from distinct brain substrates and/or local neural networks dissolved by independent component analysis (ICA) [10, 11]. Moreover, associations between spectral power changes in different brain substrates and VAS score changes were also examined by correlation analysis.

II. Materials and Methods

A. Subjects

Ten right-handed women (ages: 47.6±10.7 years) with persistent MdDS symptom lasting from 8-91 (40.5±24.2) months participated in the study (Table I). Their symptoms were triggered by different passive motion experiences (sea: 4, air: 3, land: 2, and other: 1). All subjects were screened by an experienced neurotologist (Y.H.C) with appropriate diagnostic testing to rule out other causes for their symptoms. Written informed consents were obtained from participants before the start of all procedures, and the study was approved by Western IRB.

TABLE I. Clinical Profile of Patients

Patient no.	*Ages at onset/rTMS*	*Length (months)*	*Trigger*
S1	60/63	39	Train
S2	45/46	19	Plane
S3	38/43	67	Scuba/Boat
S4	48/50	22	Plane
S5	54/54	39	Plane
S6	40/40	8	Cruise
S7	43/50	91	Cruise
S8	58/60	31	Cruise
S9	35/39	42	Amusement park
S10	24/28	47	Car

B. Study procedures and rTMS sessions

Prior to rTMS treatment on Day 1, subjects underwent high-resolution structural magnetic resonance imaging (MRI) scans that were used for neuronavigation during the stimulation sessions. Thereafter, five rTMS sessions were performed on each subject at five consecutive days, i.e., Day 1 to Day 5. rTMS stimulation was performed using the Magnenture MagPro X100 stimulator with a cooled figure-of-eight coil under neuronavigation by the Localite TMS Navigator frameless stereotaxy system (Localite GmBH, Germany). The middle of the left and right middle frontal gyrus was located by the navigation system as the center of the left and right DLPFCs for stimulations. Motor threshold was determined before each session and defined as the percentage intensity of the stimulator that generated a 50 μV motor evoked response in the contralateral abductor pollicis brevis muscle in five out of ten trials.

The present rTMS paradigm consisted of a standard protocol of a series of 1 Hz right DLPFC stimulation at 110% of MT for 1200 pulses (20 minutes) followed by a series of 10 Hz left DLPFC stimulation at 110% MT for 2000 pulses (25 minutes), since all subjects were right-handed. The 10 Hz protocol was administered as trains of 40 pulses over 4 seconds followed by 26 seconds of rest, i.e., each train was 30 seconds. Fifty 10 Hz trains were administered at each session.

On each day, subjects rated the degree of their MdDS symptoms on a VAS of 0-100, where 0 refers to no rocking sensation. The change in the VAS scores from the Day 1 to the Day 5 was used to evaluate the accumulating symptom changes induced by the 5-day consecutive rTMS treatment.

C. EEG acquisition and preprocessing

rsEEG signals of 5 minutes were recorded on Day 1 before subjects received their first rTMS treatment (i.e., pre-rTMS rsEEG session) and on Day 5 at four to five hours after the last rTMS treatment (i.e., post-rTMS rsEEG session). 126-channel EEG signals were recorded using a BrainAmp amplifier (Brain Products GmbH, Munich, Germany). The online reference channel was located at the FCz position, while the ground electrode was located at the AFz position. The impedance of all electrodes was maintained below 10 KΩ during recordings. EEG signals were recorded at a sampling frequency of 1000 Hz with an analog filter (from 0.016 to 250 Hz) and a resolution of 0.1 μV. Subjects were lying in a recliner quietly with eyes closed in a quiet darkened room when rsEEG signals were recorded.

A series of preprocessing steps, including band-pass filtering of 0.5-30 Hz, bad channel interpolation, epoching of 1 second, rejecting bad epochs, re-reference to common average, and down-sampling to 250 Hz, were separately performed on pre- and post-rTMS rsEEG data using the FASTER [12] and EEGLAB [13] toolboxes. Thereafter, two rsEEGs from one subject were concatenated for the ICA based artifact rejection, which identifies and rejects independent components (ICs) linked to ocular, cardiac and muscular activities. This can avoid possible artificial spectral power differences between pre- and post-rTMS rsEEGs due to different numbers of artifactual ICs being rejected if processed separately.

