

Request for Investigational Device Exemption for the GES 400 and STM9000 system for Suppressing Epileptic Discharges

Version 3, November 2015, Electrical Geodesics, Inc. and EB Neuro, S.p.A.

Summary

We propose a safety and feasibility trial for treating epilepsy (RESET: Registered Electrical Sources for Epilepsy Treatment). In this approach, the cortical source of epileptic discharges is first localized with dense array electroencephalography (256-channel dEEG). This localization is then registered with neuronavigator software to allow precise targeting with slow (0.5 Hz) repetitive Transcranial Magnetic Stimulation (rTMS) with the STM9000. The purpose in the feasibility study is to introduce Long Term Depression (LTD) of the seizure onset zone in order to reduce epileptiform discharges. The goal in the future pivotal trial will be to extend this approach to suppress seizures. The sponsor of this trial is Electrical Geodesics, Inc. (EGI), the manufacturer of the dEEG system (GES 400) and the US distributor of the EB Neuro STM9000 rTMS system (manufactured in Italy by EB Neuro, S.p.A.).

The eventual goal will be a pivotal trial for a de novo 510k for dEEG-guided rTMS for suppressing epileptic seizures. The more limited goal of suppressing epileptic discharges (spikes) will allow careful evaluation of safety while demonstrating feasibility of the therapeutic action. In preparing this request, we have studied the guidance on the special controls described for rTMS in the FDA Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems, Document issued on: July 26, 2011. In addition, because patients with epilepsy are at particular risk of seizures that may be induced or exacerbated by rTMS, we also address the unique risks of this population, the existing evidence on safety and efficacy of rTMS treatment of the epileptic focus, and the mitigation we propose to minimize the risks.

EGI has received an IDE for a safety and feasibility trial for treating epileptic discharges with a different method and device, the Geodesic Transcranial Electrical Neuromodulation (GTEN 100) system. The primary difference in the present proposal is the use of rTMS (instead of the GTEN 100) to induce long term depression and thus suppression of the cortical excitability at the epileptic focus. Dr. Robert Fisher, EGI's unpaid consultant on this project, has received an IRB approval at Stanford University Hospital for preliminary studies with dEEG-guided rTMS treatment of focal epilepsy with the GES 400 and STM9000.

Device Description: GES 400 and STM9000	4
Intended Use	4
Indications for Use	4
Previous Submissions	5
Rationale for dEEG Localization and rTMS Treatment	6
<i>rTMS Treatment of Epilepsy</i>	7
<i>dEEG Localization of the Interictal Discharge Focus</i>	8
STM9000 rTMS System with BrainNet Neuronavigator	10
<i>STM9000 - Device Architecture and Stimulus Waveforms</i>	12
<i>BrainNet Neuronavigator</i>	12
<i>Testing the Motor Evoked Potential (MEP) with the Amplifier - STM9000</i>	13
<i>Registering the 256 dEEG Sensors with the Patient's MRI</i>	13
<i>Localizing the Epileptogenic Zone</i>	15
<i>Individual Cortical Surface Models for Interictal Focus Targeting</i>	15
<i>Validation of the Electric Head Model with bounded Electrical Impedance Tomography (bEIT)</i>	18
<i>Software Life Cycle and Risk Management</i>	19
Risks of GES 400 dEEG Assessment and STM9000 rTMS Treatment and Mitigation of Risks	19
<i>Risks of Simultaneous rTMS with the MicroCel 100 Geodesic Sensor Net</i>	19
<i>General Risks of rTMS Treatment</i>	20
<i>Risk of Inducing Seizures by rTMS Treatment</i>	21
<i>Risk of Unwanted Plasticity</i>	22
<i>Mitigating the Risk of Unwanted Plasticity</i>	22
Safety and Feasibility Clinical Trial Design	24
<i>Overview of dEEG Acquisition, Spike Detection, and Spike Localization</i>	25
<i>Overview of the Electric Head Model Construction</i>	25
<i>Overview of rTMS Targeting</i>	27
<i>Clinical Trial Sites</i>	27
<i>Patient Recruitment</i>	27
<i>Inclusion Criteria</i>	28
<i>Exclusionary Criteria</i>	28
<i>Escape Criteria</i>	28
<i>Baseline, Treatment, and Follow up Protocols</i>	29
<i>Primary Endpoint</i>	30
<i>Secondary Endpoints</i>	30
<i>Safety Endpoint</i>	30
<i>Study Success</i>	30

<i>Pooling Data Across Sites</i>	31	
Study Procedures	31	
<i>Informed Consent</i>	31	
<i>Localizing Epileptiform Discharges (EDs)</i>		32
<i>bEIT Validation of the Head Model</i>	32	
<i>Determination of rTMS Intensity</i>	32	
<i>Review of the EEG for Safety and for Spike Counts</i>		33
<i>Additional Monitoring of Risk</i>	33	
<i>Overview of Study Protocol</i>	33	
Bibliography	35	

Device Description: GES 400 and STM9000

The proposed diagnostic and treatment protocol begins with identification and localization of interictal epileptiform discharges (including spikes and other discharges) with the Geodesic EEG System (GES) 400, including the Net Station 5 dEEG software and the GeoSource 2.0 source localization software (both FDA cleared).

The assumptions of this approach are twofold. First, when there is a single or dominant interictal discharge focus, this is typically the site of seizure onset. Second, treatment of this site with slow rTMS will result in seizure suppression (Sun, et al., 2012). For the safety and feasibility trial, the first goal will be statistically significant suppression of the patient's epileptiform discharges from the treated region.

Once the focus is localized with dEEG with the GES 400, treatment involves inducing long term depression (LTD), and thus decreased cortical excitability, with slow (0.5 Hz) rTMS pulses using the STM9000 system. The seizure focus, identified in the patient's MRI with the Net Station and GeoSource software, is then targeted with the patient's MRI with the NetBrain Neuronavigator software. This software guides the positioning of the STM9000 butterfly coil with a 3D localizer (Northern Digital Imaging's Vicrascan) in relation to the patient's MRI, thereby visualizing the location of the STM9000 pulses in relation to the patient's brain.

Safety of the procedure is evaluated through continuous dEEG monitoring with the GES 400 during and after the treatment session.

Intended Use

The intended use of the GES 400 STM9000 dEEG-rTMS system is the identification, localization, and treatment of epileptic foci in the brain for the temporary suppression of epileptiform discharges.

Indications for Use

The GES 400 STM9000 dEEG-rTMS system is indicated to temporarily reduce the frequency of epileptiform discharges in adults with focal, superficial, partial onset seizures that continue to occur despite at least two trials of anti-epileptic drugs at therapeutic levels.

Previous Submissions

Table 1 summarizes the EGI and EB Neuro products relevant to both the Geodesic EEG System (GES) 400, the STM9000, and their accessory software packages.

Product Name	Clearance Status	Description; Any Changes for dEEG-rTMS
GES 400	K131882	dEEG System. No change.
STM9000	Not cleared. Submitted as 510k for peripheral nerve stimulation (PNS).	rTMS System. No change.
NetBrain Neuronavigator	Not cleared.	Software for positioning the focus of the rTMS coil in relation to the patient's MRI.
Net Station 5.2	Letter to file	No change.
Geodesic Sensor Nets	K131882	A low-profile TMS-compatible sensor net, the MicroCel 100, has been added to the product line.
Geodesic Photogrammetry System	K043309	No change.
GeoSource 2.0	K092844	Electrical Source Imaging (ESI) with atlas model. GeoSource 3.0 will include individual head models.
Modal Image Pipeline	Not yet cleared.	To be submitted for 510k
Spike Beacon	Not yet cleared.	To be submitted for 510k

Table 1. Summary of products, clearances, and descriptions.

The GES 400 was cleared under K131882 on February 12, 2014. The intended use of the GES 400 is:

The Geodesic EEG System 400 Series (GES 400) is intended to measure and record the electrical activity of the patient's brain. It can be used on adults, children, and infants.

The GES 400 consists of a number of hardware components, proprietary electrode arrays called Geodesic Sensor Nets, and the proprietary software Net Station. As is typical in EEG, the GES 400 uses small amounts of current (less than 10 μ A) to test contact impedance of the electrodes with the scalp. The GES 400 uses two other cleared accessories: the Geodesic Photogrammetry System (K043309) for locating the sensors in 3D and the GeoSource 2.0 EEG source localization software (K092844). During this trial, we anticipate upgrade to the next generation GeoSource 3.0 software, which will soon be submitted for a 510k as an upgrade of GeoSource 2.0. Spike identification and marking by the clinician will be supplemented in the present trial with the new Spike Beacon software, which will soon be submitted separately under a 510k.

The STM9000 has been submitted to the FDA by EB Neuro under a 510k for peripheral nerve stimulation (see **Appendix 1: STM9000_Device_Description PNS**). The NetBrain Neuronavigator software has not been cleared, but will be submitted for separate clearance/approval as well.

Rationale for dEEG Localization and rTMS Treatment

Epilepsy remains refractory to drug treatment in one-third of patients. Although the drugs developed in recent years have more tolerable side effects than traditional anti-epileptic drugs, their efficacy remains limited: one-third of patients continue to have seizures (Bergey, 2013). Furthermore, the side effects of modern drugs remain significant, and these side effects degrade the quality of life for many patients who must take them. Some patients discontinue the drugs, even at the risk of continued seizures.

Neurosurgical resection of the epileptogenic zone is an effective treatment. However, particularly in the US in recent years, neurologists are reluctant to advocate for neurosurgery with patients and families. This is presumably for legal and social reasons rather than medical reasons, because the medical evidence strongly supports neurosurgical resection. Nonetheless, neurosurgical resection is now increasingly avoided (Engel, 2013).

There are several invasive technologies for electrical stimulation of the brain, including electrodes placed in the anterior thalamus, or intracranial electrodes stimulated in response to apparent seizures, or electrodes that affect the brain indirectly through stimulation of the vagus nerve. Nonetheless, even though these methods require surgery and implanted devices, the clinical efficacy of these methods remains poor, roughly on a par with that of anti-epileptic drugs (Bergey, 2013).

In this era of advanced human neuroscience, the failure to treat epilepsy effectively is a major failure of modern science and medicine. Even if their seizures are suppressed, many children suffer from the sedation of anti-epileptic drugs. If their seizures are not suppressed, the seizures may cause permanent brain damage. Uncontrolled seizures can injure the brain and lead to sudden unexpected death in epilepsy (SUDEP).

Eliminating or reducing seizures could significantly improve the quality of life for millions of people.

For the present safety and feasibility trial, we propose to define feasibility as the statistically significant suppression of epileptiform discharges, including spikes and other discharges. Although seizure suppression will be the goal of the pivotal trial, there is evidence that cognitive development is impaired in children with frequent spikes, even if seizures are controlled (Ebus et al., 2012; Rudzinski & Meador, 2013). Even though we view it primarily as a proof of feasibility of seizure suppression, spike suppression itself may be clinically significant.

Interictal spikes are imperfect surrogates for seizures. Interictal spiking tends to decrease before a seizure (Lange, Lieb, Engel, & Crandall, 1983) and increases after seizures, but not with changes in medication (Gotman & Koffler, 1989). Low interictal spike frequency in patients with unilateral mesial temporal sclerosis predicts a good postsurgical outcome (Krendl, Lurger, & Baumgartner, 2008), but it is not known whether reducing spike frequency would contribute to reducing seizures with surgical or medical therapies. Several studies have investigated the effects of neurostimulation on spike counts, usually finding that stimulation reduces spiking (Labar et al., 2013). Spike reductions have been observed with stimulation of the vagus nerve (Koo, 2001; Kuba et al., 2010; Olejniczak et al., 2001), centromedian thalamus (Velasco, Velasco, Marquez, & Velasco, 1993; Velasco et al., 1995) and hippocampus (Vonck, Boon, Achten, De Reuck, & Caemaert, 2002). Responsive cortical stimulation produced changes in spiking consistent for an individual patient, but with increases for some and decreases for others (Labar et al., 2013). Most relevant are two studies showing spike reductions with rTMS (Cantello et al., 2007; Fregni et al., 2006). The study by Cantello (Cantello, et al. 2007) saw interictal spikes decrease in one third of patients receiving rTMS ($p=n.s.$), but not in patients receiving placebo stimulation. Fregni (Fregni, et al. 2006) documented a mean 31% reduction of interictal spiking immediately after rTMS ($p<0.0012$), still present at week 4 and 8 following a 5-day stimulation paradigm.

rTMS Treatment of Epilepsy

In a review of the initial case reports and uncontrolled trials treating epilepsy with rTMS, Nitsche and Paulus (Nitsche & Paulus, 2009) observed considerable variability in the patients (nature of epilepsy and localization of the seizure focus), methods (frequency and intensity of rTMS), and the results (therapeutic effect). In three randomized and sham controlled trials (RCT), two of the trials treated patients with focal epilepsy with high intensity rTMS delivered at a slow (1 Hz) rate: one of these reported suppression of seizures that was statistically significant, whereas the second study reported marginally significant suppression. In the third RCT, patients with mixed etiology were included,

the rTMS was lower intensity, and only suppression of epileptiform discharges rather than seizures was observed.

The importance of careful targeting of epileptic foci with high intensity slow (in this case 0.5 Hz) rTMS was emphasized in the successful suppression of seizures reported by Sun, et al (Sun et al., 2012). In a RCT design, the high intensity treatment was at 90% of resting motor threshold (rMT), whereas the sham condition was 20% of rMT. The epileptic focus was determined from conventional 10-20 System EEG, semiology, and MRI. In many of these patients a frontal or parietal focus allowed the presumed epileptogenic tissue to be targeted within the reach of rTMS, which is roughly a depth of 2 to 3 cm (Wagner, Zahn, Grodzinsky, & Pascual-Leone, 2004). Both groups had an average of 9 seizures per week prior to treatment. The sham (20%) group continued at about 9 per week for the 10 weeks of follow up after treatment. In contrast, the active 90% rMT treatment group had an average of 2 seizures per week starting at the first week after treatment and continuing for the ten weeks of follow up. In addition, the patients in the active rTMS treatment group reported a significant reduction on 7 of 9 psychiatric symptom scales on the SCL-90 questionnaire. Impressed with the Sun, et al., results, we have adopted several elements of their methodology in the present design.

