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Epilepsy & Behavior Case Reports

Case Report

Repetitive transcranial magnetic stimulation directed to a seizure focus localized by high-density EEG: A case report

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ABSTRACT

We demonstrate feasibility of using high-density EEG to map a neocortical seizure focus in conjunction with delivery of magnetic therapy. Our patient had refractory seizures affecting the left leg. A five-day course of placebo stimulation followed a month later by active rTMS was directed to the mapped seizure dipole. Active rTMS resulted in reduced EEG spiking, and shortening of seizure duration compared to placebo. Seizure frequency, however, improved similarly in both placebo and active treatment stages. rTMS-evoked EEG potentials demonstrated that a negative peak at 40 ms - believed to represent GABAergic inhibition - was enhanced by stimulation.

1. Introduction

Neurostimulation is beneficial against seizures when applied to the left vagus nerve [1–3], bilateral anterior nucleus of thalamus [4] or the seizure focus [5]. All of these require surgery. A noninvasive therapeutic neurostimulation method would be of value. Repetitive transcranial magnetic stimulation (rTMS) is one possible therapeutic method, but results of small controlled trials to date have been mixed, with five negative [6–10] and three positive [11–14] trials. Observation of altered seizure counts can require months, so a biomarker of a potentially useful therapeutic effect would be useful. Cortical evoked potentials in response to the repetitive transcranial magnetic stimulation pulses may be such a marker [15–20]. The EEG-based rTMS evoked response is multiphasic. Prior studies have suggested that the negative peak at about 40 ms reflects local cortical GABA-A receptor mediated inhibition [21–23]. Treatments that enhance the N40 peak might therefore be useful candidates for treating seizures.

Commonly employed butterfly (figure-of-eight) rTMS coils deliver local and relatively superficial currents to brain [24]. Therefore, rTMS would be expected to be most effective in treatment of superficial, well-localized seizure foci. This issue was explored in one study [9] utilizing a combination of MRI, video-EEG, FDG-PET, and SISCOM SPECT to localize seizure foci, but results were negative. In the present case

report, we demonstrate the feasibility of targeting rTMS to a seizure focus localized by inverse dipole methods using high-density EEG.

2. Methods

2.1. Institutional approval

The protocol was approved by the Stanford IRB, and conducted under the FDA's investigator device exemption (IDE) G150216-A001 held by Electrical Geodesic, Inc. The subject met the safety exclusion criteria of Rossi and Hallett [25]: no hearing problems or ringing in ears; not pregnant; no metal in the brain or skull (except for dental fillings); no cochlear implants; no implanted neurostimulator, except that the seizure and loss of consciousness criteria were not used as exclusions, since the subject did have epilepsy.

2.2. Study design

This was a single-blind prospective placebo-controlled, n-of-one study. After a baseline period, placebo stimulation was done over for 5 consecutive days and then active stimulation was performed for 5 consecutive days beginning a month later. The subject kept a daily log of seizure frequency, severity and duration. The subject was blinded as to treatment arm, but the investigators were not. Ancillary measures included stimulation tolerability, neuropsychological measures, EEG spikes, inter-channel EEG connectivity and rTMS-evoked potentials. The goal was to show feasibility for a larger double-blinded study.

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2.3. Head modeling

Head modeling was performed according to the protocol of Electrical Geodesics, Inc. (EGI) Phillips Holding USA, Inc.; Eugene, OR [26,27]. A high-quality MRI was performed with T1 sequences showing good grey-white matter discrimination and imaging to below the jaw. A photogrammetry system [28] took pictures of electrode placements on the scalp via the 256-contact Gel-cap (EGI®) [29]. Each electrode was labeled and registered to the MRI. Images were imported into the Osirix® environment [30,31]. Tailairach landmarks were chosen to correspond to the anterior and posterior commissures in the midline. Each MRI slice was then reviewed to verify by visual inspection and edited to remove artefactual or obviously inaccurate portrays of the cortical folds. The software then created a 4800-voxel head model, which could be displayed on the Galileo NT system (EB Neuro SpA, Firenze, Italy), coupled with a Polaris Vicra infrared camera (NDI, Waterloo, Canada), which uses infrared tracking of coil and head position in relation to the registered MRI. Tailairach coordinates for the inverse dipole solution of interictal spike location were transferred to the navigator system.

