Transcranial Magnetic Stimulation (TMS) for Benign Epilepsy with Centrotemporal Spikes (BECTS) [TMS4BECTS]

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OVERVIEW

Epilepsy affects 1% of all children, and patients with epilepsy report that cognitive problems diminish their quality of life as much or more so than seizures. [1,2] Benign epilepsy with centrotemporal spikes (BECTS) is the most common pediatric epilepsy syndrome, accounting for 15-25% of all cases. Children have frequent, focal, sleep-potentiated interictal epileptiform discharges (IEDs) emerging from one or both motor cortices, but typically have only rare seizures occurring nearly exclusively out of sleep. BECTS self-resolves in adolescence, so treatment is often not initiated.[3] Despite the relatively mild course, children with BECTS develop a variety of cognitive deficits, most prominently in language[4–6] that may persist even after the epilepsy resolves.[7,8] Language difficulties correlate with atypical maturation of the language network. Specifically, lateralization of language function to the left hemisphere is either delayed[9–11] or permanently disrupted[8] and functional connectivity within the language network[10–13] is decreased. *We do not understand the pathophysiology of language dysfunction in BECTS and have no specific treatments to target it.*

Many speculate that frequent IEDs disrupt language development in BECTS, but studies focusing on the correlation between IED frequency and cognition have had variable results.[8,14–18] Several lines of evidence suggest that the interaction between IEDs and the language network may be critical. First, children with BECTS and left-lateralized IEDs have greater language dysfunction than those with right-lateralized IEDs.[8,17,18] Second, functional magnetic resonance imaging (fMRI) shows that the inferior frontal gyrus, a key structure in the language network, has increased blood flow during IEDs. Third, plasticity of the motor cortex correlates strongly with children's performance on language learning tasks.[19] Current pharmacologic therapies for BECTS focus on stopping seizures but not IEDs. **The impact of IEDs on language presents a critical gap in our knowledge with both biological and clinical significance.**

High-density electroencephalogram (**HD-EEG**) alone and high-density EEG paired with single pulses of transcranial magnetic stimulation (**spTMS-EEG**) can help map the impact of IEDs on brain connectivity in children with BECTS. HD-EEG is a minimally-invasive, well-established method for assessing connectivity between brain regions with much greater temporal specificity than fMRI. TMS-EEG is the only non-invasive way to directly assess the influence of one brain region over another. In TMS, an extracranial magnetic field is used to induce an intracranial electrical current, which can be traced to structurally and functionally linked regions. While

spTMS-EEG interrogates the brain state at the moment of stimulation, repetitive trains administered in specific patterns (**repetitive TMS or rTMS**) can change underlying cortical excitability.[20] Studies of rTMS to treat seizures[21] as well as our preliminary data in BECTS patients suggest that IEDs transiently decrease in frequency after rTMS. Therefore, rTMS will allow us to test how connectivity changes with IED suppression.

The purpose of this study is to evaluate if rTMS to the motor cortex: (1) reduces IEDs in children with BECTS; and (2) changes brain connectivity between the motor cortex and language regions.

Literature Review

i. Children with BECTS have disturbed language skills. Detailed neuropsychological profiles show deficits in many language domains, including reading, expressive and receptive language, and phonological processing.[4,5] Children have near-normal language abilities at the time of diagnosis of BECTS but their language skills lag behind their peers over time,[4,22] suggesting that BECTS can be classified as a mild epileptic encephalopathy. The few studies to formally assess language in adults with a history of BECTS have found persistent deficits.[7,8]

ii. Maturation of the language network is also altered in BECTS. Language typically lateralizes to the left hemisphere in childhood. Neurocognitive, evoked potential,[8,18] and fMRI[23–25] studies find that this process is delayed[9–11] or permanently disrupted[8] in BECTS. Language performance varies with the degree of disruption.