Other evidence for therapeutic efficacy has come from rTMS treatment for sustained or repetitive seizures. Rotenberg and associates (Rotenberg, Bae, Takeoka, et al., 2009) reported applying fast (20 to 100 Hz) bursts or sustained slow (1 Hz) rTMS in 7 patients with epilepsy partialis continua (EPC). In three patients there was a brief (20-30 minute) suppression of the seizures. In two more of these patients the suppression lasted up to one day. In six additional reports that Rotenberg et al found in the literature, three patients showed suppression of seizures with rTMS treatments (Rotenberg, Bae, Muller, et al., 2009). Importantly, none of the patients showed worsening of seizures with rTMS. This relative safety of rTMS in epileptic patients is consistent with the review of TMS safety by Rossi et al (Rossi, Hallett, Rossini, & Pascual-Leone, 2009), with the important caveat that patients must not be taken off their anti-epileptic medication.

dEEG Localization of the Interictal Discharge Focus

In several of case reports on treating refractory status epileptics (RSE) with rTMS at Beth Israel Deaconess Medical Center (BIDMC), the investigators have reported not only that rTMS is practical in the ICU setting (Liu, Pang, Herman, Pascual-Leone, & Rotenberg, 2013), but that it can be guided effectively by dEEG localization of the epileptic focus. Vanhaerents et al report on a young man with progressive epilepsy leading to drug-refractory status epilepticus, defined as repetitive seizures without full recovery of consciousness (VanHaerents, Herman, Pang, Pascual-Leone, & Shafi, in press). Treatment efforts included trials of multiple anti-epileptic drugs (AEDs), at dos-

es that led to impaired cognitive status, multiple admissions to the ICU for treatment to burst-suppression coma with IV anesthetics, and high dose corticosteroids. Nonetheless, the patient continued to have up to 30 seizures per day.

Localization of the patient's focal seizures with EGI's 256 dEEG and the GeoSource 2.0 software showed a medial left occipital focus. Guided by the Sun et al. (2012 results, this focus was treated with daily sessions of 1800 high intensity (95-100% of motor threshold) rTMS pulses at 1 Hz. Both seizures and spikes over the occipital focus declined to zero by the fourth day of treatment, and the patient was seizure free at discharge. At one month after start of treatment, he received three additional rTMS treatments. At seven months, his EEG showed increased interictal discharges, and he received 5 additional rTMS treatments, which reduced the discharges. A nine months, he has remained seizure free and has been able to reduce AEDs to the point that he can return to his academic work (Van Haerents, et al., in press).

In a more recent unpublished case by the same group of investigators at BIDMC, a similar effective course of rTMS treatment was observed with another young man with frequent daily focal seizures. This case is particularly important because it underscores the importance of accurate dEEG localization. The initial rTMS treatment, guided by GeoSource 2.0 localization (with typical sensor positions and the atlas head conductivity model) and by the patient's semiology (auditory aura apparently induced by the seizure) was ineffective. Using the GeoSource 3.0 software (with the Modal Image Pipeline), an individual head conductivity model was constructed using the patient's T1 weighted MRI, including cortical surface extraction for establishing oriented cortex di-

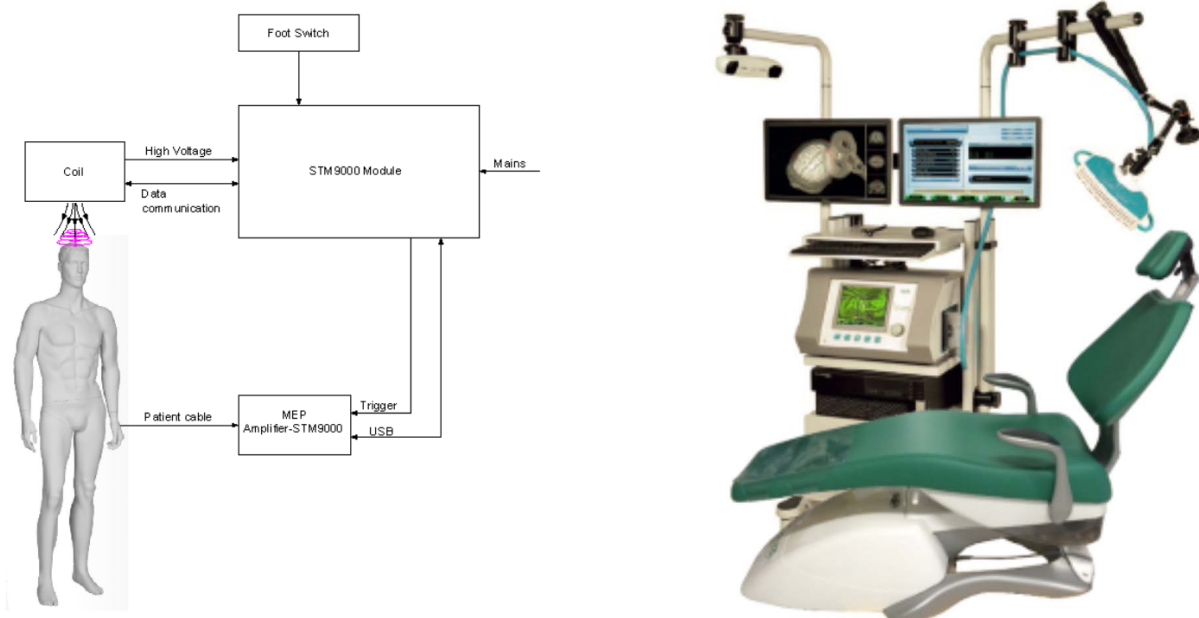


Figure 1. Left: Block diagram of the major components of the STM9000. Right: Photo of the STM9000 configured with chair and BrainNet Neuronavigator.

pole patches (Li, Malony, & Tucker, 2006; Li, Papademetris, & Tucker, in press-b). Actual sensor positions were obtained with the Geodesic Photogrammetry System (Russell, Eriksen, Poolman, Luu, & Tucker, 2005) and registered precisely with the patient's MRI. The source localization of the interictal discharge then showed a slightly different focus in the temporal lobe, more inferior than auditory cortex. Targeting of this focus with high intensity slow (1 Hz) rTMS resulted in a cessation of the seizures. Three weeks after the treatment, the patient had remained seizure free.

STM9000 rTMS System with BrainNet Neuronavigator

The STM9000 rTMS system (**Figures 1 and 2**) is a conventional Transcranial Magnetic Stimulator (TMS) composed of a current generator that produces energy discharges on a stimulating probe (Coil) placed to contact with the patient's skin. **Appendix 1** provides a detailed technical device description (oriented to peripheral nerve stimulation), that follows the guidelines for rTMS in the FDA Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems, Document issued on July 26, 2011.

The butterfly coil of the STM9000 generates conventional rTMS waveforms, as shown in the measurements in **Figure 3 (and Appendix 1)**. In the TMS device, a capacitor C is charged to a high voltage. The energy stored in the capacitor C is supplied to

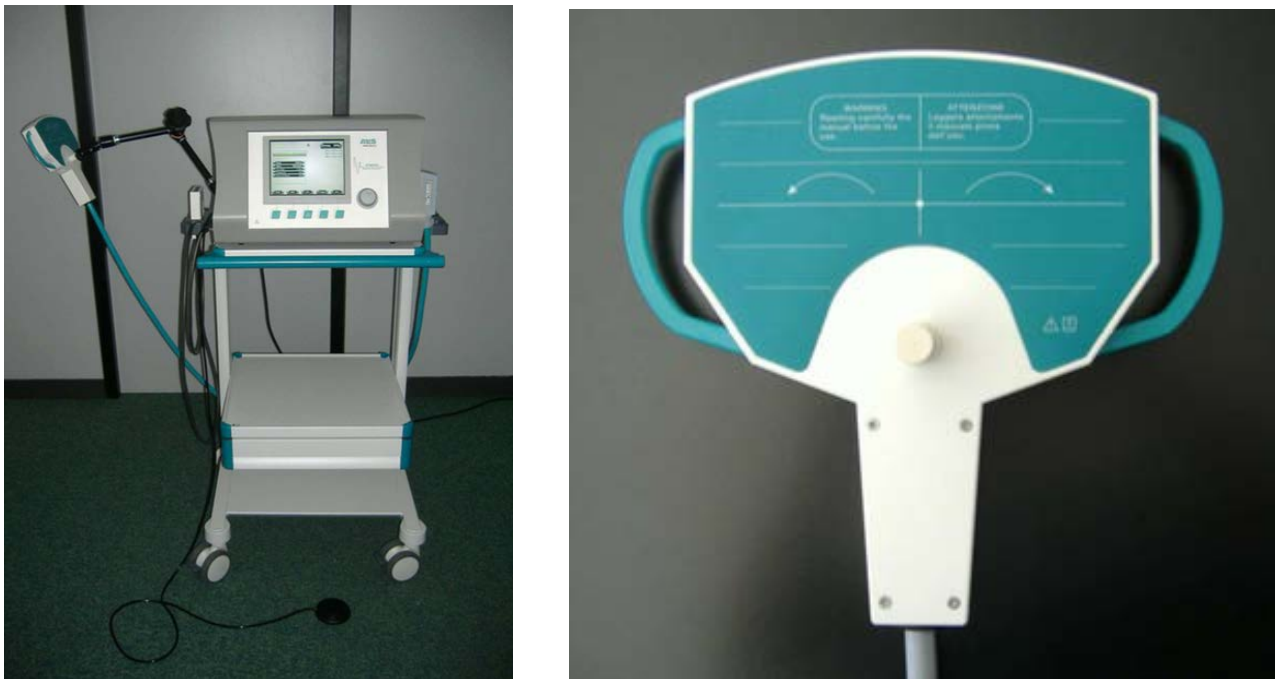


Figure 2. Left: Alternate configuration of STM9000 on cart without neuronavigator. Right: Air Cooled 70 mm Butterfly coil.

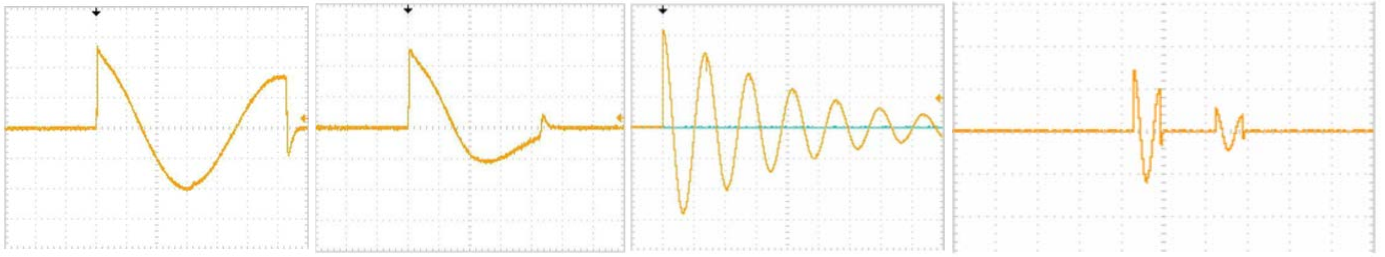


Figure 3. Left to right: Biphasic waveform; Monophasic waveform; Damped sinusoid waveform; double or two-pulse waveform.

the coil, which generates a magnetic field having a damped sine waveform. The magnetic field induces electric current in the body, which creates the physiological effect.

The STM9000 is provided with a hardware module for recording TMS-induced MEP (Motor Evoked Potentials) named the *Amplifier- STM9000*. The Amplifier-STM9000, if connected to STM9000, is able to detect the electromyographic (EMG) response of the patient to TMS-induced activity of the motor cortex. The video monitor of STM9000 displays the motor evoked potential so detected, allowing the operator to detect and quantify the motor threshold level for the patient (**Appendix 1**).

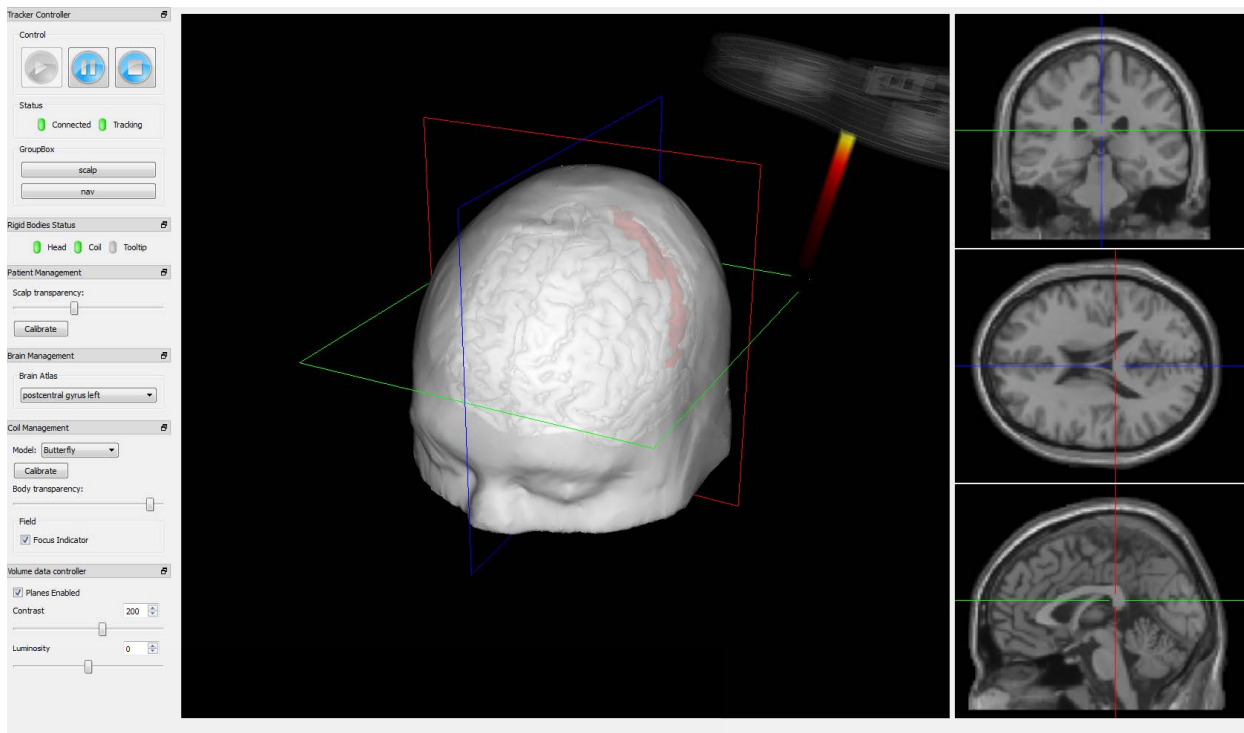


Figure 4. BrainNet Neuronavigator showing position of the rTMS coil (upper right of top image) with its electric field distribution (visualized with hot metal, red-yellow, color palette), and then positioned over the motor cortex (bottom image).