2.4. EEG recording

Two high density EEG recordings were taken before first stimulation, another after placebo stimulation, and a fourth after active rTMS. A 256-channel Gel-cap was applied to the head during each rTMS session. Saline sponge electrodes could not be used, because high impedances degraded the low amplitude rTMS-evoked potentials (TEPs) and the sponges moved the stimulating coils away from the cerebral targets. Otherwise, the EGI recording system was not modified. Flat disk electrodes were used in conjunction with regular EEG electrode paste. TEPs were recorded and digitized with a Net Amps 400 amplifier (EGI®), at 1 kHz sampling and a band width from DC to 2 kHz. Net Station Acquisition and spike marking was done with Net Station (EGI®) software. Spikes were identified and counted by a Board-licensed electroencephalographer, who was unblinded as to placebo versus active treatment arm.

Repetitive transcranial magnetic stimulation: rTMS was delivered with an STM9000 stimulator (EBNeuro SpA®, Firenze, Italy) with a 70 mm air-cooled flat butterfly coil delivering biphasic pulses. The maximum machine output is approximately 3.2 Tesla. EMG skin electrodes were placed over the right first dorsal interosseous muscle to determine resting motor threshold (RMT), defined as the minimal stimulation intensity able to produce a visible twitch in at least 5 of 10 trials [32]. RMT was determined once at the start of the experiment for each subject. The coil was placed tangentially to be as close to the scalp as possible without touching, positioned at a 45° angle to the midline, with the handle aimed posteriorly [33]. Coil position and orientation were monitored by a Galileo NT system (EB Neuro SpA, Firenze, Italy), coupled with a Polaris Vicra infrared camera (NDI, Waterloo, Canada). This permitted repeated targeting of the interictal spike focus. Earplugs protected hearing [34] and reduced auditory evoked potential artifacts.

Each of the five consecutive (Mon-Fri) daily sessions required about 1 h of EEG setup and 2 h of stimulation, including two 10-minute breaks per session. The first 5-daily sessions used a placebo coil (EBNeuro™, butterfly cooled placebo coil 70 mm, Model E2108, setting the same as for active stimulation) that generated scalp sensations, but with a coil configuration that cancelled the majority of deeper stimulation to brain. The subject was unaware of which session was placebo and which was active therapy. A second run of 5 daily stimulation sessions occurred at least a month after the placebo run, using an active stimulation coil. To record baseline TEPs, 50 pulses were delivered at 110% of motor threshold at a frequency of 1 pulse every 3 s before delivery of rTMS. This was repeated after delivery of rTMS.

For our patient, rTMS was targeted to the best dipole fit to generate his distribution of scalp EEG potentials during interictal spikes. This was concordant with the right brain parasagittal motor cortex area for the left leg. Individual stimuli above motor threshold could variably evoke left leg twitches, sometimes coupled with less vigorous right leg twitches. Stimulation was delivered as three 500-pulse blocks at 1 Hz, separated by 10-min breaks for a total of 1500 pulses. Stimulation intensity was set to 90% of motor threshold. Hand EMG was monitored with a Physio16 input box at 1 kHz sampling, and occasionally indicated when the incrementing current was close to producing finger movement. EMG also provided a quantitative way to correlate EEG changes with evoked motor changes.

2.5. TEP analysis

rTMS-evoked potentials were processed offline using MATLAB (Mathworks®). The 50 test pulses before and after rTMS were averaged to form pre-rTMS and post-rTMS datasets. rTMS artifacts were eliminated by a 20-ms spline interpolation from 10 ms before to 10 ms after rTMS. After interpolation, EEG signals were high-pass filtered above 1 Hz. Pulses were epoched from 300 ms before the pulse to 500 ms after. Because rTMS produced a large DC shift, baselines were corrected with respect to the TMS-free pre-stimulation interval from 300 to 50 ms prior to the stimuli. Independent component analysis was performed on epochs to separate electrical artifacts from physiological response to TMS pulse.[70–75] Components with muscle activity, eye blinks and residual of TMS artifacts were removed. Finally, the average of epochs was computed for further analyses.