iii. Interictal epileptiform discharges (IEDs) may interrupt normal language development. Substantial evidence indicates that IEDs cause transient changes in perception, processing, and reactivity.[26] Disorders like Landau-Kleffner Syndrome – in which patients experience a sudden language regression accompanied by constant IEDs throughout sleep but few EEG abnormalities during the day – suggest that frequent nocturnal IEDs may be sufficient to disrupt cognition.[27] In BECTS, the effects of IEDs have largely been inferred from studies correlating diurnal[14] and nocturnal[15,16] IED burden with degree and type of cognitive dysfunction, though not all studies have found a correlation.[4] Location of IEDs likely matters; of the 60% of BECTS patients with unilateral discharges, those with left-lateralized IEDs have greater language dysfunction while those with right-lateralized IEDs have greater spatial dysfunction.[8,17,18]

iv. Brain connectivity is altered in BECTS, potentially due to IEDs. fMRI studies suggest that in BECTS, the epileptogenic motor cortices have abnormal structural and functional connections with various regions.[10–13,28–33] Broader resting state networks[33–35] are also altered. A series of studies[9–11,36] found that BECTS patients have *decreased* connectivity between the motor cortex and language regions, but these studies did not account for the effect of IEDs. In contrast, Xiao et al.[33] found that connectivity between the motor cortex and inferior frontal gyrus increases after IEDs, and that greater connectivity correlates with worse language function. This literature suggests that the immediate impact of IEDs on connectivity may differ from persistent connectivity changes that develop with chronic IED exposure. This highlights a need to investigate both types of connectivity. Furthermore, connectivity differences may be especially prominent during language tasks compared to when at rest.[24]

v. EEG-based connectivity analysis offers superior temporal specificity for the study of IEDs. Assessment of IEDs using fMRI is limited by the poor temporal specificity of fMRI. IEDs last hundreds of milliseconds whereas blood flow changes measured by fMRI require multiple seconds. In contrast, EEG is a temporally-precise method for studying the impact of IEDs on network connectivity.[37] High-density EEG (HD-EEG) specifically estimates the underlying source of this activity. Surprisingly, however, few EEG connectivity analyses have been done in children with BECTS.[38–41] Only one study assess the impact of IEDs in wakefulness and it is limited by a small sample size of children with only right hemispheric IEDs, thus obscuring the impact of IEDs on language network connectivity. Furthermore, all EEG connectivity studies in BECTS have been done in the resting state, whereas language network connectivity is likely to be better measured when the network is engaged in a task. Therefore, a significant gap persists in understanding connectivity in BECTS.

EEG connectivity analysis has been limited by the concern for volume conduction, a problem that arises when activity in nearby electrodes is correlated not because the regions are connected but rather because the electrodes are picking up neuronal activity from a single common source. Fortunately, new connectivity metrics, such as the **weighted Phase Lag Index (wPLI)**,[42] are quite robust against volume conduction. To calculate wPLI, the EEG signal is broken down into frequency bands (i.e. alpha, beta) and the phase of the waveforms in each band is compared across brain regions; non-zero phase lags are considered true connectivity.[42] wPLI is a continuous metric ranging from 0-1, where 0 indicates no connectivity and 1 indicates perfect connectivity. wPLI offers better spatial-specificity when it is calculated from a high number of EEG electrodes.

vi. Combining transcranial magnetic stimulation with EEG (TMS-EEG) will shed new insight into BECTS by directly probing the epileptogenic motor cortex. TMS is the only non-invasive method to directly interrogate the influence of one brain region over another. Single pulses of TMS (spTMS) introduce a current into the stimulated cortex, the immediate downstream effect of which can be mapped by EEG on the order of milliseconds.[20] The strength of the magnetic pulse required to induce a muscle twitch (typically in an intrinsic hand muscle like the abductor pollicis brevis [APB]) is known as the **motor threshold (MT)**. The EEG data recorded immediately after TMS pulses can also be analyzed with connectivity measures like wPLI. Additionally, TMS elicits **motor evoked potentials (MEPs)** recorded by surface EMG as well as **TMS-EEG evoked potentials (TEPs)** broadly across the brain. Finally, **repetitive trains of TMS (rTMS)** induce long-lasting changes in brain excitability,[43,44] and inhibitory rTMS can reduce IED frequency in epilepsy patients.[21,45] rTMS can therefore be used to model how changes in IED frequency affect brain connectivity.

Significance

The impact of IEDs on children with BECTS and other epilepsies is not understood. We typically do not treat IEDs due to our poor understanding of their significance. In this trial, we will evaluate if rTMS could be a treatment for focal IEDs in pediatric epilepsy and will assess the impact of such a treatment on the language network. Successful completion of the proposed studies will determine if IEDs directly alter connectivity between the motor and language regions in children with BECTS, if such connectivity differences persist even during IED-free periods, and whether connectivity differences correlate with language dysfunction. We will utilize rTMS as a novel method to suppress IEDs in BECTS in order to determine if rTMS could be a treatment for focal IEDs and what the impact of such treatment on the language network might be. Together, these data lay the groundwork for highly innovative future neurostimulation trials targeting IEDs in not only BECTS but also a wide range of pediatric epilepsy syndromes.