STM9000 - Device Architecture and Stimulus Waveforms

The magnetic stimulator STM9000 works on the principle of the RLC-series circuits. A capacitor C is charged to a relatively high voltage, by means of a high voltage power supply (HVPW Module), the process is controlled by a microcontroller circuit (HVI Module). The same circuit (HVI Module) activates a power switch that connects the capacitor C to the inductance L of the coil. Therefore the energy stored in the capacitor C is sent to the coil, which generates a magnetic field having a damped sine waveform. The damping is due to a resistive component R in the circuit connecting the capacitor C and inductance L of the coil. The waveform can be controlled and limited to the following morphologies: *biphasic*: the first period of a damped sinusoid; *monophasic*: the first period of a rectified damped sinusoid; *sinusoid*: a damped sinusoid. The STM9000 is able to generate a double stimulation in temporal succession, using a double capacitor C and a double control circuit (HVI Module) with relative switch (**Appendix 1**). This architecture supports two-pulse stimulation protocols. The monophasic pulse is used in the present protocol, with the 0.5 Hz stimulation rate.

BrainNet Neuronavigator

The positioning of the rTMS current delivery in relation to the patient's brain is achieved by importing the structural MRI into the BrainNet Neuronavigator software (**Figure 4**). The position of the rTMS coil in space is calibrated with the Vicrascan (Northern Digital, Inc.) 3D locator hardware shown in **Figure 1**. The position of the patient's head is calibrated similarly, with a 3-ball locator affixed to the headband. An estimate of the electric field distribution is built from the coil model and imaged in color

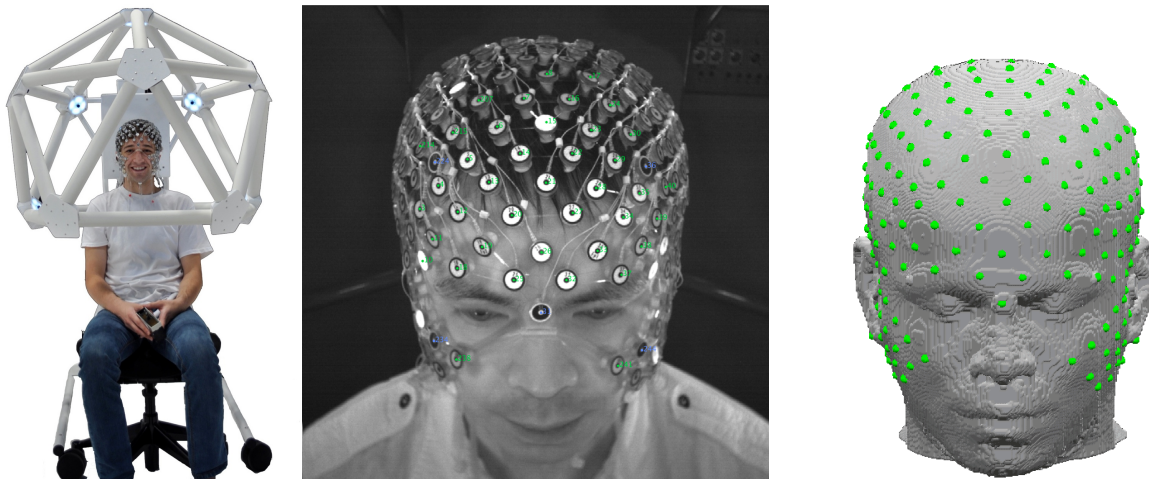


Figure 5. **Left:** With 11 video cameras, the exact 3D sensor positions are captured with EGI's Geodesic Photogrammetry System (GPS). **Middle:** the infrared images allow computer vision detection of all sensors in the Geodesic Sensor Net. **Right:** The 3D sensor coordinates are then registered with the individual's MRI to allow precise planning of current delivery in relation to the person's head tissues.

in **Figure 4**, allowing the operator to position the coil in a way that optimizes the targeting of the desired location.

Testing the Motor Evoked Potential (MEP) with the Amplifier - STM9000

Our testing of the STM9000 over the last two years has used the *Amplifier - STM9000* to measure the MEP evoked by the STM9000 to establish the motor threshold. In the recently completed study of the efficacy of the pulsed GTEN (Geodesic Transcranial Electrical Neuromodulation) protocol in inducing Long-Term Depression or LTD of the cortex (Luu, et al., in preparation), the *Amplifier - STM 9000* was used to measure the MEP as the primary dependent variable reflecting the GTEN-induced LTD. It performed safely and reliably in all these studies.

In the GTEN normal validation study, we examined 12 normal subjects over 3 sessions each and observed that slow (0.5 Hz) cortical-surface-cathodal electrical GTEN pulses (100 ms each) resulted in significant depression of cortical excitability as measured by the MEP. The sham GTEN procedure did not change the MEP. Cortical-surface anodal GTEN decreased cortical excitability but not significantly so.

The procedure for determining TMS motor threshold targeted the cortical area creating the MEP from the first dorsal interosseous muscle (FDI muscle) with relaxed muscle tone. Based on the Rossini et al protocol, initial TMS intensity was set to 35% of the maximum stimulator output. The intensity was increased by intervals of 5% until MEPs in the right FDI muscle are consistently above 50uV (peak-to-peak amplitude). Then the stimulator output level was decreased by 1% until 5 out of 10 MEPs were above 50uV and 5 out of 10 MEPs were below 50uV. This output level is then determined as the resting motor threshold.

For evaluating GTEN efficacy, the baseline MEP was elicited with 130% of TMS power determined for the subject's motor threshold. Using this same TMS power, the MEP amplitude was assessed at 5 min intervals up to 30 min, then at 60 and 90 min.

A similar protocol will be used with the *Amplifier - STM9000* to determine the patient's motor threshold in the present clinical trial for dEEG-guided rTMS treatment of neocortical epilepsy.

Registering the 256 dEEG Sensors with the Patient's MRI

To achieve close registration of the rTMS treatment with the localization of the epileptic focus as defined by the dEEG, the dEEG sensors are located in space with the Geodesic Photogrammetry System (GPS; **Figure 5**) and then registered with the MR image with the Modal Image Pipeline software (**Figure 6**).

The Modal Image Pipeline is a set of software modules that allow processing of MRI, CT, images and sensor positions in preparation for Electrical Source Imaging or ESI with the individual's MRI data. Key features of the Modal Image Pipeline are automated tissue segmentation (scalp, skull, cerebrospinal fluid, gray and white matter)

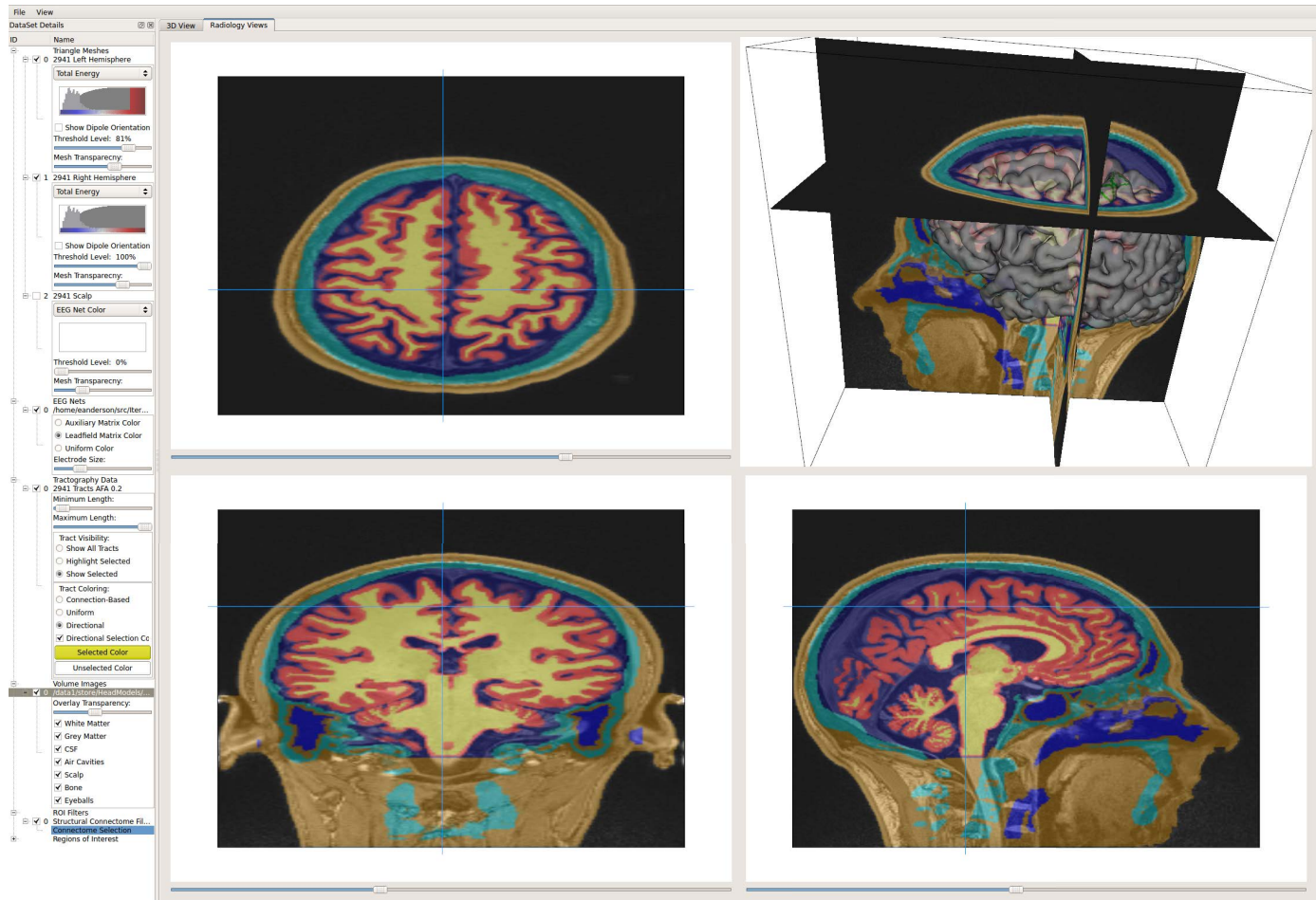


Figure 6. EGI's Modal Image Pipeline software provides segmentation of each major head tissue type, to allow a high resolution electrical (finite difference method) model that simulates how electrical currents, both natural and impressed, propagate through the head. The extraction of the cortical surface (upper right) is important for specifying the location and orientation of cortical sources in Electrical Source Imaging (ESI).

and cortical surface extraction (**Figure 6**). The Modal Image Pipeline (for preparing the individual head model) and GeoSource 3.0 (for Electrical Source Imaging with the individual head model) are being prepared for FDA submission. That submission will present validation results showing that localizing spikes and seizures with the individual head models are at least as accurate as the results with atlas models with GeoSource 2.0. Those atlas model results have been validated by comparison with intracranial recordings and by surgical outcome.

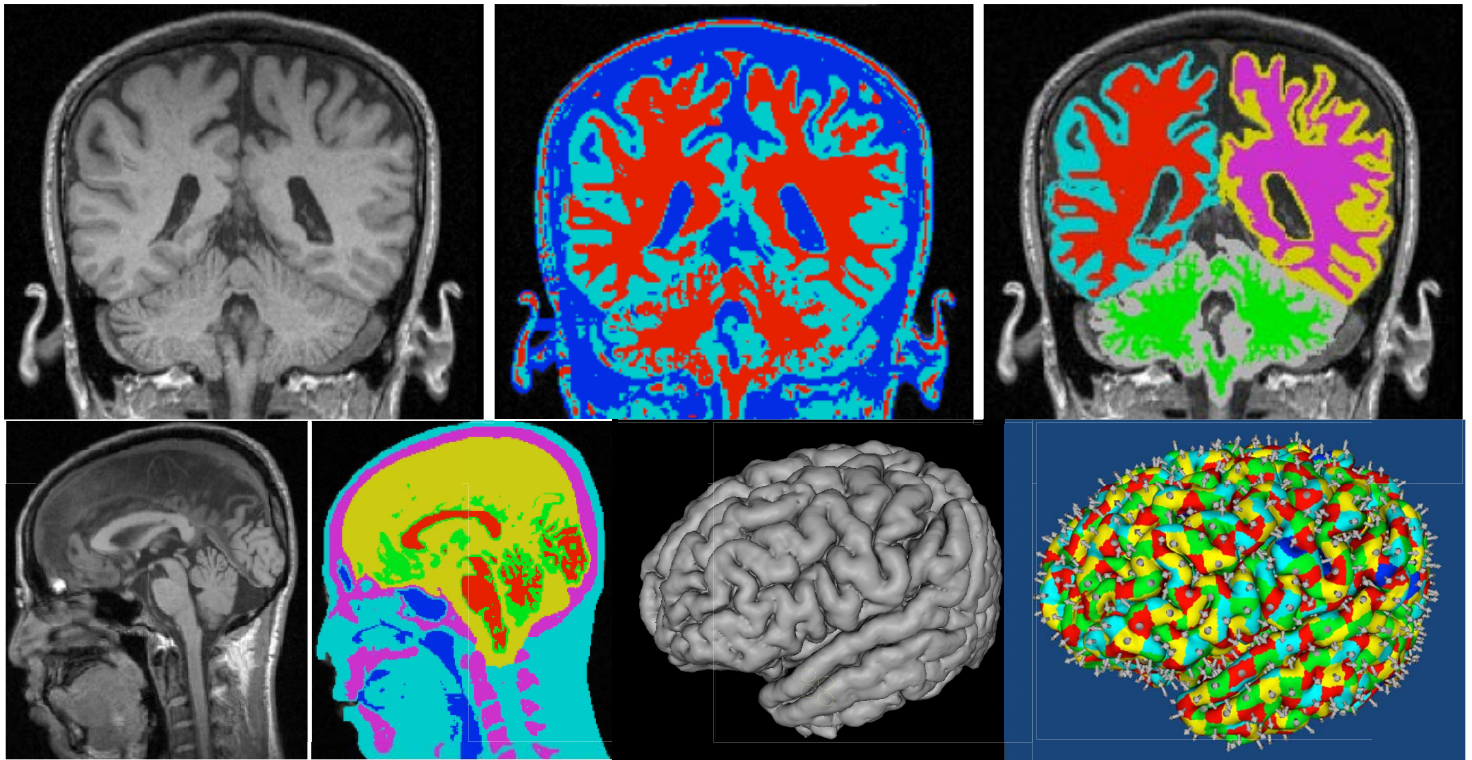


Figure 8. The Modal Image Pipeline begins with tissue segmentation from the individual’s MRI (upper left), with white matter extraction (upper middle) and gray matter extraction and hemisphere separation (upper right). If the patient’s CT is not available, the skull and bones are modeled by nonlinear warping of a database CT to the subject’s MRI (lower left). The cortical surface extraction (lower middle right) is followed by tessellation of the cortical surface into patches, such as 1 sq cm, with an equivalent dipole computed for the net (vector sum) orientation of that patch (lower right).