2.6. Connectivity analysis

Connectivity analysis was performed offline using the TRENTOOL3 Open-Source MATLAB toolbox for transfer entropy estimation [35] in MATLAB (Mathworks®). Transfer entropy estimation can be considered an extension of Granger causality [36] with greater tolerance for nonlinear relations and outliers. Predictive information transfer was calculated from 15 min of resting state data from each treatment condition (pre-rTMS, post-placebo, and post-rTMS) between the electrode directly beneath the site of rTMS stimulation as described above ("the target electrode"), and electrodes F4, C4, P4, O2, F3, C3, P3, O1, Fp2, F8, T8 (T4), P8 (T6), Fp1, F7, T7 (T3), P7 (T5), Fz, and Pz per the international 10–20 electrode system. Prediction time was set to 100 ms, the optimization method utilized the Ragwitz criterion for choosing modeling parameters in TRENTOOL3, and the nearest neighbor method of estimation was used. Surrogate data for statistical analysis was created using the "block reverse" method within TRENTOOL3. The Faes method [37] was utilized to minimize volume conduction effects. Statistical significance was calculated using a 2-tailed independent samples t-Test looking for transfer entropy (condition) > transfer entropy (shifted data). Correction for multiple comparisons was achieved by using the False Discovery Rate method [38].

3. Case report

The subject was a 56-year-old right-handed East Indian software engineer with no previous history of seizures or recent travel. Around 21 days prior to admission, he began experiencing new symptoms of fluctuating bitemporal headache, 8/10 in severity, with associated neck pain, photophobia and fevers of 39.4 °C. After two days of treating symptoms with acetaminophen and ibuprofen, he was observed by his physician sister to cry out, twitch in the left foot and up the left leg, followed by forced head-eye version to the left and a bilateral tonic-clonic seizure. At his local hospital, recurrent seizure activity was responsive to levetiracetam. Lumbar puncture showed normal cell and protein counts, negative for Herpes simplex virus DNA. Initial brain MRI with contrast was normal. Over the following week, he exhibited increasing frequency and severity of seizures. He was transferred to the Stanford ICU, where he remained for 87 days, treated with various anesthetics to a level of EEG suppression burst.
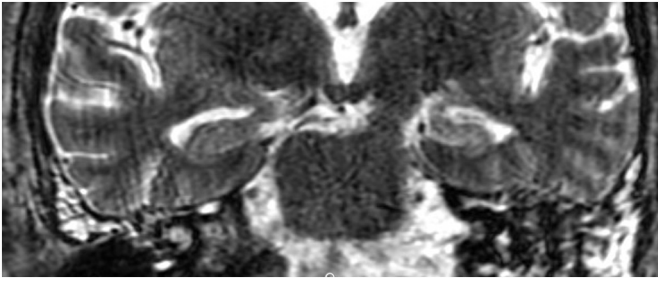
Fig. 1. T2 sequences from a #T non-contrast MRI showing left hippocampal atrophy.

Seizures were mostly focal motor (awareness not determinable while under anesthesia), beginning in the left leg with spread and with concurrent right superior fronto-parietal discharges (see below). Independent right body seizures and left motor cortex region EEG discharges occasionally occurred.

A repeat contrast MRI included a T2 sequence showing a hyperintense left frontal lobe signal lesion and emerging left hippocampal atrophy. Biopsy of the left frontal lesion demonstrated only non-specific gliosis. Follow-up lumbar punctures showed 1–4 white cells, 0–12 red cells, glucose within normal range/ratio to serum measures, protein 49–67. Gram stain, bacterial and fungal cultures were negative. CSF

was again negative for Herpes simplex virus and HHV-6 DNA by PCR, and blood or CSF were negative for tests of CMV, Epstein-Barr IgM or DNA PCR, hepatitis markers, Cryptococcus antigen, Varicella DNA PCR, West Nile virus DNA PCR or HIV. Anti-thyroglobulin and TPO antibodies were negative, TSH, and B12 were normal, ANA was negative. Serum and CSF antibodies for additional autoimmune or paraneoplastic biomarkers were negative according to testing at the Mayo Clinic, but serum from Quest Diagnostics (Nichols Institute) showed an anti-GAD65 antibody of 4.0 U/mL with normal reference levels less than 1.0 U/mL. The cause of the recurrent seizures was never clearly established, but limbic encephalitis was suspected.