D. Group-wise Independent Component Analysis

To make identified differences in spectral powers more specific to underlying brain substrates, a group-wise ICA (gICA) scheme was applied. Specifically, preprocessed rsEEG epochs from individuals were separately normalized using a z-transform to reduce inter-subject variations, and temporally concatenated after short-time Fourier transform (STFT) for a gICA analysis using a complex ICA model of 25 ICs with real-valued mixing matrix [10, 11]. The ICs' epoch-wise spectral dynamics were calculated from the same STFT-transformed and temporally concatenated rsEEG epochs (without z-transform) using the ICA un-mixing matrix, and reorganized into pre-and post-TMS sessions for each

individual. Finally, the ICs that evidently link to underlying brain substrates based on spatio-spectral patterns of ICs [14] and related literature [11, 15-17] were selected for subsequent analysis.

E. Spectral Powers of ICs

rsEEG changes were examined in spectral powers of selected ICs. In both pre- and post-TMS sessions, EEG spectral powers at four frequency bands, i.e., theta (4-7 Hz), low alpha (8-10 Hz), high alpha (11-13 Hz), and beta (14-30 Hz) band, were obtained by averaging spectral powers over frequency bins (1 Hz resolution) in each band. Its statistical difference between pre- and post-TMS rsEEGs at each frequency band was examined by a paired t test (two-tailed) for each IC, and the significant level was set at $p<0.05$.

F. Linking Spectral Power Changes to VAS Score Changes

To link changes in EEG spectral powers and changes in VAS scores between pre- and post-rTMS sessions, a cross-subject Pearson correlation analysis was performed for all selected ICs. The correlation coefficients (CCs) with $p < 0.05$ were considered to be of statistical significance.

III. Results

A. VAS Score Changes

A range of VAS score changes were reported in this cohort of ten patients. Symptom improvements were observed in five subjects (S1-S5, Fig. 1) with evident reductions (changes > -30) in three subjects (S1-S3), while symptom increases were observed in three subjects (S7-S10). The other two subjects have no reported symptom changes (S5 and S6). It is also noted in Fig.1 that the degree of VAS score decrease is more substantial than that of VAS score increase. No significant correlation between the duration of symptom (Table I) and VAS score changes was revealed.

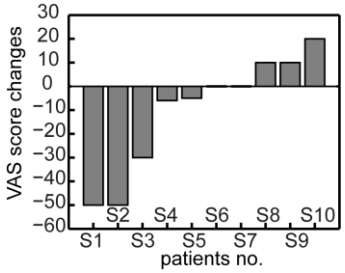

Figure 1. Summary of VAS score changes in 10 subjects.

B. Brain Substrates of Interests Disentangled by gICA

Thirteen distinct ICs indicating different brain substrates and/or local neuronal networks were selected. It is observed in Fig. 2 that these selected ICs have typical spatial-spectral characteristics to different brain areas, and are consistent with previously reported ICs from rsEEG in literature [11, 15-17]. The topographies of these ICs are well explained by a single dipolar source or two bilateral symmetric dipolar sources [14] in occipital (IC1-IC5), parietal (IC8 and IC9), temporal (IC6 and IC7), central (IC10 and IC11), and prefrontal cortex (IC12 and IC13). In terms of spectral patterns, there are evident alpha spectral peaks in all thirteen ICs (Fig. 2(B)), and evident beta peaks in two prefrontal ICs (IC12 and IC13) and one supplementary motor area (SMA) IC (IC11). Moreover, though no evident theta peaks were observed, the two prefrontal ICs had more elevated theta powers as compared with other ICs. All these data suggest the validity of the selected ICs.

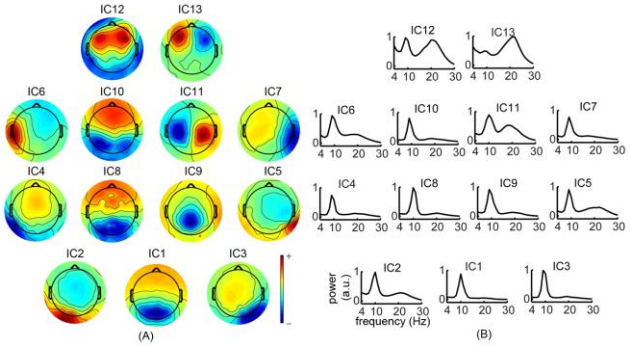

Figure 2. Thirteen ICs that were selected in the present study: (A) Spatial patterns of ICs; (B) Grand-averaged spectral powers of ICs.

C. Spectral Power Changes

From 13 ICs, only 4 ICs were detected with the spectral power changes between pre- and post-rTMS sessions in at least one of four frequency bands (Fig. 3). Significant changes in theta band powers were observed in IC2, IC8 and IC12, while significant changes in low alpha and high alpha bands powers were in IC8 and IC11, respectively. Moreover, the detected spectral power changes were all enhanced after rTMS.