Localizing the Epileptogenic Zone

In the application of rTMS to suppress epileptiform discharges (and eventually seizures), Electrical Source Imaging (ESI) is first conducted with the dense array EEG (dEEG) to localize epileptiform events with EGI’s GeoSource software. As illustrated in **Figure 7**, dense array ESI with GeoSource 2.0 has been shown to be accurate in determining the epileptogenic zone, as verified by intracranial recordings and by neurosurgical outcome in suppressing or eliminating seizures (Brodbeck et al., 2010; M. Holmes et al., 2010; M. D. Holmes et al., 2008; Yamazaki, Terrill, Fujimoto, Yamamoto, & Tucker, 2012; Yamazaki, Tucker, et al., 2012; Yamazaki, Tucker, Terrill, Fujimoto, & Yamamoto, 2013).

Individual Cortical Surface Models for Interictal Focus Targeting

The next generation of ESI will be enabled by individual electric head models for Finite Difference Method calculations of electrical volume conduction and sources constrained to the oriented cortical surface (**Figures 8 and 9**). These anatomical and cortical

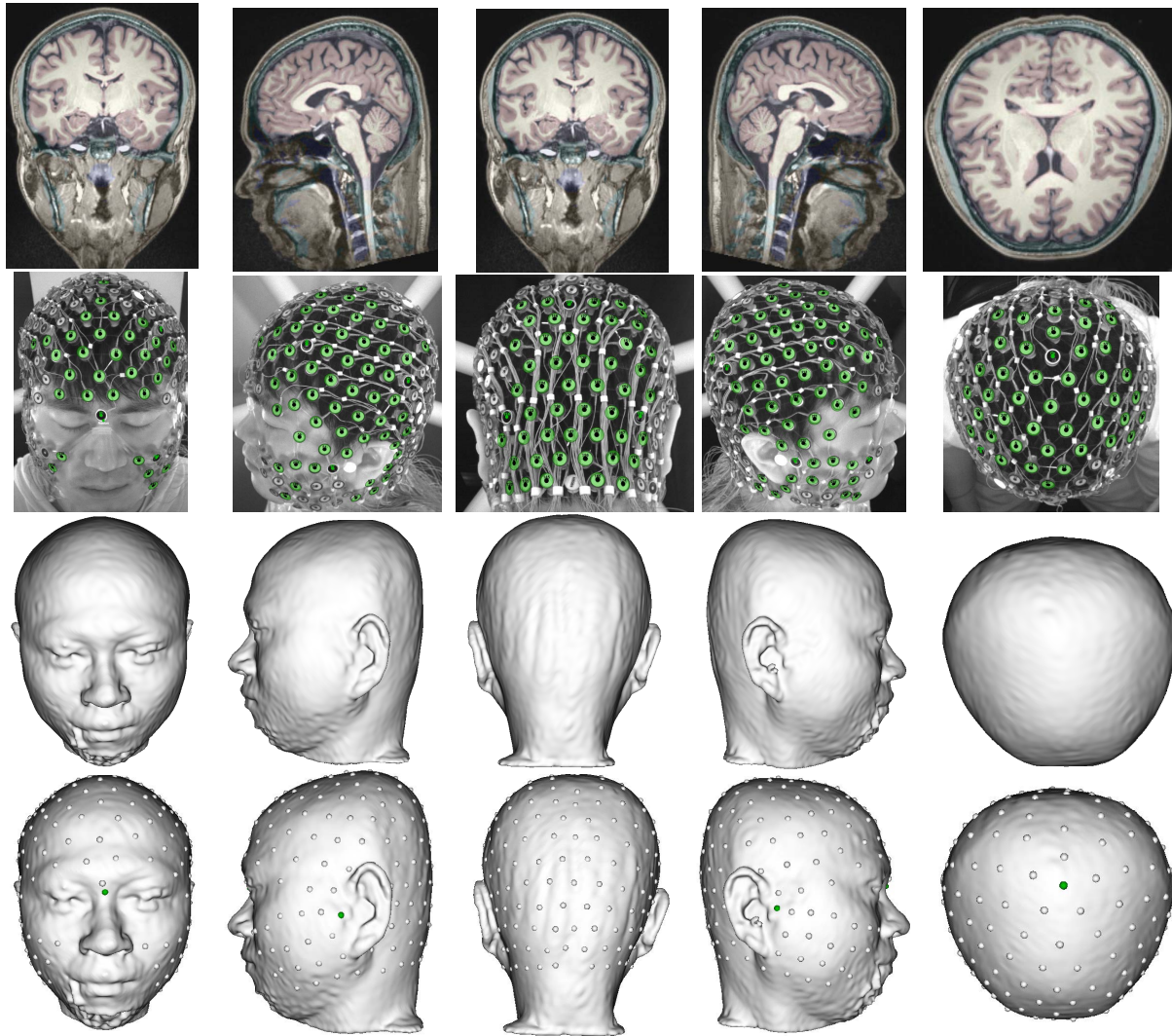


Figure 9. Construction of an individual electrical head model for the GeoSource 3.0 software. FromTop: Tissue segmentation for the Finite Difference Model; Photogrammatic location of EEG sensors; Scalp rendering of the MRI; Registration of the sensor positions with the scalp surface to exactly match the positions in the photographs.

surface geometry data, along with the exact sensor positions, are imported into the GeoSource 3.0 ESI software. The visualization interface for GeoSource 3.0 is called the *Reciprocity Engine* (**Figure 10**) because it integrates the reciprocity of the dEEG measurement of the brain's electrical fields with the impress of current for head model verification (with bEIT) and with Geodesic Transcranial Electrical Neuromodulation (described in EGI's IDE G150023).

The first step in electrical source imaging is review of the electric head model to confirm the accuracy of tissue segmentation, CT skull registration, and cortical surface extraction (**Figure 10, top**). With the improvements in accuracy of the anatomically correct electric head model, the localization of the epileptiform activity as has been validat-

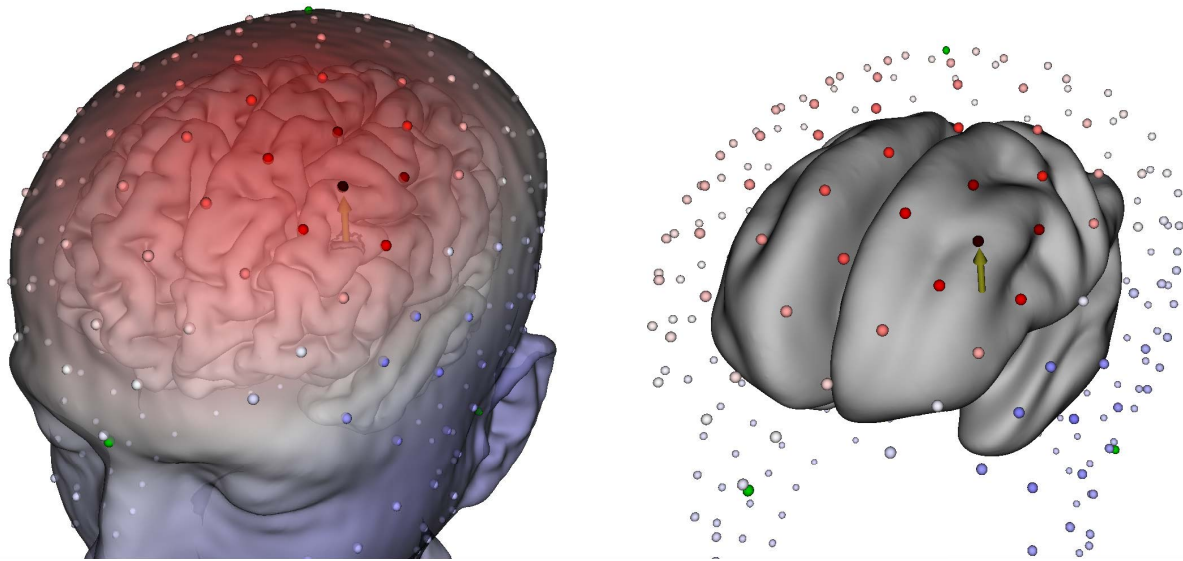
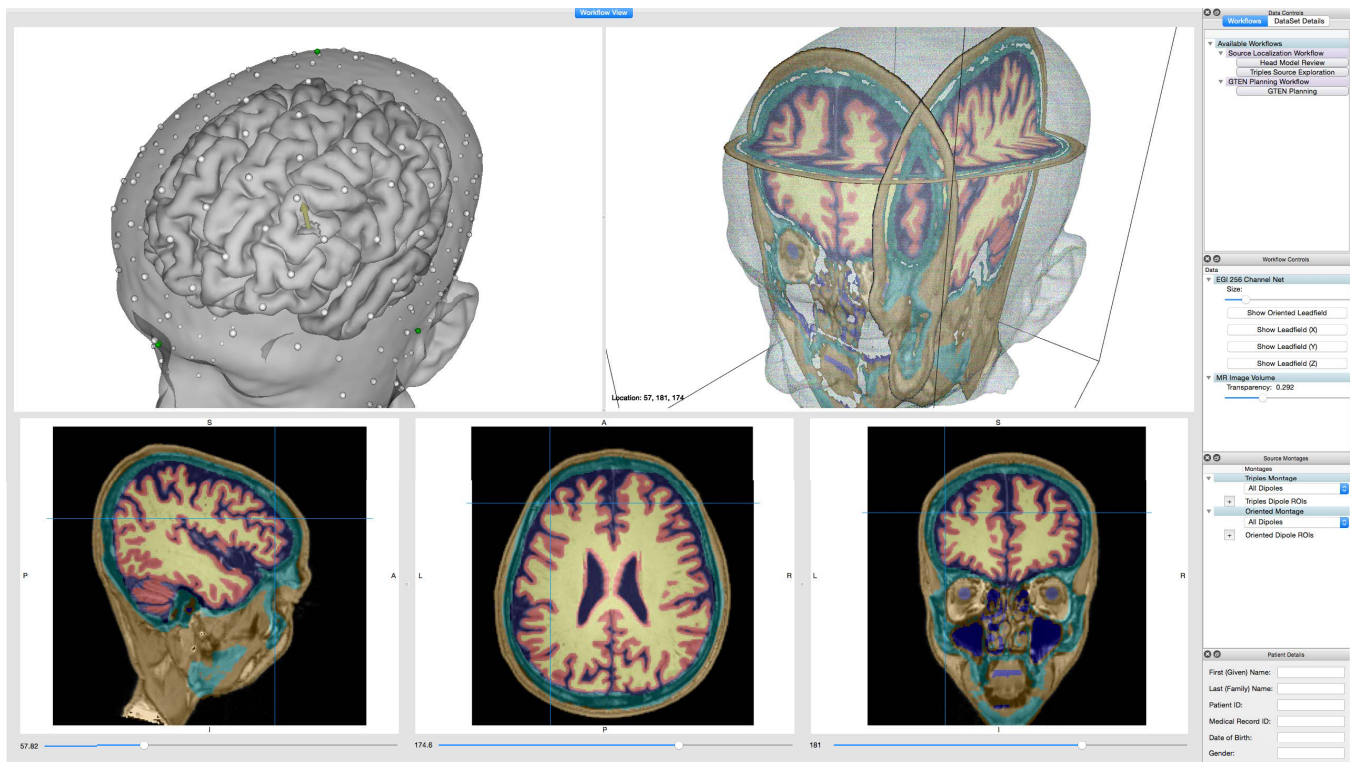


Figure 10. Electrical Source Imaging (ESI) of epileptiform activity with GeoSource 3.0 and the Reciprocity Engine visualization software. The individual head model (top) includes the segmentation of tissue compartments with appropriate conductivity values for flesh (gold), skull and bone (green), CSF (dark blue), gray matter (red), white matter (yellow), eyeballs, and air (light blue). Cortical surface extraction (top left) is evaluated in relation to gray and white matter segmentation (top right). The electrical fields recorded in the EEG (positive = red; negative = blue; bottom left) are modeled by dipolar sources (gold arrow).

ed within reasonable accuracy with GeoSource 2.0 (**Figure 7**) can be improved further through integrating the analysis with the patients individual anatomy.