The subject was treated with eight anti-seizure medications, intravenous magnesium sulfate, the protocol drug SAGE-547 via compassionate use, corticosteroids, intravenous immune globulin, plasmapheresis, hypothermia to 33 °C and a course of the ketogenic diet. Seizures slowly improved. He developed an ICU neuropathy and myopathy and was discharged to rehabilitation. At time of discharge, he could barely walk with support and spoke fluently, but with impaired memory.

In the outpatient setting, focal aware (simple partial) motor seizures persisted at a rate of about 1–4 per day. He described 3 seizure types, all of which were variations on the same theme (in his words): A: "Left leg shaking with left hand moving up. Duration is short lasting a few seconds. Sometimes no shakes in leg nor left hand moving up, but tingling sensation in left hand with some loss of control of left hand"; B: "Left leg

Fig. 2. Best inverse dipole map of generator for interictal spikes. Selected EEG channels are shown for 42 averaged interictal spikes projecting to the right fronto-parietal region. Yellow marks the region of the spikes, mapped to the MRI.
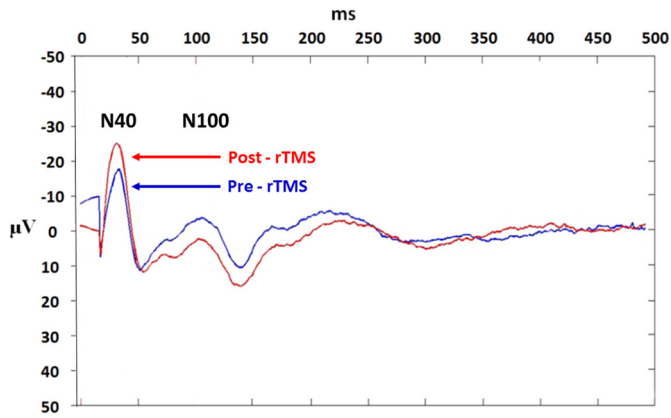
Fig. 3. Evoked-EEG responses before (blue) and after (red) 1500 1-Hz rTMS pulses. Each trace is an average of 50 pulses delivered at 0.33 Hz, from the C4 electrode over the non-dominant hand rear of cortex. The increase in the negative component at approximately 45 ms may reflect enhanced cortical GABAergic inhibition.

Table 1
Neuropsychological test results before and after 5 days of rTMS.

Test	PRE-rTMS Raw score/Z-score	POST rTMS Raw score/Z-score
CVLT-II short form trials 1–4	27/0.0	25/-0.45
Short delay free recall	7/0.0	4/-2.0[a]
Long delay free recall	8/1.0	4/-1.0[a]
Long delay cued recall	8/1.0	5/-1.0[a]
Total recog discrim (d')	2.3/0.0	2.0/-0.5
WCST categories	1	2
Trials administered	128	128
% Conceptual level responses	22	38
Perseverative responses	56	31[b]
Non-perseverative errors	26	28
QOLIE-31P	Weighted raw score	Weighted raw score
Energy/fatigue	7.27	7.20
Emotional well-being	11.40	10.20
Social functioning	6.09	8.19
Cognitive functioning	11.47	11.92
Medication effects	0.50	0.50
Seizure worry	2.51	3.76
Overall QOL	9.10	7.70
Total score	48.34	45.71

[a] CVLT II indicates California Verbal Learning Test. Significant differences between pre- and post-test scores [40].
[b] WCST indicates Wisconsin Card Sorting Test. Significant difference between pre- and post-test scores [41]. QOLIE indicates Quality of Life in Epilepsy. No significant changes [42].

shaking with left hand shaking backwards mildly. Seizure lasting for 15–20 s."; C: "Left leg shaking violently with left hand shaking backwards. Duration lasting more than 20 s – approx 30 s to over a minute, as well as feeling of rapid shaking on left side of chest/stomach." He was maintained on levetiracetam, phenobarbital and lamotrigine.

Because of ongoing seizures, the patient enrolled in a research protocol to treat seizures with repetitive transcranial magnetic stimulation. Placebo stimulation was delivered 455 days and active stimulation 490 days after his first seizure.

4. Results

4.1. Baseline testing

Fig. 1 shows a 3T MRI taken prior to rTMS treatment. The left hippocampus is atrophied and with indistinct architecture.