D. Association between Spectral Power Changes and VAS Score Changes

Two ICs (IC2 and IC9) were detected with the significant CC between spectral power changes and VAS score changes. IC2 indicated a significant negative CC in the high alpha (CC=-0.64; $p<0.05$) and beta (CC=-0.73; $p<0.02$) bands. IC9 indicated a significant positive CC in the beta band (CC=0.67; $p<0.05$).

IV. Discussion and Conclusion

In the present study, a novel rTMS protocol, which sequentially applied two rTMS stimulations of 1 Hz and 10 Hz over bilateral DLPFC, was proposed and performed in MdDS patients. To examine the long lasting effects of rTMS, a five consecutive days' treatment was conducted. The possible efficacy of the proposed rTMS paradigm on MdDS

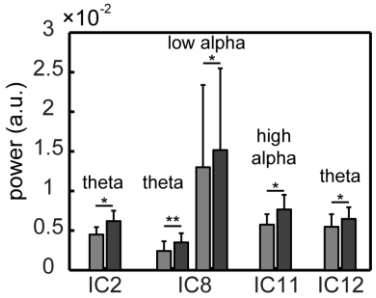

Figure 3. ICs of significant spectral power changes in one of four frequency bands.* $p<0.05$ and ** $p<0.005$.

was examined in terms of subjective reported symptom changes in VAS scores and directly measured resting state brain activity changes in multiple neural substrates and/or local networks reflected in different ICs. Moreover, to measure the long-term "stacked" effects of rTMS rather than the acute change that immediately followed by rTMS sessions, the post-rTMS rsEEG and VAS score was recorded 4-5 hours after the last rTMS session.

Consistent with previous pilot study [5], the present study also revealed promising clinical efficacy of rTMS for MdDS in terms of VAS score changes. Half the subjects indicated symptom reductions, in which three subjects had significant reductions in VAS scores over 30 points. Although unchanged or increased symptom was also observed in this cohort, it is noted that the degree of increased changes (≤ 20) is less than that of decreased changes. In addition, symptom reductions were also observed in patients with long duration of symptoms, e.g., S3, which suggests the potential benefit from the sequential treatment of rTMS in refractory MdDS patients.

The significant rsEEG spectral power changes revealed in multiple neural substrates and/or local networks by the ICA method clearly demonstrate the broad modulation effects of rTMS not only in local areas at the stimulation site (IC12: left and right DLPFC), but also in remote anatomically and/or functionally connected areas (IC2: left primary visual cortex; IC8: default mode network [17]; IC11: SMA). The significant changes were mainly in low frequency bands (i.e., theta band), which is consistent with the concept that low frequency oscillations are responsible for long-range neuronal communication [18]. Theta and alpha waves are considered as a marker of cortical inhibition [19]. Therefore, observed increases of theta and alpha oscillatory powers after rTMS could be interpreted as an increase in cortical inhibition or executive control over corresponding areas, e.g., DLPFC, which is also in line with our expectation of the present rTMS protocol. In particular, the increased prefrontal executive control induced by rTMS (i.e., IC12) might also indicate the treatment effect of rTMS, since hypometabolism in the prefrontal cortex has been reported in MdDS [9], although it does not significantly correlate with symptom changes.

Direct correlation between rsEEG spectral power changes and symptom changes were detected over two neural substrates in high frequency bands (IC2: left visual cortex, and IC9: posterior parietal cortex), with IC2 simultaneously detected with significant changes from pre- to post-rTMS. The detected high frequency oscillations (i.e., high alpha and beta bands) is known for local neuronal communication [18]. As the symptom improves, cortical inhibition increases in the left visual cortex (alpha power increases in IC2) whereas cortical activation decreases in posterior parietal cortex (beta power decreases in IC9), suggesting suppressed spatial information processing in these areas, which can potentially reduce imbalance sensations in MdDS patients [9]. Moreover, observed oscillatory power changes in these areas suggest that the posterior parietal and occipital areas might be additional or even better targets for rTMS in treating MdDS patients.

In sum, the present study combines rsEEG and VAS measures to evaluate the possible efficacy of a novel sequential rTMS protocol over bilateral DLPFC for five consecutive days. The promising treatment effects of the rTMS paradigm are reflected in the long lasting symptom improvements and spectral power changes over multiple MdDS-related brain substrates or local networks. These findings demonstrate that the present rTMS paradigm is a viable treatment option for MdDS, and would thus warrant further studies with more patients and a sham-controlled condition.

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