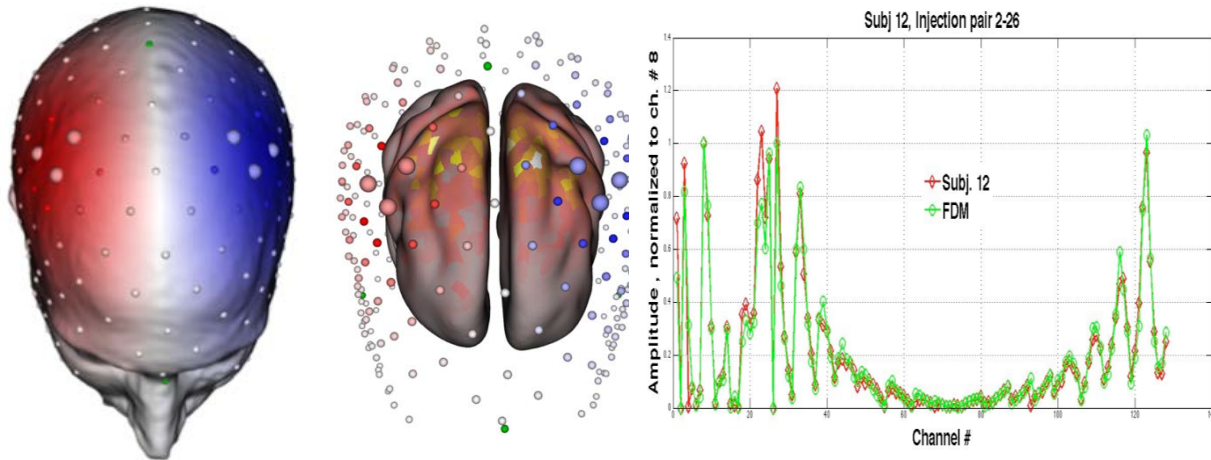


Figure 11. The bEIT validation procedure evaluates the prediction of the electric head model against the measured paths of injected currents through head tissues. **Left:** Illustration of the selection of three source electrodes (red) and 3 sink electrodes (blue). **Middle:** The forward projection of the electrical currents that are estimated to be impressed at the cortical surface. **Right:** The validity of the estimated current paths is tested through the bEIT computation, in which the EEG potentials at all non-injecting electrodes predicted by the Finite Difference Method (FDM, green) is compared to the measured potentials created by the injected currents between channels 2 and 26 for Subject 12 (red).

Validation of the Electric Head Model with bounded Electrical Impedance Tomography (bEIT)

Once the anatomical (geometric) components of the electric head model are verified by inspection, the electrical conductivity of the head tissues is tested for each patient with the bounded Electrical Impedance Tomography (bEIT) protocol (**Figure 11**) that we have optimized and validated over the last ten years (Salman et al., 2006; Volkov, Zherdetsky, Turovets, & Malony, 2009). EIT is a well-known method of visualizing the internal tissues of the body through injecting current, measuring the potential created on the body surface, and computing the impedance or conductivity of the body tissues through Ohm's law (Salman et al., 2006). Because we know the geometry of the tissues from segmenting them from MRI and CT images (**Figures 8 and 9**), we developed *bounded* EIT to bound or constrain the problem with the known geometry of the MRI (or atlas), together with the exact sensor positions from geodesic photogrammetry.

The resulting bEIT protocol is not the ill-posed imaging reconstruction of classical EIT, but a well-posed fitting of the conductivity to each tissue compartment (whose image or geometry is now easily obtained from MRI or an MRI atlas). When applied within the dEEG assessment workflow, the bEIT validation (**Figure 11**) can be completed through impressing high frequency (200 Hz) low power signals between multiple pairs of source and sink electrodes in a scanning pattern to interrogate multiple regions of the head (particularly of the various skull bone plates). The current is limited to 100 μ A in hardware, and the electrodes are 1 cm² in surface area (including electrolyte), so that the

current density is limited to $100 \mu\text{A}/\text{cm}^2$. If the potentials created at the head surface are within 10% of the prediction by the electrical head model for 90% of the channels, then we consider the accuracy of the currents impressed on the cortical surface to be verified within the noise limits of the typical recording.

Software Life Cycle and Risk Management

EB Neuro has developed the BrainNet neuronavigator software under the CE Medical Device Directive, with equivalent requirements for a moderate level of concern. The Net Station, GeoSource 2.0 and 3.0, , have been developed under EGI's Quality System for a moderate level of concern. EGI's Quality System is audited internally on a regular basis, and it is audited externally by a CE notified body as well as by the FDA (March 2015). Design documents for the GTEN 100 include the Design Concept Report, Marketing Requirements Document, and Software Requirements Specification. Key functional components of the software have been designed and tested at the unit level, with regular regression testing and hazard reviews.

Risks of GES 400 dEEG Assessment and STM9000 rTMS Treatment and Mitigation of Risks

Many of the risks of dEEG-guided rTMS treatment of epilepsy with the GES 400 and STM9000 system are described by the FDA guidance document, Repetitive Transcranial Magnetic Stimulation (rTMS) Systems, Document issued on: July 26, 2011. We first address these general risks and their mitigation. In addition, the risk of inducing seizures is particularly important for patients with epilepsy. We provide Appendix 1, which details the design of the STM9000 in relation to the FDA 510k submission for peripheral nerve stimulation.

Risks of Simultaneous rTMS with the MicroCel 100 Geodesic Sensor Net

The MicroCel 100 Geodesic Sensor Net (**Figure 14**) is a low-profile Net designed to allow close placement of the TMS coil to the head. The electrodes are carbon-fiber ABS plastic coated in AgCl, configured with the electrode and strain relief to stand off the head less than 5 mm. Use of the slow (0.5 Hz) rTMS pulses of the present protocol with the STM9000 directly over the electrode results in no perceptible heating of the electrodes.

Direct application of the butterfly coil's discharge with fast repetitive stimulation over an EEG electrode can cause heating of the electrode. The Instructions for Use provide guidelines for avoiding this hazard. The proposed clinical trial involves a slow (0.5 Hz) stimulation rate that does not cause noticeable heating even when applied directly

over an electrode. This was first verified in the Hazard Review of the STM9000 and GES 400 on July 3, 2013. This was confirmed with testing of heating under various stimulation rates in the MicroCel 100 design hazard review, March 20, 2014. It was verified after review of one year of experience with combined dEEG and rTMS in our internal use in the GES 400 hazard review, May 11, 2015. As noted by the Safety of TMS Consensus Group (Rossi et al., 2009), the risk of electrode heating from TMS pulses are non-existent to rare, depending on stimulation protocol. For single and paired TMS pulse protocols, there are no risks associated with scalp electrode heating. Induction of currents in electrical circuits, which can impair operating of medical devices (such as EEG), is also possible but only when the TMS pulse is delivered near the device's circuitry. TMS use with scalp EEG does not pose this risk, as the TMS stimulating coil is not placed near the EEG amplifier.

General Risks of rTMS Treatment

Two important risks, identified by the FDA rTMS guidance document, are failure to identify the correct patient population and ineffective treatment. These are related risks, because effective treatment requires that the targeted cortical region (the focus of the epileptic spikes and the presumed seizure onset zone) be within reach of rTMS targeting. The GES 400 STM9000 dEEG-rTMS system is intended for suppressing epileptiform discharges (and eventually seizures) in patients with focal, superficial, partial onset seizures. The restriction to superficial cortical sites is because the magnetic field fall off from the TMS butterfly coil limits effective induced electrical current flow to ~ 2 cm from the head surface (Wagner, et al., 2004). As shown by the Wagner, et al., simulations, the induced current is limited primarily to the crown of the cortical gyrus, although the cortical surface radial induced current (aligned with the pyramidal neurons and thus thought to be most effective) is then limited to the most superficial walls of the adjacent sulcus.

We will attempt to mitigate this risk by careful selection of patients whose interictal foci can be localized with confidence with the GES 400 and GeoSource software and re found to be within likely reach of the STM9000 coil (**Appendix 1**). The most successful rTMS treatment of epilepsy was reported by Sun, et al (2012), who state that most of the patients who responded successfully had frontal and parietal foci (within reach of the TMS coil), whereas those with medial temporal lobe foci did not respond as well. We visited Dr. Sun in March of 2015 and reviewed her targeting protocol, as well as the advances that could be made with the individual head modeling and ESI with the 256 dEEG from the GES 400, analyzed in GeoSource 3.0 and the Reciprocity Engine. We are reasonably confident at this point that the limitation to patients with superficial foci will allow us to achieve precision in the target planning and therefore mitigate the risk of ineffective treatment.

Another general risk of rTMS is scalp discomfort, damage, or other adverse effects. The magnetic field and electrical induction of the STM9000 is tested by bench tests, as shown in **Figure 3** and in **Appendix 1 (STM9000_Device_Description PNS.pdf)**. There is risk of minor pain or irritation, to the scalp and head muscles, during rTMS treatment, including the slow (0.5 Hz) rate of pulses used here. The informed consent form describes the potential for this pain and irritation and lets the subjects know they can stop the procedure at any time.

The Instructions for Use provide warnings of potential hazards for other medical devices, which must be kept distant from the STM9000 and butterfly coil. The STM9000 must not be used with patients who have implanted medical devices. We have not seen adverse tissue reaction to the use of the STM9000 rTMS coil.

In addition, we have tested the joint operation of the STM9000 rTMS system with the GES 400 dEEG system, including the artifacts introduced in the dEEG recording by rTMS operation. With adequate attention to the anti-aliasing filter (for the A/D converter) the signal quality of the dEEG remains adequate with rapid (< 10 ms) recovery after the rTMS pulse. This is important to allow safety monitoring with dEEG during rTMS treatment.

The GES 400 dEEG system is tested for electrical safety by CSA. We have evaluated electrical safety in the joint operation of the GES 400 with the STM9000, such as required for dEEG monitoring of the brain's response to rTMS treatment. Extensive testing of joint operation has been conducted over the last two years of preclinical studies and has been documented in the hazard review of the MicroCel 100, March 20, 2014, and of the GES 400, including the MicroCel 100, May 15, 2015 (available on request).

If the noise of the rTMS coil exceeds OSHA standards for the interval of treatment, as measured with a sound pressure level meter, the patient will be fitted with earplugs.

Risk of Inducing Seizures by rTMS Treatment

It is well known that repeated electrical stimulation of the normal brain may lead to augmenting or after-discharges, leading to seizures. Persons with epilepsy may show enhanced cortical excitability that places them at increased risk. However, the research evidence suggests that seizures are highly unlikely with slow rTMS pulses (at 0.5 Hz), even with patients with epilepsy, as shown in a recent review of the literature (Bae et al., 2011). The important caution is that patients with epilepsy must not be take off their anti-seizure medication. When seizures have been observed during the slow rTMS treatment session, the seizures that have been recorded have been the patient's typical seizures in both duration and semiology, suggesting these were not induced by the treatment (Rotenberg, Bae, Muller, et al., 2009).

Nonetheless, the risk of inducing seizures or increasing seizure likelihood is a serious concern, and we consider it a significant risk. To mitigate the risk, we will monitor carefully for seizures during and after the treatment. During the three pretreatment

evaluations in the one-month baseline, we will characterize the patient's interictal events, plus any ictal events that are recorded, during the dEEG evaluations sessions. We will train the treatment technician to monitor the EEG for these specific epileptiform events (spikes and other discharges) for that patient during each treatment session. Because the source site of the interictal events is also the presumed epileptogenic zone and the target of the rTMS treatment, this is also the site (and scalp topography) that would be expected to generate seizures if the treatment causes or kindles seizures. The preparation for each patient's treatment will identify not only the source of the epileptiform discharges, but the scalp topography, such that the technician can select a specific montage (screen arrangement) for the channels that reflect the patient's spikes (and likely seizures).

During the 17 minute rTMS treatment intervals, all dEEG channels will be monitored. The 24 bit ADs of the NA 400 allow adequate dynamic range (+/- 200 mV) with a DC input coupling (avoiding the RC network of AC coupling), such that even channels nearby the rTMS pulses seldom clip. During the rest (resting EEG and break) intervals, all 256 channels will be monitored. To assure seizures are not worsened, the post treatment monitoring for safety is continued for 3 hours after the first treatment session.

If there is any increase in epileptiform activity during the treatment or the monitoring interval, interictal or ictal, the consulting epileptologist will review the EEG, the baseline EEGs, and the patient's history to decide if treatment should be discontinued. The patient and if relevant the family will be consulted in this decision.

Risk of Unwanted Plasticity

The short term effects of transcranial neuromodulation including rTMS are typically assumed to be mediated by increasing or decreasing of cortical excitability. The longer term effects appear to reflect stable changes in cortical plasticity, including long-term potentiation (LTP) and long-term depression (LTD) (Monte-Silva et al., 2013). The rationale of the present interventions is that inducing long term depression (with slow rTMS pulses at 1 per 2 sec) in the epileptogenic zone will be effective in suppressing seizures. However, the scientific understanding of this manipulation is limited, such that there is risk of changing plasticity in ways that are unwanted or maladaptive.

Mitigating the Risk of Unwanted Plasticity

In addition to manipulating epileptiform activity, the rTMS treatment may change other aspects of the patient's cortical function that may create unwanted changes in brain function or plasticity. The large general literature for slow rTMS suggest there are unlikely to be serious unwanted changes. The primary effect on the target brain region is expected to be the induction of long-term depression. We will evaluate general cognitive function in each patient with scores on the California Verbal Learning Test and the Wisconsin Card Sorting Test, paying close attention to any changes from the expected

improvement in performance with practice from the normative data. We will review the Quality Of Life In Epilepsy ratings and the seizure diary with each patient and family, systematically reviewing any complaints or reports that may suggest the treatment is creating unwanted changes in brain function.