His high-density EEG and corresponding inverse solution to the source dipole is portrayed in Fig. 2. In the baseline recording, the most frequent (n = 42) spikes group was averaged, demonstrating a sharp wave with phase reversals over the right superior frontal-parietal regions. An inverse dipole model of generating dipoles using the LAURA algorithm [39] with data from all 256 channels localized an extracellularly negative current dipole over the right Brodman area 3 on the postcentral parietal gyrus.

4.2. Repetitive transcranial magnetic stimulation

rTMS was delivered to the dipole target in the right superior parietal midline region. The first 5 days of 1500 pulses per day used placebo stimulation, producing only scalp sensations. The second 5 stimulations, initiated 35 days after placebo stimulation, were with active rTMS at 90% of RMT, 1 Hz for 1500 pulses, in 3 blocks of 500 pulses. No adverse events were encountered.

Fig. 3 shows the increase of the N40 potential after (red trace, negative up-going) 5 days of active rTMS, compared to before (blue trace).

4.3. Connectivity analysis

Connectivity analysis demonstrated no significant predictive information transfer between the target electrode and electrodes F4, C4, P4, O2, F3, C3, P3, O1, Fp2, F8, T8 (T4), P8 (T6), Fp1, F7, T7 (T3), P7 (T5), Fz, or Pz in any of the conditions with correction for multiple comparisons (data not shown). When correction for multiple comparisons was not performed (Fig. 4A, B), both the pre-rTMS and post-placebo conditions demonstrated predictive information transfer from electrode F4 to the target electrode (p = 0.0129 and p = 0.0131 respectively), and the post-placebo condition also showed predictive information
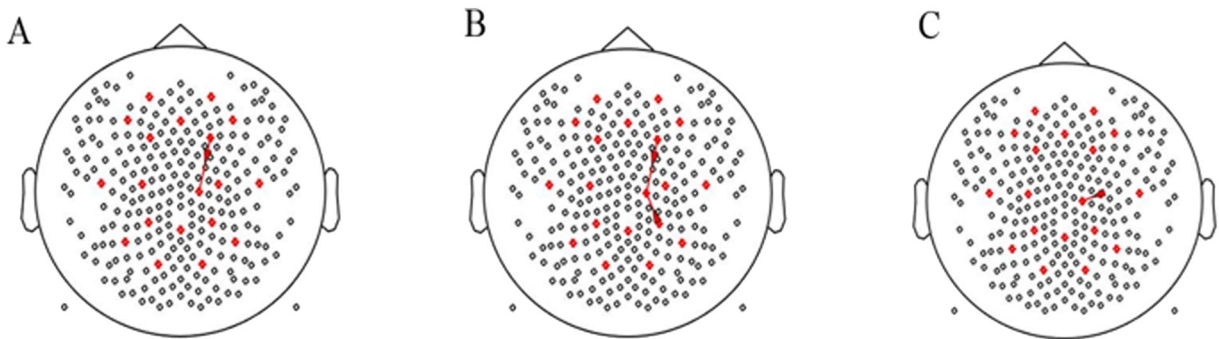

Fig. 4. A) Uncorrected predictive information transfer from electrode F4 to target electrode (electrode immediately beneath rTMS coil) in pre-rTMS condition. B) Uncorrected predictive information transfer from electrodes F4 and P4 to target electrode in post-placebo condition. C) Uncorrected predictive information transfer from electrode C4 to target electrode in post-rTMS condition.

Table 2
Seizure counts.

	Baseline	Placebo	Active rTMS	t-Tests (2-tail, independent)
Daily seizure count	2.36 ± 1.07	1.62 ± 1.10	1.64 ± 1.01	Baseline vs. placebo, $p < 0.001$ Baseline vs. active, $p < 0.001$ Active vs. placebo, $p = 0.92$
Severity	1.63 ± 0.623	1.29 ± 0.46	1.16 ± 0.37	Baseline vs. placebo, $p = 0.01$ Baseline vs. active, $p < 0.001$ Active vs. placebo, $p = 0.215$
Duration	1.58 ± 0.51	1.14 ± 0.36	1.00 ± 0.00	Baseline vs. placebo, $p < 0.001$ Baseline vs. active, $p < 0.001$ Active vs. placebo, $p = 0.016$

transfer from electrode P4 ($p = 0.0202$). Without correction for multiple comparisons, the post-rTMS condition (Fig. 4C) demonstrated predictive information transfer from electrode C4 to the target electrode ($p = 0.0028$).