RISKS/BENEFITS

Potential Risks:

(1) Risks of EEG Recording*:* EEG does not cause harmful effects, though some children may find the EEG caps uncomfortable.

(2) Risks of TMS: TMS is considered very safe in both adults and children.[46–49] The main concern is that TMS could induce a seizure, but this is a truly rare phenomenon. In our preliminary study of 14 children with BECTS, none had seizures with TMS; a separate study also reported no seizures in children with BECTS.[19]

a. In considering the TMS literature more broadly, the main risk of seizures is in individuals: a) receiving high-frequency repetitive (>2Hz) stimulation or stimulation using the H-coil (which allows for deeper stimulation); or b) taking certain psychiatric medications.

b. TMS is safe in children. In the most recent review of over 4000 children with and without neuropsychiatric disease, the 3 reported new seizures all occurred with high frequency TMS; in addition, 2 of these children were on psychiatric medications and one child received H-coil stimulation.[49] Another recent study found no seizures in 165 healthy children receiving a form of repetitive TMS.[50]

c. Risks of seizures induced by TMS is also not clearly elevated in patients with epilepsy. In one study of 152 patients with epilepsy having weekly TMS at 1 Hz or less, none had induced seizures.[47] A review[51] found that 4 of 280 epilepsy patients had a seizure around time of TMS, reflecting a risk of 1.4%. However, these patients also had refractory and frequent spontaneous seizures at other times. In children with epilepsy, TMS is very safe; some children with very difficult to control seizures (multiple per day at baseline) self-reported a slight increase in seizures for 3 days after TMS but then a return to baseline. The authors felt this was a minimal increase in risk in this population.[49]

d. Other potential risks of TMS include hearing problems from the sound of the coil or scalp burns if the EEG electrodes are excessively heated by the magnet. These are mitigated by the use of noise-cancelling ear protection and by specially-cooled coils. Minor potential side effects include scalp discomfort, headache, lightheadedness and boredom. There is a theoretical risk that rTMS could lead to a change in mood, but this is highly unlikely when applied to the motor cortex. Procedures to minimize the risk of TMS are described in more detail below.

(3) *Risks of Collecting Personal Information:* One potential risk is breach of confidentiality related to the collection of sensitive information, but this will be minimized by following standardized procedures to protect all such information.

Protection Against Risk:

Risk of EEG: We will monitor the children during the studies and can adjust or remove the EEG caps if there is any discomfort.

Risk of TMS: We protect against the risk of seizure by having a pediatric epileptologist (Dr. Baumer) in the room during all TMS procedures and actively monitoring the EEG during stimulation so that stimulation can be stopped if there are any concerns. Furthermore, we use only single pulse stimulation and low-frequency repetitive stimulation (<1Hz), both of which have been well studied and are quite safe. Dr. Baumer will be present for all TMS sessions. She has extensive experience performing TMS in children and clinical expertise in the management of seizures in children. Furthermore, all TMS will be done at Stanford University in close proximity to Lucile Packard Children's Hospital. Any persons assisting with the TMS will undergo TMS safety training and seizure training. All children wear noise-cancelling

headphones to protect their ears from the TMS click. Scalp burns are prevented using cooled-coils. We speak with children throughout the TMS session so will actively monitor them for any other discomfort. If there is minor discomfort due to the TMS, the study will be paused and potentially halted.

Risk of Loss of Privacy: To maintain confidentiality, we will restrict access of private health information exclusively to the PI, necessary personnel of the Data Safety Monitoring Board and research staff. We will de-identify all data obtained from subjects. We will store all data on a PGP encrypted server within the School of Medicine at Stanford University. All hard copies of data, including medical records and copies of informed consent, will be maintained in a locked file cabinet in the lab. All members of the research team will undergo HIPPA training.

Additional Protections for Children: The study is recruiting children as BECTS is a pediatric condition not present in adults; there are also no good animal models of this condition. The study procedures will be reviewed with the children in language they can understand before the protocol begins and children will be told they can stop the study at any time. Parents of children participating will also be informed that they are free to choose not to participate and may withdraw at any time. We will obtain assent from children who are of an appropriate age (typically >8yo of age). We will frequently check-in with children throughout the study to ensure that they are comfortable with continuing the procedures.