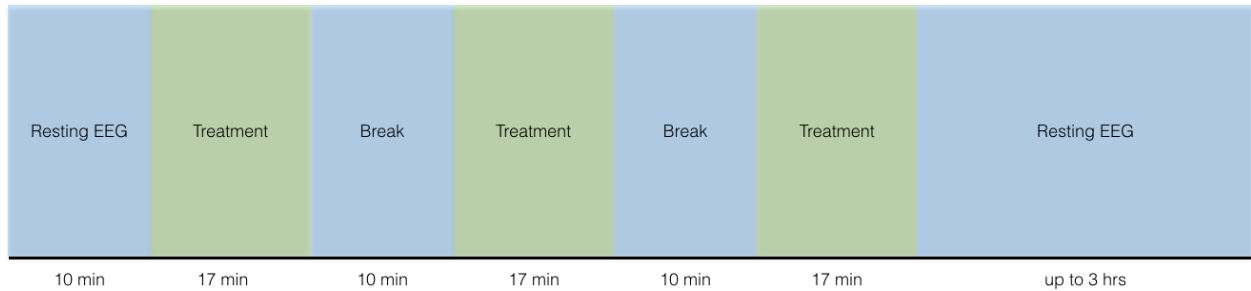


Figure 12. The protocol for interleaving rTMS treatment and dEEG assessment (recorded and evaluated during the breaks as well as the resting EEG intervals).

5606 • J. Neurosci., April 16, 2014 • 34(16):5603–5612

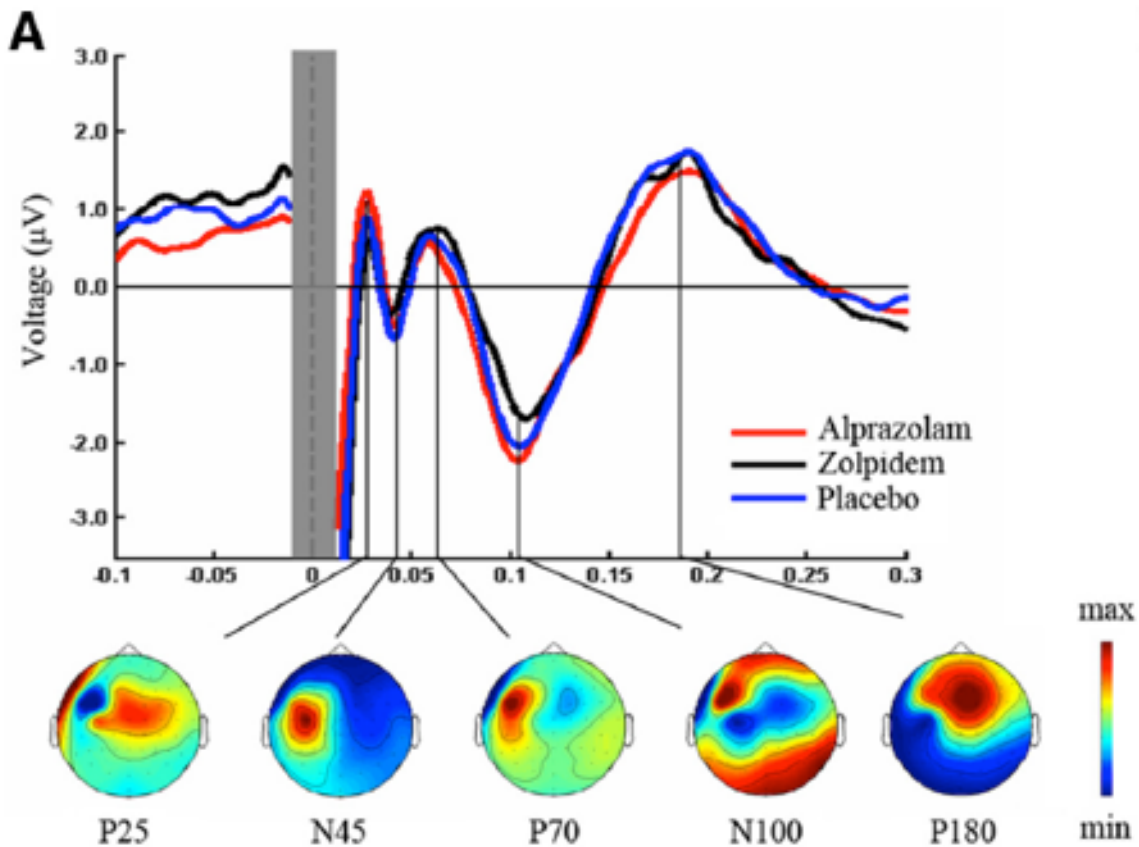


Figure 13. EEG response to TMS as affected by anti-epileptic medication and placebo.

Safety and Feasibility Clinical Trial Design

To achieve long lasting suppression of epileptiform activity, including seizures, the two most effective studies both applied slow rTMS with repeated treatment over successive sessions (Fregni et al., 2006; Sun et al., 2012). One of these (Sun, et al., 2012) was particularly effective, achieving significant seizure suppression (an average of 2 seizures per week versus 8 or 9 per week for the sham treated group) for up to ten weeks. These investigators applied blocks of slow rTMS separated by rest intervals.

In the proposed safety and feasibility trial, we will implement the within-session timing of the slow rTMS protocol of Sun et al., (2012), administering this protocol for five days for one week (rather than the two weeks of Sun, et al), given that our more limited objective for demonstrating feasibility is a statistically significant suppression of epileptic discharges. Each treatment block consists of 500 pulses, each monophasic, at a rate of 0.5 Hz (2 per second). With 500 pulses over 1000 seconds, each of the three treatment intervals is 17 min (**Figure 12**).

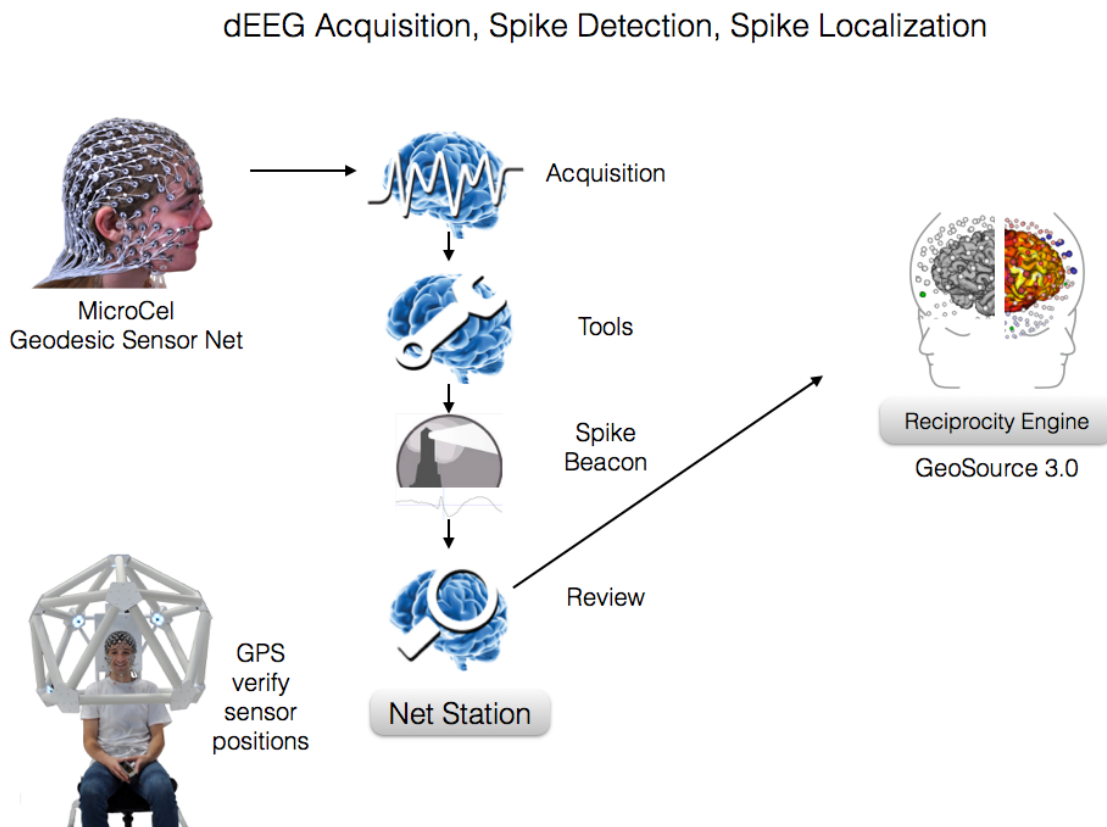


Figure 14. Overview of dEEG evaluation session, EEG review, spike detection, and spike localization.

During rTMS, we will continuously record the EEG. Later, off-line averaging will be performed for the first 60 stimuli (minutes 1-2) and the last 60 stimuli (minutes 16-17) of the 17 minute session. **Figure 13** from Premoli, Castellanos et al. (2014) shows the averaged evoked EEG waveform with rTMS. Premoli, et al., have shown that the N45 potential reflects GABAA receptor mediated interneuronal activity and the N100 potential GABAB receptor mediated potentials. Changes in N45 and N100 will provide a picture of functional inhibition in that region of brain during rTMS.

Once safety and feasibility have been determined (meeting endpoints of safety, comfort, and preliminary efficacy), the pivotal trial will then evaluate the full two weeks of daily (5 days per week) treatment against the sham rTMS control.

Overview of dEEG Acquisition, Spike Detection, and Spike Localization

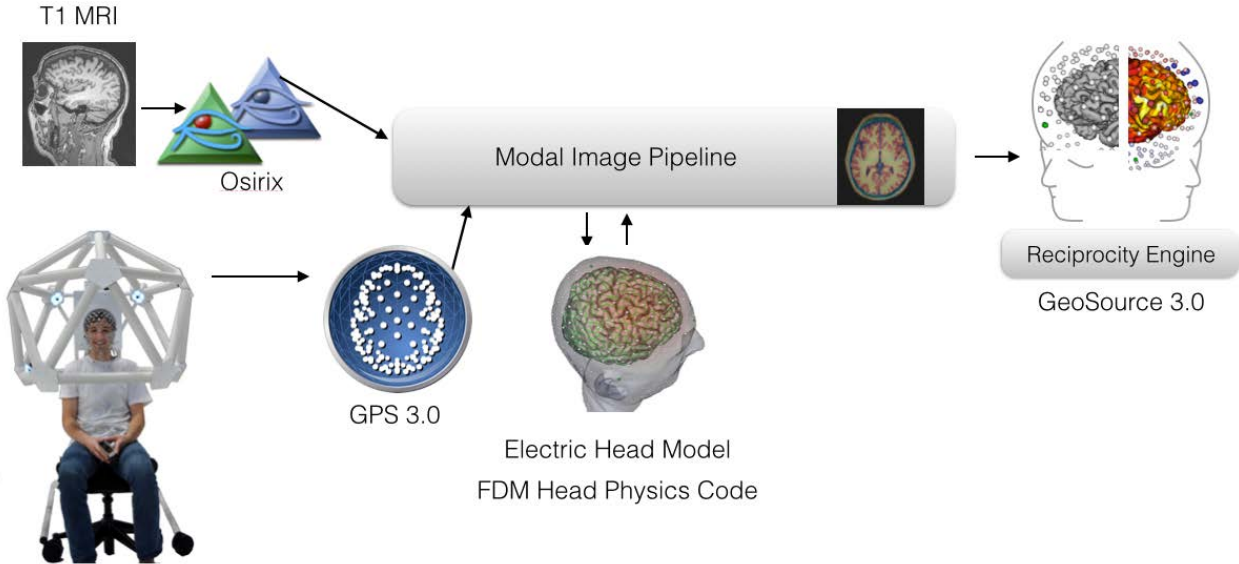
Figure 14 shows the assessment workflow that is conducted for each evaluation session. These evaluation sessions are typically 40 minutes to one hour and include the initial patient evaluation, the weekly dEEG evaluations during the baseline, the dEEG evaluation conducted during each of the 5 rTMS treatment sessions, and the monthly dEEG evaluation during the three-month follow-up. The MicroCel Geodesic Sensor Net is applied to collect 256 dEEG (about 10 min) and the positions of the sensors are digitized with the Geodesic Photogrammetry System (GPS). The positions from the first session are then registered with the patient's MRI to create the Electric Head Model (**Figure 15**). Subsequent Net applications are verified against the GPS photos from the first session and the positions adjusted so that the same Electric Head Model is accurate for all sessions.

To quantify and localize the patient's interictal epileptiform activity, the Net Station (5.2) software includes modules for dEEG Acquisition, analysis Tools (filtering, bad channel replacement, artifact detection and cleaning). During the project, we will introduce spike detection and counting with the Spike Beacon software (to be submitted). The epileptologist reviews the dEEG (and the Spike Beacon results) to assure that the spike detection (manual or automated) is accurate and representative for the patient's typical, dominant, spike focus. Localization of the spike onset is conducted with the GeoSource 2.0 software. However we plan to introduce the GeoSource 3.0 software as an amendment to the present protocol once all validation studies are completed and FDA clearance is obtained, using the Electric Head Model constructed from the patient's MRI with EGI's Modal Image Pipeline (**Figure 15**).