4.4. Neuropsychology

Neuropsychological test results before and after a course of stimulation are listed in Table 1. Learning of a 9-item word list did not differ before and after treatment with rTMS, but short and long-delay recall scores declined following rTMS. Recognition discrimination for the list items versus distractor items did not differ. The subject had significantly less perseverative responses, a measure of executive functioning, following rTMS. There were no significant differences between the subject's quality of life ratings pre- and post-rTMS.

4.5. Spike and seizure counts

Each EEG was recorded for 2 h. The first baseline EEG contained 66 interictal spikes or sharp waves, the second baseline 71, the post-placebo study 16 and the post-active rTMS study 0 spikes. Seizure information is shown in Table 2 and the plot of total daily seizure counts in Fig. 5.

The mean number of seizures per day was 2.36 ± 1.07 (mean ± standard deviation) in the baseline phase, 1.62 ± 1.10 after placebo stimulation and 1.64 ± 1.01 after active rTMS. Despite a reduction of seizures compared to baseline ($p < 0.001$), there was no significant

difference in counts after placebo versus active stimulation ($p = 0.92$). Fig. 4 shows a plot of daily seizure frequencies over time.

The subject, blinded as to placebo vs. active stimulation, keep a log of seizure severity (1 for mild, 2 for medium, 3 for strong) and duration (1 for short, 2 for normal, 3 for long). Both measures improved markedly ($p \leq 0.001$) from baseline to either placebo or active stimulation. Seizure severity was less, but not significantly, in baseline versus placebo ($p = 0.215$). Seizure duration was significantly shorter in the active treatment stage ($p = 0.016$).

5. Discussion

This case report demonstrates proof-in-principle of delivering rTMS to a seizure focus via high-density EEG targeted to the spike dipole demonstrated by the inverse dipole algorithm. Placebo stimulation can be used effectively in subjects with epilepsy. The cortical potentials evoked by repetitive transcranial magnetic stimulation can be recorded with standard EEG technique [15,17–20,43–46] and displayed after suitable signal processing, as has been described by others [47–49]. Our patient showed an increase in the N40 potential after a course of rTMS. This component of the rTMS evoked EEG potential is believed to reflect fast GABAergic inhibition in cortex [21–23], and therefore an increase might signal enhanced inhibition, potentially useful in limiting seizures. It is also possible to record changes in inter-channel EEG connectivity after stimulation, as has previously been reported [44,50,51]. The results in this single case are suggestive of connectivity changes induced by rTMS, but not conclusive, mainly because significance is reduced by
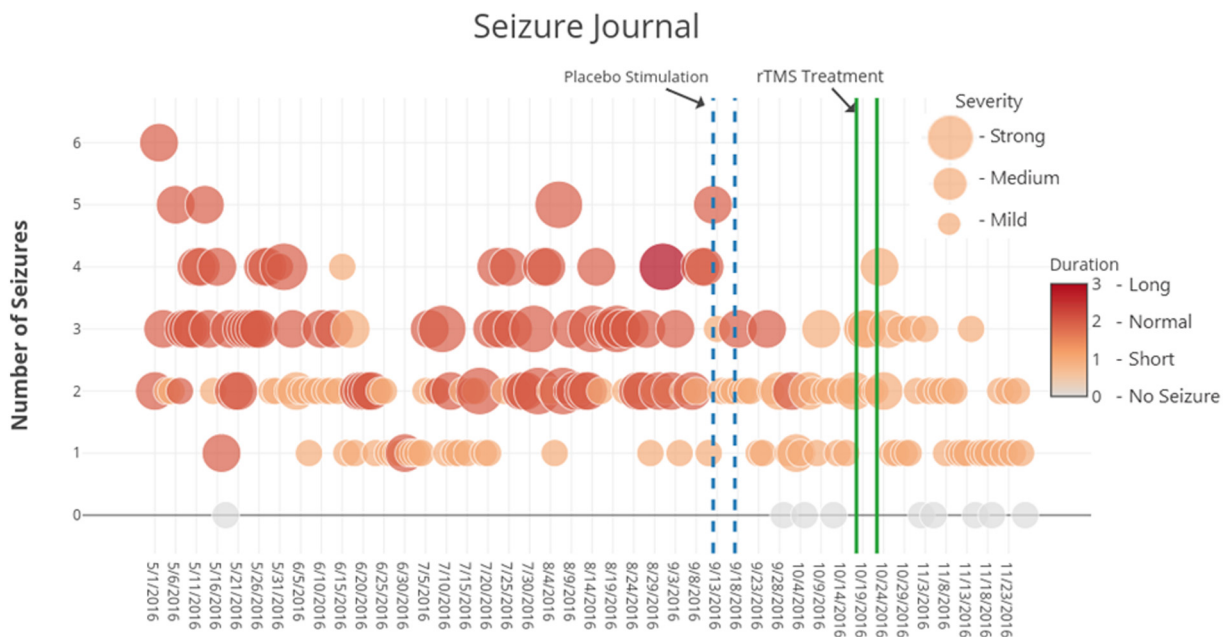