Potential Benefits: IEDs lead to cognitive problems in some children. Participants may benefit by having a reduction in IEDs at least temporarily. Additionally, we will learn more about the pathophysiology of BECTS, which may improve treatment in the future.

OBJECTIVES & ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	RATIONALE
To evaluate if rTMS reduces the frequency of IEDs in children with BECTS.	Change in IEDs/minute induced by active rTMS vs. change induced by sham rTMS. Change will be calculated by comparing IED count in the 20 minutes after rTMS with IED count in the 20 minutes before rTMS.	This will assess if rTMS reduces IED frequency when compared to a sham control.	There is evidence that rTMS reduces cortical excitability and hence may reduce generation of IEDs.
To evaluate if rTMS reduces connectivity between the motor and language regions in children with BECTS.	Change in weighted phase lag index (wPLI) (an EEG-based connectivity measure) between the stimulated motor cortex and the left inferior frontal gyrus induced by active rTMS vs. sham rTMS. Change will be calculated by comparing wPLI in the 20 minutes after rTMS vs. the 20 minutes before rTMS. We will collect 2 types of EEG data before and after the active/sham rTMS: (a) spTMS-EEG, and (b) resting-state EEG; and Connectivity will be calculated for each of these data types separately.	This endpoint will help us determine the downstream effect of rTMS on other brain networks.	Epilepsy is a network disorder and fMRI studies suggest that IEDs from the motor cortex increase connectivity between the motor cortex and inferior frontal gyrus. Therefore, inhibition of IEDs and increased inhibition of the motor cortex may decrease connectivity between the motor cortex and inferior frontal gyrus.

STUDY DESIGN

Overview: Children with BECTS will undergo both active rTMS and sham rTMS to the epileptogenic motor cortex. We will compare the impact of active vs. sham rTMS on: (a) IED frequency; and (b) motor-to-language connectivity. We hypothesize that active rTMS induce a greater decrease in: (a) IED frequency and (b) motor-to-language cortex connectivity than sham rTMS.

Study Stage: Stage 0

Study Design: Sham-controlled cross-over study in which all participants will receive both active and sham rTMS, with randomization of order of intervention. We will have repeated-measures data as subjects will undergo both sham and real rTMS on different days. The potential missing data issue will be evaluated thoroughly prior to the analysis. Multiple imputation will be applied if needed.

Assignation Methods: Not applicable, subjects will undergo both active and sham rTMS.

Study Arms: All subjects will participate in each arm, and arm order will be randomized on a per-subject basis. Participation in each arm will take approximately 4 hours (including set-up of equipment and data recording). Arms will be separated by at least 1 week.

> Arm 1 (active rTMS): 1000 pulses of rTMS administered via an active TMS coil at 1Hz to the motor cortex. EEG and spTMS-EEG data will be recorded during the 20 minutes prior to and following the rTMS.
> Arm 2 (sham rTMS): 1000 pulses of rTMS administered via a sham TMS coil at 1Hz to the motor cortex. EEG and spTMS-EEG data will be recorded during the 20 minutes prior to and following the rTMS.

Control Groups: As above, each subject will receive sham rTMS and thus serve as their own control. This within-subject analysis is meant to reduce the influence of inter-subject variability in IED frequency (which can be high) on the results. A potential limitation is that a sham-control may be excessively stringent, given that other studies have found clinically meaningful improvements when sham rTMS is used (i.e. in post-stroke motor recovery), suggesting that even sham rTMS can exert a meaningful physiologic influence. A second limitation is that IED frequency and connectivity may be influenced by behavioral state, which may change between days or behavioral states; we will interact with participants and monitor EEG to maintain behavioral state.

rTMS Intervention: The 1000 pulses of 1Hz rTMS will be delivered in 2 blocks of 500pulses administered over a total of 16-20minutes. Changes in cortical excitability after 1Hz rTMS typically last approximately the duration of the rTMS itself, so we will measure changes to IEDs and connectivity in the 15-20minutes directly before and after rTMS. If a subject only tolerates 500 pulses, we will restrict measurements to the 10 minutes before and after the rTMS; we will shorten the second intervention accordingly. If a subject does not tolerate 500 pulses, they will be excluded for inability to tolerate the protocol. We will separate the active and sham rTMS session by at least 1 week to ensure adequate wash-out of effects, as is standard in rTMS trials.