Overview of the Electric Head Model Construction

Constructing the Electric Head Model begins with the patient's T1-weighted MRI, typically acquired through a DICOM server, with the Osirix MD software (**Figure 15**). A plugin for Osirix provides export to the format for EGI's Modal Image Pipeline (MIP)

Electric Head Model Construction



rTMS Targeting and Treatment

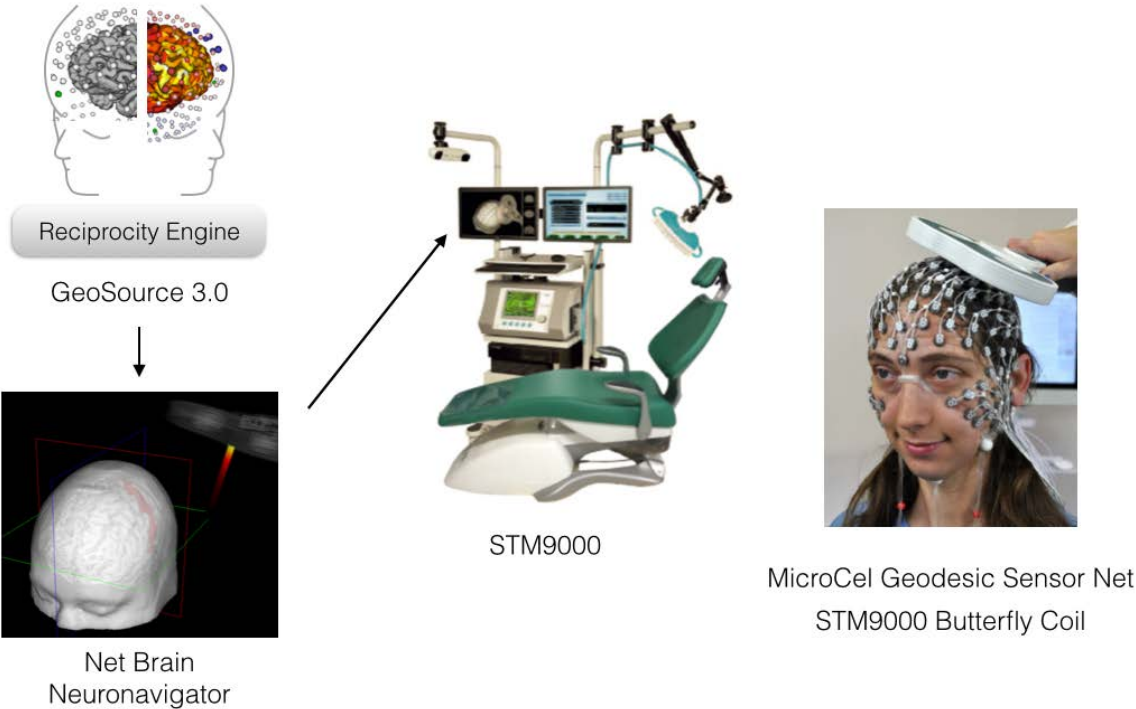


Figure 16. Overview of export of interictal focus localization to the Net Brain rTMS neuronavigator software, which then guides the rTMS targeting with the STM9000.

software. The processing in the Modal Image Pipeline (Li, Papademetris, & Tucker, in press-a) is summarized in **Figures 8 and 9**. The Reciprocity Engine is the visualization software for examining the anatomical correctness of the individual Electric Head Model, and for visualizing the source localization results with GeoSource 3.0 (**Figure 10**).

Overview of rTMS Targeting

Once the interictal focus is identified with GeoSource 2.0, the Talairach coordinates are then transferred to the rTMS targeting software, EB Neuro's Net Brain (**Figure 16**). There are two methods for placing the coil to achieve accurate targeting of the identified interictal focus (**Figure 16**). The cart for the STM9000 includes a mechanical arm that holds the butterfly coil in place. In addition the butterfly rTMS coil can be held manually. For both methods, the Net Brain Navigator software provides continuous feedback on the relative position of the coil energy (and thus induced current flow) with the patient's MRI model that is registered to the head position (that is tracked continuously by the Northern Digital camera system).

Clinical Trial Sites

At the present time, four clinical sites are planned (Eugene, Seattle, Palo Alto, Boston), depending on the availability of funding (such as with an application to the the NINDS CREATE Devices SBIR mechanism). An expert epileptologist will provide medical guidance at each site. Data analysis will be supervised by the Study Monitoring Committee, composed of the epileptologists and principal investigators from all sites, plus EGI's statistician Dr. Jasmine Song. Racial and gender composition will be as it appears in each sample.

Patient Recruitment

To determine safety and feasibility, 10 adult patients (22 and older, including males and females) are recruited who continue to have seizures after having achieved adequate dosage on each of two antiepileptic drugs. Patients are selected who have focal spikes (and other discharges of focal onset, including seizures) identified through Electrical Source Imaging (ESI) applied to a routine dense array EEG (dEEG) evaluation. The patients must have superficial focal spikes, close enough (~ 2 or 3 cm) to the head surface to be reachable by rTMS. Where possible, preference is given to patients with frequent spikes (estimated as > 30 per hour in the diagnostic EEG session), to allow adequate measurement of the spike frequency reduction endpoint. All patients agree to maintain their current antiepileptic drug dose throughout the study, including the one month baseline and the ten week follow-up period.

Inclusion Criteria

- (1) Failure of adequate seizure control with prior use of at least 2 anti-seizure drugs.
- (2) at least one clearly identified and localizable likely seizure onset focus, as defined by the discharges (typically epileptiform spikes) and as identified by dEEG assessment through one or more routine clinical dEEG evaluations. This focus must be 2 to 3 cm from the head surface (to be reachable by TMS). Where multiple spike foci are present and meet these criteria, then the focus with either clinically relevant symptoms or the most spikes (or both) will be chosen as the target for treatment.
- (3) two or more partial seizures, with or without secondary generalization, in the last month, but less than 10 seizures per day.
- (4) Anti-seizure drug regimen has remained unchanged for the month before study entry, and there is reasonable likelihood of stability for the duration of the study, with the exception of allowing short-term rescue medications, such as lorazepam.
- (5) a history of epilepsy for at least 2 years.
- (6) age of 22 years and older.

Exclusionary Criteria

- (1) If of childbearing potential, the patient must agree to use an effective method of birth control during the study and cease participation if pregnant.
- (2) Nursing mothers are excluded.
- (3) A history or condition of progressive brain disorders, serious systemic diseases, symptomatic cerebrovascular disease, cardiac disease, or alcohol abuse. Special conditions, for example, non-malignant brain tumors and vascular malformations, can be considered for entry on a case-by-case basis. Patients are not excluded on the basis of previous psychiatric hospitalizations or suicide attempts.
- (4) A history or condition of status epilepticus or psychogenic seizures.
- (5) Presence of a cardiac pacemaker, vagus nerve stimulator, or metal implantation in the body (other than the teeth) including neurostimulators, cochlear implants, and implanted medication pumps.
- (6) Previous surgery involving opening the skull.
- (7) Unable to express presence of pain or discomfort.

Escape Criteria

For individual patients, the study will be terminated for any of the following reasons:

- (1) Unacceptable discomfort or pain in response to the rTMS treatment.
- (2) A tonic-clonic seizure occurring during a stimulation session.
- (3) Emergence of a first-in-life tonic-clonic seizure at any time during the study.

- (4) Status epilepticus.
- (4) Doubling or more of the baseline seizure frequency.

The study will be halted if 3 subjects meet escape criteria (other than unacceptable pain or discomfort) and the FDA consulted to review the adverse events before the study is restarted. The Data and Safety Monitoring Board will be informed if one subject meets escape criteria (other than unacceptable pain or discomfort).

Baseline, Treatment, and Follow up Protocols

The length of the baseline evaluation period is adjusted to insure that sufficient seizures are captured for that patient to allow determination of the patient's typical seizure rate. This will allow confidence that any increase in the seizure rate during treatment is a safety concern. As recommended by our consultant, Dr. Robert Fisher of Stanford University Hospital, the baseline monitoring period will be 5 times the length of time between the patient's typical seizures. Thus a patient with one seizure per two weeks will have a baseline monitoring of 10 weeks. The minimum monitoring interval will be one month. At least two two-hour routine dEEG evaluations will be conducted in the baseline evaluation period, including the opportunity for sleep for patients who may have interictal events in sleep or drowsiness. The patient (and/or family) will maintain a seizure diary during the baseline, treatment, and 10 week follow-up intervals. The seizure diary will be reviewed by the study coordinator in a phone contact once per week.

After the baseline evaluation period, the two-hour dEEG-rTMS treatment session then targets the identified focal epileptogenic zone 5 days per week for one week. In each treatment session there are three 17 minute blocks of treatment, with 500 pulses each. To assure seizures are not worsened, the post treatment monitoring for safety is continued for 3 hours after the first treatment session.

Both evaluation and treatment sessions are conducted by personnel who are trained in the dEEG assessment and rTMS operation, including the ability to recognize epileptiform discharges in the dEEG signals. At least one person on the research staff at each session will be certified in first aid in the case that a seizure occurs. The epileptologist at each trial site will provide medical supervision, including recognition of possible adverse events and decision to terminate treatment.

The one week treatment period is followed by a weekly 90 minute follow up session on **months 1, 3, and 6** of the follow up period. Each follow up session includes 30 minutes of dEEG evaluation, a review of the seizure diary, cognitive function testing with the California Verbal Learning Test, the Wisconsin Card Sorting Test, and the Quality of Life in Epilepsy report. If the patient has interictal events in sleep or drowsiness,

the 30 minute dEEG evaluation in follow up will be extended to up to two hours to allow sleep (both in the baseline and in the post-treatment follow-up sessions).

Primary Endpoint

The primary endpoint is the frequency of epileptiform discharges (spike rate expressed per hour) for the six evaluation sessions over the 10 weeks following treatment, in comparison to the mean frequency for the pre-treatment evaluation sessions (at least 2 baseline sessions over one month). Spike detection will be conducted with the Spike Beacon software, including methods of topographic clustering as well as template matching. The spike count will be expressed as spikes per hour, with a minimum of 20 minutes of quality EEG recording required for each follow up session. Once the parameters for automated detection are set for the baseline evaluation, these will be applied for each treatment and follow-up assessment. The epileptologist at each site will review the spike detection and quantification to assure the measures are clinically relevant.

Secondary Endpoints

A secondary endpoint is the weekly frequency of seizures, as recorded in the seizure diary, during the one week of treatment and each of the ten weeks of follow up. This will be the primary endpoint for the pivotal trial. This frequency will be contrasted with the seizure frequency (expressed as a weekly rate) for the pretreatment baseline and statistical tests will examine the statistical contrast with baseline for each post-treatment evaluation plus the trends over time.

In case there is a change in a patient's seizure medication during the treatment or follow up, the analysis for this patient will be considered to have no change in seizure frequency from baseline.

Additional secondary endpoints will be any improvement of cognitive function testing beyond the practice effect (estimated from norms), and any improvement in quality of life ratings.

Safety Endpoint

The safety endpoint will report all adverse events from baseline through the 10 week follow-up for each patient in the study.

Study Success

The statistical endpoint for demonstrating treatment feasibility is a significant suppression of spike frequency at the $p < .10$ level or better for at least 4 of the evaluation sessions in the 10-week followup, in contrast to baseline for this group of 10 sub-

jects. The missing data during one or more of the follow-up evaluations will be interpolated by the adjacent sessions data for the statistics, including trend analysis.

Statistical analyses of the seizure suppression will be examined to provide suggestions of effect size for the power analyses for the pivotal trial.

Pooling Data Across Sites

Although a separate statistical analysis will be conducted at each site, pooled analysis across the several sites will be assembled unless the individual site analyses provide indication that the populations or treatment effects are substantially different for a given site. Each site is supervised by a different principal investigator/epileptologist and is regulated by a separate Institutional Review Board or ethics board, such that decision making is unique to that site. Local decisions are attentive and optimally responsive to any safety issues. Nonetheless, the investigators have agreed to uniformity of all factors of patient selection, localization of foci, and treatment protocols, such that there are no known contraindications at this point to data pooling across sites.

Power Analysis and Missing Data Analysis

The present Safety and Feasibility Study is focused on spike suppression. We have no preliminary data for estimate of the effect size. Nonetheless, we expect adequate power for statistical analysis assuming we are able to recruit patients with frequent spikes.

Study Procedures

Informed Consent

Both the recruitment information and the informed consent document explain several aspects of the study:

- Only patients whose dEEG exam confirms that their spikes (and seizures when recorded) have at least one focal onset are eligible for the slow rTMS experimental treatment trial.
- rTMS (repetitive Transcranial Magnetic Stimulation) is a method of applying magnetic fields through the head in order to induce electrical currents in the cortex of the brain. The goal of these currents, applied at a slow rate (one pulse every two seconds) is to achieve a lasting decrease in the neuronal activity of the epileptic (seizure-causing) zone of cortex. The experimental treatment protocols have been designed on the basis of previous scientific studies, including successful suppression of epileptic seizures with TMS (in the Fregni, et al., 2006 and Sun, et al., 2012 trials).

- There is a risk that the treatment will cause seizures. However, the slow pulsed rTMS protocol has been applied in several studies of epilepsy, and there is no evidence that it caused seizures, or that it made seizures worse or more frequent. Nonetheless, there is always a small risk of causing seizures, and medical procedures are in place both to monitor for seizures (with the dEEG recording in each session) and to provide first aid if a seizure occurs.

- The primary feeling of the rTMS pulse is a brief tingling sensation. There is the risk of scalp itching and/or scalp pain. Each patient should understand that they should speak up if there is any discomfort, that the technician is trained to carefully monitor their comfort level, and that they can quit the treatment at any time by simply saying they want to quit. If there is any emergency, the patient is shown how to simply pull the Geodesic Sensor Net off the head.

Localizing Epileptiform Discharges (EDs)

The cortical target for rTMS treatment is the presumed seizure onset zone, which is estimated by localizing the source of epileptiform discharges (spikes) with the dEEG recording. The EDs are recorded during the baseline in three routine (typically half hour or 40 minute) dEEG evaluations. A nap or sleep EEG may also be collected if seizures typically occur during sleep or sleep transition. Only patients with a single clearly identifiable site of epileptiform discharge (ED) onset will be included. EDs will typically involve spikes or sharp waves, although more complex seizure-like EDs and clinical seizures recorded during the routine dEEG will be included. In order to be able to target the ED with the rTMS treatment, the ED must be within 2 or 3 cm of the head surface.

bEIT Validation of the Head Model

The effectiveness of treatment depends on the accuracy of the localization of the epileptic discharges. During at least one of the baseline dEEG sessions, the bounded Electrical Impedance Tomography (bEIT) procedure (**Figure 11**) is used to verify the electric head model developed for that subject. If the mean prediction of the recovered bEIT signal across recording electrodes is not within 10% for 90% of the electrodes, the model is judged to be flawed and the treatment is postponed until an accurate targeting model is created.

Determination of rTMS Intensity

The resting motor threshold (rMT) will be recorded from the left motor cortex, with the motor evoked potential (MEP) recorded from the contralateral abductor pollicis brevis (APB) muscle with the MEP Amplifier of the STM9000. The rMT is defined as the minimum stimulus intensity that evokes a MEP above 50 μ V in the contralateral

APB muscle at least five out of 10 consecutive stimulations. The rTMS treatment intensity will be set to 90% of the patient's rMT for that session.