Fig. 5. Daily total seizure counts during the baseline period, placebo stimulation and active rTMS stimulation. All seizures were focal aware motor (simple partial) seizures.

multiple comparisons of various electrode pairs. With a priori declaration of which electrode pairs are being investigated (e.g., the electrode under the stimulus and the contralateral corresponding electrode, or surrounding electrodes), this problem could in the future be minimized.

rTMS was well-tolerated by our patient with ongoing focal seizures and a history of prolonged severe focal status epilepticus. No adverse events were encountered. Minor changes in neuropsychological test scores occurred after rTMS. It is possible that the declines in short and longer recall scores may have been related to difficulty with word retrieval rather than encoding. Encoding of new information was not hindered as recognition performance was similar across the two time periods. In a systematic review of cognitive effects of low-frequency rTMS that included normal controls, as well as individuals with mood disorders, stroke, and other organic syndromes, one study [35] reported decline in verbal fluency and verbal retrieval. Only one study of rTMS [13] included patients with epilepsy and no declines were noted on any measure, but instead suggested improvement.

This study was not designed or powered to demonstrate efficacy, in that spike and seizure counts were not blinded, and the order of placebo and active therapy was not randomized; thus, we cannot rule out non-specific time/recovery effects. The single-blind placebo was key in demonstrating superiority of rTMS for post-treatment versus baseline seizure counts, but not for placebo versus active treatment, emphasizing the importance of placebo controls in clinical trials of rTMS. Spike frequency improved to zero in a single post-treatment record, but this is not significant in a single case.

The mean and standard deviation data obtained in this subject can be used to make a very rough sample size calculation for a future larger study. Assuming that a 25% reduction is clinically significant and using the baseline seizure frequency and square root of the variance, alpha error of 0.05 and beta error of 0.2, the number needed in each group would be 94 subjects [52]. A 33% reduction would require 53 subjects in each group and a criterion of 50% reduction would require 23 per group.

These findings may be helpful in design of a prospective, randomized trial of rTMS for epilepsy by targeting the stimulation to the spike dipole revealed by high-density EEG recordings.

6. Conclusions

Some studies suggest that repetitive transcranial magnetic stimulation (rTMS) can reduce seizures, but others have been negative. A relatively superficial and properly targeted seizure focus might be important for the success of rTMS. We present a case report that shows feasibility of using high-density EEG to map a neocortical seizure focus in conjunction with delivery of magnetic therapy. Our patient had probable autoimmune-mediated focal aware and impaired awareness seizures and status epilepticus affecting the left leg. After hospital discharge, a five- day course of placebo stimulation followed a month later by active rTMS was directed to the mapped seizure dipole near right leg region motor cortex. Active rTMS resulted in reduced EEG spiking, and shortening of seizure duration compared to placebo treatment. Seizure frequency, however, improved similarly in both placebo and active treatment stages. Neuropsychological testing revealed decline in verbal memory after stimulation but no decline in executive function or quality-of-life ratings. Some measures of inter-electrode connectivity were altered by stimulation. Experience with this case and sample size estimates based upon variability can facilitate a more definitive trial of rTMS delivered according to EEG dipole mapping.

Acknowledgments

Conflicts of interest

Dr. Fisher has no conflicts relevant to this paper, but he holds stock in Avails Medical, Smart-Monitor, Cerebral Therapeutics, Zeto, and he has consulted for Engage Therapeutics.

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