RECRUITMENT & RETENTION

Anticipated number to be screened: We expect to recruit 36-40 subjects and anticipate screening 70-80 subjects to reach this target enrollment.

Anticipated Sample Size: We expect to recruit 36-40 subjects over 4 years, at a rate of 9-10 subjects per year. Subjects will be between the ages of 5-16 years. Based on the typical epidemiology and presenting age of BECTS, we expect 60-70% of subjects to be male and 80% of subjects to be between the ages of 7-12 years. Based on the demographics of the patient

population served by Lucile Packard Children's Hospital and other Bay Area medical centers, subjects are expected to be 35% Caucasian/Non-Hispanic, 25% Caucasian/Hispanic, 30% Asian, 4% African American, and 6% Mixed/Other. Adults will not be included as BECTS resolves in adolescence.

Planned Recruitment Strategies: The study will recruit children with BECTS seen at Lucile Packard Children's Hospital (LPCH) outpatient neurology clinic or the neurophysiology laboratory. Additionally, children will be recruited if they are referred to the study from surrounding child neurology practices. The catchment area for LPCH extends south into California's Central Valley, north to the Oregon border and east to Reno, Nevada. The patient population is ethnically and socioeconomically diverse. In addition to direct referrals, we will screen the LPCH medical records to identify potential participants and request referrals from their treating providers. We will advertise the trial online and during speaking/outreach events with patient advocacy groups to allow for direct referrals from interested patients and their families. Screening and data gathering will not occur in a public setting.

Retention: Subjects must return for 2 sessions separated by at least 1 week. To improve retention, we will endeavor to schedule the 2 sessions as close together as possible, and specifically within 4-8 weeks of one another. We will frequently check-in with the participant, allow for flexibility in the scheduling, send reminder emails and phone calls, and provide a reasonable stipend for the child's time ($25/session).

Participant Incentives: Children will be given a $25 gift card at the completion of each session. This is meaningful enough to thank the child for his or her effort without being significant enough to unduly influence the parents when they are providing informed consent. The parents will also be reimbursed for travel costs such as parking.

JUSTIFICATION FOR STUDY DESIGN AND DOSE

Active rTMS: The active intervention is 1Hz rTMS applied with an active coil to the motor cortex. Low frequency (1Hz or slower) rTMS can induce changes in brain excitability lasting minutes to hours [43,44] and has been shown to reduce IED frequency in patients with refractory focal epilepsy.[21,45] Focal changes induced by rTMS have downstream effects on brain regions connected to the stimulated motor cortex. Theoretically, 1Hz active rTMS will reduce cortical excitability of the epileptogenic motor cortex, thus reducing IED frequency. Furthermore, it will alter connectivity between the epileptogenic motor cortex and other connected cortices. Thus, we are measuring IED frequency and EEG-based connectivity.

Sham rTMS: The sham control is 1Hz rTMS administered with a sham coil, which will help account for the impact of other components of the experimental session (i.e. fear, boredom, variable attention).

rTMS Administration: The rTMS (sham and active) will be administered by a study team including Dr. Baumer and a research assistant over the course of 2 sessions separated from one another by at least a week. This will occur in a room dedicated to the TMS session. The rTMS will be administered as 2 blocks of 500 pulses applied at 1Hz to the motor cortex. A break of 2-3 minutes between blocks is acceptable if needed to allow for maximum participation. The sham rTMS will be administered using the same parameters and same stimulation site, but the intensity of the sham coil is such that it is not expected to induce an intracranial current.

RANDOMIZATION & BLINDING:
The order of conditions (active vs. sham rTMS) will be randomized on a per-subject basis. A random number generator will be used to create a random list using numbers 1-40. Subjects whose recruitment lines up with an even number will receive active rTMS in the first session and sham rTMS in the second session and vice versa for odd numbers. Participants will be blind to the condition order. The sham rTMS will be administered using the same parameters and same stimulation site as the active stimulation. The intensity of the sham coil is such that it is expected to create a scalp sensation without inducing an intracranial current. It is possible that some subjects will recognize a difference between the 2 sessions, and we will ask them after each session to assess if it was active vs. sham rTMS. If subjects can consistently identify a difference, than we will report that blinding was not successful in our final analyses.