The rTMS coil will be positioned over the interictal focus, as determined by the GeoSource 3.0 software and translated to the Net Brain neuronavigator in relation to the patient's MRI anatomy. The consistency of coil placement during each treatment session is assured by auditory feedback from the Net Brain neuronavigator software if the coil "hot spot" is allowed to drift off of the designated focus target.

Review of the EEG for Safety and for Spike Counts

The dEEG is reviewed during each treatment session by the dEEG technician, who is trained on the typical epileptiform events shown by that patient. The dEEG is then reviewed after each treatment and follow up session by a trained electroencephalographer. To supplement the manual spike counting, spikes are counted with an automated spike detection and clustering algorithm (EGI's Spike Beacon software). If there is an apparent change in the spike (and possibly seizure) localization, as indicated by the spike topography clustering, Electrical Source Imaging is conducted with GeoSource to determine if there is a change in localization. If there is a change in localization, or a doubling of spike frequency over the baseline, or if there is non typical seizure activity, the results are conveyed to the epileptologist supervising the clinical trial to evaluate the risk for the patient's continuation of the trial. These safety criteria are in addition to the escape criteria stated above.

The experimental procedures for each patient session are summarized in Table 3.

Additional Monitoring of Risk

In the follow up sessions, routine dEEG evaluations, cognitive function assessments, and quality of life ratings are conducted at weeks 1, 2, 4, 6, 8, 10. At each follow up session, cognitive function is assessed with the California Verbal Learning Test, a widely used and easily administered test (www.pearsonclinical.com), the Wisconsin Card Sorting task, a well-known measure of executive function that is normed for repeat assessment, and quality of life is assessed with the Quality of Life In Epilepsy Questionnaire (http://www.rand.org/health/surveys_tools/qolie.html).

Overview of Study Protocol

Table 3 presents an overview of the treatment protocol. An exception is that the dEEG will be monitored for seizures for 3 hours after the first treatment session.

Session	Procedure
Pre-Treatment Evaluation	<p>At least two dEEG evaluations in the pre-treatment baseline (which is at least one month long).</p> <ul style="list-style-type: none"> • artifact free dEEG recording of at least 20 minutes during each evaluation to capture epileptiform discharges. • Review of seizure diary. • MRI to build the individual electric head model. • California Verbal Learning Test & Wisconsin Card Sorting Test • Quality of Life Questionnaire • bEIT scan to verify electrical head model.
Each (of 5) Treatment Sessions	<ul style="list-style-type: none"> • Application of the Geodesic Sensor Net. • Geodesic Photogrammetry System (GPS) to localize sensors. • 10 minutes resting dEEG. • rTMS treatment, 3 sets of 500 pulses (dEEG during 600s intervals between sets). • 30 minutes resting dEEG.
Follow up sessions, months 1, 3, and 6.	<ul style="list-style-type: none"> • Review of seizure diary. • Application of the Geodesic Sensor Net. • Geodesic Photogrammetry System to localize sensors. • 30 minutes resting dEEG. • California Verbal Learning Test & Wisconsin Card Sorting Test • Quality of Life Questionnaire

Table 3. Summary of treatments and assessments.

Bibliography

- Bae, E. H., Schrader, L. M., Machii, K., Alonso-Alonso, M., Riviello, J. J., Jr., Pascual-Leone, A., & Rotenberg, A. (2007). Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. *Epilepsy Behav*, 10(4), 521-528. doi:10.1016/j.yebeh.2007.03.004
- Bae, E. H., Theodore, W. H., Fregni, F., Cantello, R., Pascual-Leone, A., & Rotenberg, A. (2011). An estimate of placebo effect of repetitive transcranial magnetic stimulation in epilepsy. *Epilepsy Behav*, 20(2), 355-359. doi:10.1016/j.yebeh.2010.12.005
- Bergey, G. K. (2013). Neurostimulation in the treatment of epilepsy. *Exp Neurol*, 244, 87-95. doi:10.1016/j.expneurol.2013.04.004
- Brodbeck, V., Spinelli, L., Lascano, A. M., Pollo, C., Schaller, K., Vargas, M. I., . . . Seeck, M. (2010). Electrical source imaging for presurgical focus localization in epilepsy patients with normal MRI. *Epilepsia*, 51(4), 583-591. doi:EPI2521 [pii] 10.1111/j.1528-1167.2010.02521.x
- Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., . . . Fregni, F. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul*, 5(3), 175-195. doi:10.1016/j.brs.2011.03.002
- Cantello, R., Rossi, S., Varrasi, C., Ulivelli, M., Civardi, C., Bartalini, S., . . . Rossini, P. M. (2007). Slow repetitive TMS for drug-resistant epilepsy: clinical and EEG findings of a placebo-controlled trial. *Epilepsia*, 48(2), 366-374. doi:10.1111/j.1528-1167.2006.00938.x
- Ebus, S., Arends, J., Hendriksen, J., van der Horst, E., de la Parra, N., Hendriksen, R., . . . Aldenkamp, B. (2012). Cognitive effects of interictal epileptiform discharges in children. *Eur J Paediatr Neurol*, 16(6), 697-706. doi:10.1016/j.ejpn.2012.05.010
- Engel, J., Jr. (2013). Progress in the field of epilepsy. *Curr Opin Neurol*, 26(2), 160-162. doi:10.1097/WCO.0b013e32835ee5a3
- Esler, B., Lyons, T., Turovets, S., & Tucker, D. (2010). Instrumentation for Low Frequency EIT Studies of the Human Head and its Validation in the Phantom Experiments. *J. Phys., Conf. Ser.* 224 012007.

- Fregni, F., Liebetanz, D., Monte-Silva, K. K., Oliveira, M. B., Santos, A. A., Nitsche, M. A., . . . Guedes, R. C. (2007). Effects of transcranial direct current stimulation coupled with repetitive electrical stimulation on cortical spreading depression. *Exp Neurol*, 204(1), 462-466. doi:S0014-4886(06)00557-7 [pii] 10.1016/j.expneurol.2006.09.019
- Fregni, F., Otachi, P. T., Do Valle, A., Boggio, P. S., Thut, G., Rigonatti, S. P., . . . Valente, K. D. (2006). A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. *Ann Neurol*, 60(4), 447-455. doi:10.1002/ana.20950
- Gotman, J., & Koffler, D. J. (1989). Interictal spiking increases after seizures but does not after decrease in medication. *Electroencephalogr Clin Neurophysiol*, 72(1), 7-15. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/2464478>
- Holmes, M., Tucker, D., Quiring, J., Hakimian, S., Miller, J., & Ojemann, J. (2010). Comparing Noninvasive Dense Array and Intracranial Electroencephalography for Localization of Seizures. *Neurosurgery*, 66(2), 354.
- Holmes, M. D., Brown, M., Tucker, D. M., Saneto, R. P., Miller, K. J., Wig, G. S., & Ojemann, J. G. (2008). Localization of extratemporal seizure with noninvasive dense-array EEG. *Journal of Pediatric Neurosurgery*, 44, 474-479.
- Koo, B. (2001). EEG changes with vagus nerve stimulation. *J Clin Neurophysiol*, 18(5), 434-441. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11709649>
- Krendl, R., Lurger, S., & Baumgartner, C. (2008). Absolute spike frequency predicts surgical outcome in TLE with unilateral hippocampal atrophy. *Neurology*, 71(6), 413-418. doi:10.1212/01.wnl.0000310775.87331.90
- Kuba, R., Nesvadba, D., Brazdil, M., Oslejskova, H., Ryzi, M., & Rektor, I. (2010). Effect of chronic vagal nerve stimulation on interictal epileptiform discharges. *Seizure*, 19(6), 352-355. doi:10.1016/j.seizure.2010.05.009
- Labar, D., Dakov, P., Kobylarz, E., Nikolov, B., Schwartz, T. H., & Fisher, S. (2013). Effects of responsive electrical brain stimulation on intracranial electroencephalogram spikes. *Neuromodulation*, 16(4), 355-361; discussion 362. doi:10.1111/ner.12039
- Lange, H. H., Lieb, J. P., Engel, J., Jr., & Crandall, P. H. (1983). Temporo-spatial patterns of pre-ictal spike activity in human temporal lobe epilepsy. *Electroencephalogr Clin Neurophysiol*, 56(6), 543-555. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/6197273>

- Li, K., Malony, A. D., & Tucker, D. M. (2006). A multiscale morphological approach to topology correction of cortical surfaces. Paper presented at the Proceedings of the Third International Workshop on Medical Imaging and Augmented Reality - MIAR, Shanghai, China.
- Li, K., Papademetris, X., & Tucker, D. M. (in press-a). BrainK for Structural Image Processing: Creating Electrical Models of the Human Head. *Computational Intelligence and Neuroscience*.
- Li, K., Papademetris, X., & Tucker, D. M. (in press-b). BrainK for Structural Image Processing: Creating Electrical Models of the Human Head.
- Liu, A., Pang, T., Herman, S., Pascual-Leone, A., & Rotenberg, A. (2013). Transcranial magnetic stimulation for refractory focal status epilepticus in the intensive care unit. *Seizure*, 22(10), 893-896. doi:10.1016/j.seizure.2013.06.014
- Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimul*, 6(3), 424-432. doi:10.1016/j.brs.2012.04.011
- Nitsche, M. A., & Paulus, W. (2009). Noninvasive brain stimulation protocols in the treatment of epilepsy: current state and perspectives. *Neurotherapeutics*, 6(2), 244-250. doi:10.1016/j.nurt.2009.01.003
- Olejniczak, P. W., Fisch, B. J., Carey, M., Butterbaugh, G., Happel, L., & Tardo, C. (2001). The effect of vagus nerve stimulation on epileptiform activity recorded from hippocampal depth electrodes. *Epilepsia*, 42(3), 423-429. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11442163>
- Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*, 120(12), 2008-2039. doi:10.1016/j.clinph.2009.08.016
- Rotenberg, A., Bae, E. H., Muller, P. A., Riviello, J. J., Jr., Bourgeois, B. F., Blum, A. S., & Pascual-Leone, A. (2009). In-session seizures during low-frequency repetitive transcranial magnetic stimulation in patients with epilepsy. *Epilepsy Behav*, 16(2), 353-355. doi:10.1016/j.yebeh.2009.08.010
- Rotenberg, A., Bae, E. H., Takeoka, M., Tormos, J. M., Schachter, S. C., & Pascual-Leone, A. (2009). Repetitive transcranial magnetic stimulation in the treatment of epilep-

- sia partialis continua. *Epilepsy Behav*, 14(1), 253-257. doi:10.1016/j.yebeh.2008.09.007
- Rudzinski, L. A., & Meador, K. J. (2013). Epilepsy and neuropsychological comorbidities. *Continuum (Minneapolis, Minn)*, 19(3 Epilepsy), 682-696. doi:10.1212/01.CON.0000431382.06438.cd
- Russell, G. S., Eriksen, K. J., Poolman, P., Luu, P., & Tucker, D. M. (2005). Geodesic photogrammetry for localizing sensor positions in dense-array EEG. *Clin Neurophysiol*, 116(5), 1130-1140. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15826854
- Salman, A., Turovets, S., Malony, A., Poolman, P., Davey, C., Eriksen, J., & Tucker, D. (2006). Noninvasive conductivity extraction for high-resolution EEG source localization. *Advances in Clinical Neuroscience and Rehabilitation*, 26(1), 27-28.
- Sun, W., Mao, W., Meng, X., Wang, D., Qiao, L., Tao, W., . . . Wang, Y. (2012). Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: a controlled clinical study. *Epilepsia*, 53(10), 1782-1789. doi:10.1111/j.1528-1167.2012.03626.x
- Turovets, S., Salman, A., Malony, A., Poolman, P., Davey, C., & Tucker, D. (2006, 2007). Anatomically constrained conductivity estimation of the human head tissues in vivo: computational procedure and preliminary experiments. Paper presented at the IFMBE Proceedings, Seoul, Korea.
- VanHaerents, S., Herman, S. T., Pang, T., Pascual-Leone, A., & Shafi, M. M. (in press). Repetitive transcranial magnetic stimulation: A cost-effective and beneficial treatment option for refractory focal seizures. *Clinical Neurophysiology*.
- Velasco, F., Velasco, M., Marquez, I., & Velasco, G. (1993). Role of the centromedian thalamic nucleus in the genesis, propagation and arrest of epileptic activity. An electrophysiological study in man. *Acta Neurochir Suppl (Wien)*, 58, 201-204. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8109294>
- Velasco, F., Velasco, M., Velasco, A. L., Jimenez, F., Marquez, I., & Rise, M. (1995). Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long-term studies. *Epilepsia*, 36(1), 63-71. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8001511>
- Volkov, V., Zherdetsky, A., Turovets, S., & Malony, A. (2009). A 3D Vector-Additive Iterative Solver for the Anisotropic Inhomogeneous Poisson Equation in the Forward

EEG problem. Paper presented at the Proceedings of the International Conference on Computational Science 2009.

Vonck, K., Boon, P., Achten, E., De Reuck, J., & Caemaert, J. (2002). Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. *Ann Neurol*, 52(5), 556-565. doi:10.1002/ana.10323

Wagner, T. A., Zahn, M., Grodzinsky, A. J., & Pascual-Leone, A. (2004). Three-dimensional head model simulation of transcranial magnetic stimulation. *IEEE Trans Biomed Eng*, 51(9), 1586-1598. doi:10.1109/TBME.2004.827925

Yamazaki, M., Terrill, M., Fujimoto, A., Yamamoto, T., & Tucker, D. M. (2012). Integrating dense array EEG in the presurgical evaluation of temporal lobe epilepsy. *ISRN Neurol*, 2012, 924081. doi:10.5402/2012/924081

Yamazaki, M., Tucker, D. M., Fujimoto, A., Yamazoe, T., Okanishi, T., Yokota, T., . . . Yamamoto, T. (2012). Comparison of dense array EEG with simultaneous intracranial EEG for interictal spike detection and localization. *Epilepsy Res*, 98(2-3), 166-173. doi:10.1016/j.eplepsyres.2011.09.007

Yamazaki, M., Tucker, D. M., Terrill, M., Fujimoto, A., & Yamamoto, T. (2013). Dense array EEG source estimation in neocortical epilepsy. *Front Neurol*, 4, 42. doi:10.3389/fneur.2013.00042