Researchers will not be blinded during the session, but the data will be coded prior to analysis and the person performing the analysis will be blinded to the session type.

STUDY PROCEDURES
Screening: For subjects referred by their physician, the study team will confirm the diagnosis of BECTS with the referring provider. Parents of participants will then be called by a member of the research team and screened on the inclusion and exclusion criteria. If the parents primarily speak a different language than English, the screening will be conducted with the help of an interpreter or by a study team member fluent in that language.

For subjects who self-refer to the study, the study team will review the inclusion and exclusion criteria with the family. Subjects who screen-in and consent to the study will be asked to bring a physician's note stating their diagnosis and prior EEG findings.

Screening will be done within 2 months of participation. If this time window is delayed, the inclusion/exclusion criteria will be reviewed on the day of the first intervention to ensure the subject is still eligible.

Informed Consent & Assent: Since informed consent is required from both parents and/or legal guardians if they are reasonably available (i.e. not deceased, imprisoned, whereabouts unknown or not involved in the care of the child), informed consent will be first obtained over the telephone with the help of an interpreter if necessary. Assent will be obtained from the participating child on the day of the first rTMS session.

Coding of Subjects & Randomization: Subjects will be assigned a study-number based on the order of consent. This will be used to label all information and the CRF. In addition, the study number will be compared against a list of randomly generated numbers to determine if the subject will receive active or sham rTMS first (as described in the section on randomization).

Baseline Assessments:
Clinical & Demographic Data*:* We will collect the following variables: age, gender, age of first seizure, number of lifetime seizures, anti-seizure medications, and side of centrotemporal IEDs (left, right or bilateral) from the medical chart. We will measure degree of right-handedness with the Edinburgh Handedness Questionnaire[51] and parental education and socioeconomic status with The Hollingshead Four-Factor Index. This coded data will be kept in subject-specific binders.

Anti-Seizure Medication Dose and Level: We will record the daily dose (both absolute and dose-by-weight) of all medications that the subject is receiving. If the subject is on an anti-seizure medication, we will record a level within 2-4 weeks of the first intervention day. We will

use a clinically-drawn level if this is available or otherwise draw a serum level as part of the experimental procedure.

Neurocognitive Testing: All subjects will complete the Weschler Abbreviated Scale of Intelligence – Second Edition (WASI-II)[52] to measure IQ and the Test of Variable Attention (T.O.V.A.)[53] to provide a continuous measure of attention. The Clinical Evaluation of Language Fundamentals 5 (CELF-5)[54] core language score will be collected to provide an age-normalized measure of language function. These may be collected anytime in the 2-8 weeks prior to the first intervention.

MRI: If subjects have undergone an MRI as part of clinical care, we will request that they bring a copy of this MRI on disc to be used for neuro-navigation for the rTMS session. If an MRI is not available, we will use a dummy head model.

First rTMS Session: BECTS subjects will wear a 64-channel TMS-compatible high-density EEG cap while watching a video and listening to white noise. We will use neuro-navigation software to co-register the head and electrode positions to a representative pediatric brain or to the subject's MRI if one is clinically available. At the beginning of the session, we will monitor the EEG recording to determine if IEDs are unilateral or bilateral. We will then measure the resting motor threshold (rMT) for the hemisphere with the higher IED burden or the left hemisphere if IEDs are bilateral. The rMT will be established in the standard way.[55] We will apply 150 single pulses of TMS (spTMS) at 90% rMT in 2 blocks, with additional resting-state EEG (without spTMS) data gathered between these blocks. The patient will then receive either 1000 pulses of 1Hz rTMS at 90% rMT or 1000 pulses of sham 1Hz rTMS to the motor cortex, depending on the prior randomization. After the rTMS, we will repeat the blocks of spTMS interspersed with resting-state EEG.

Second rTMS Session: The second session will occur at least one week after the first session, but ideally will be done within 2-4 weeks of the first. In the second session, the procedures will be repeated as above except the other intervention will be administered. Of note, occasionally IED-predominance shifts hemispheres between EEGs. We will stimulate the same side as received rTMS during the first session unless >80% of IEDs are emerging from the contralateral hemisphere. If this occurs, we will stimulate the contralateral hemisphere and request that the subject come in for a third "tie-breaker" session.

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Other Rationale