G150023/S003/A003
Supplement Request for Amending the IDE for EGI's Clinical Feasibility Trial of the Geodesic Transcranial Electrical Neuromodulation (GTEN 100) for Suppressing Epileptic Discharges

March 2016 *Electrical Geodesics, Inc.*

Overview

In this supplement (S003/A003), we corrected the text of the original IDE (an obsolete version was used in S003/A002). We request the following modifications to the IDE:

- Remove references to the "blocked sustained tDCS" protocol.
- Add a "probe treatment evaluation" protocol.
- Propose that GTEN treatment may be applied during sleep if the patient's spikes were recorded during sleep.
- Propose to extend the inclusion to patients with temporal lobe as well as neocortical foci for their interictal discharges.

Changes Requested	Reason for Change	Located on Page:
Drop reference to Blocked Sustained tDCS Protocol	Only the Pulsed GTEN Protocol will be used	Multiple pages, marked in red.
Specify 2 US and 1 China sites	No funding for other US sites	28
Describe Probe Treatment and Evaluation	Pilot Treatment for Brief Safety and Feasibility Test	30
Propose GTEN treatment during sleep if possible	Many patients show most spikes during sleep during the evaluation sessions	33, 34
Propose including patients with primary temporal lobe foci	Most patients show medial temporal as well as neocortical foci	31, 35
Reformat the Informed Consent Document for the UW IRB Format, plus include the probe test	The UW IRB requires its own Consent Form; plus the probe test was added	37, 37

Overview to Original IDE Request (at the end of Q140561):

[EGI requests an Investigational Device Exemption (IDE) for the GTEN 100, following FDA's guidance that this device presents significant risk when used to suppress spikes and seizures in adults and adolescents with epilepsy. We have now revised our analysis of risk, and the mitigation of that risk, in this proposal for a clinical feasibility trial. The purpose of this trial is to determine safety and preliminary evidence of efficacy of the GTEN 100 for temporary suppression of epileptic discharges (spikes). If the clinical feasibility trial proves successful, we would then propose a pivotal trial, to evaluate suppression of seizures, in a future presubmission request.

In this revision, we retain the key material from the previous presubmission supplement, and focus this revision on the restatement of risk and the mitigation of that risk, following the feedback in the FDA document "Q140561-S001 Comments to Sponsor" and the FDA-EGI phone conference of January 15, 2015, as summarized in EGI's notes.]

Table of Contents

GTEN 100 Device Description

The Geodesic Transcranial Electrical Neuromodulation (GTEN 100) device is a hardware and software modification of the Geodesic EEG System 400 Series (GES 400). The hardware modification changes the current injection from 100 μA total for the GES 400 (for impedance testing and the bounded Electrical Impedance Tomography or bEIT scan) to up to 2 mA total (and limited to 200 μA per electrode). Note that these levels are higher than the 1 mA total and 100 μA per electrode in the first Q140561 Pre-Sub request. This increase in current will improve the therapeutic dose delivered to the brain, and this does remains within the safety guidelines for tDCS (2.5 mA total dose) recommended by a recent international panel of experts (F Fregni et al., in press). In addition, we have succeeded in minimizing scalp pain by adding lidocaine to the electrolyte, such that the 200 μA dose is comfortable with the 1 cm2 electrodes of the GTEN 100.

The guidelines for estimating both the safety and the efficacy of neuromodulation with the intracranial current levels achieved by the GTEN 100 comes from the literature on transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), as reviewed below.

The software upgrade of the GES 400 for the GTEN 100 is a new GTEN Control Interface window in the Net Station 5.0 software to allow the physician (or supervised technician) to select the electrodes and waveform for current delivery for the neuromodulation protocol. There is also a GTEN Planning Module that allows computation of the estimated dose in relation to head tissue conductivity and cortical surface reconstructed from the patient's MRI and bounded Electrical Impedance Tomography (bEIT) recordings.

Double Sentinel Circuit for Fault Protection

The GTEN 100 design has been modified to add a second Sentinel Circuit, in series with the first one, to assure that total current will be limited to 2 mA (and thus 2 A/m2 as in the FDA "Q140561-S001 Comments to Sponsor". A triple fault (circuit fault and two Sentinel Circuit faults) is still possible, of course, but the risk is now very small.

Impedance Conditioning and Lidocaine Iontophoresis

In preparation for the neuromodulation session, an accessory for the the GTEN 100 is a new protocol for decreasing electrode-to-skin impedance (the Dermal Iontophoretic Bond or DIB protocol) by applying DC currents in order to draw ions from the electrolyte across the outer skin layer (stratum corneum) with iontophoresis. Scalp contact impedances are typically decreased from an initial ~ 100K Ohms to 20 to 40K Ohms after a few minutes of treatment.

This iontophoretic impedance conditioning protocol now allows the use of lidocaine with the gel electrolyte, such that the iontophoretic transfer results in topical anesthesia around the anode electrode sites, allowing higher current levels (200 μA) to be applied painlessly. The iontophoretic current delivery includes cathodal (sink) electrodes adjacent to the anode

(lidocaine delivery) electrodes, so that there is minimal or no current delivery to the brain during iontophoretic delivery. Once the topical anesthesia is achieved, the anodal current can then be discontinued for those electrodes that will be cathodes (sinks) in the treatment protocol, while the topical anesthesia remains.

Computational Modeling of Head Tissues for Treatment Planning

The GTEN 100 includes an accessory software module, the GTEN Planning Module, that uses computational modeling of a finite difference model of electrical volume conduction through head tissues to target specific brain regions. The GTEN Planning Module includes the capacity for verification with bounded Electrical Impedance Tomography (bEIT), in which small (10 μA) currents are injected at a specific frequency to test the planned GTEN targeting; if potentials measured at that frequency at multiple non-injecting electrodes are consistent with the model prediction, then the current flow through the head must also be consistent with the prediction, and the GTEN plan is acceptable.

The GTEN 100 can be used with an atlas model of the head (similar age and sex as the patient). The atlas model has been validated for Electrical Source Imaging (ESI) in epilepsy diagnosis with EGI's FDA cleared GeoSource 2.0 software. In addition, the GTEN 100 can also be used with an individual electrical head model for the patient, which can be constructed from the patient's MRI (and the patient's CT or an atlas CT to characterize the skull bone density). The patient specific head model, and the warping of the atlas brain conductivity model to the patient's head shape (defined by photogrammetric localization of the 256 sensors and fiducial points) is constructed with the Modal Image Engine software and prepared for Electrical Source Imaging (ESI) with GeoSource 3.0 software. GeoSource 3.0 will be submitted for 510k clearance later in 2015 with GeoSource 2.0 as the predicate device and the Modal Image Engine as accessory software.

Intended Use

The intended use of the GTEN 100 is the application of electrical current to the brain for the purpose of manipulating the function and plasticity of the brain.

Indications for Use

The Geodesic Transcranial Electrical Neuromodulation 100 system is indicated to temporarily reduce the frequency of epileptic spikes in adults and adolescents over 12 years of age with partial onset seizures that continue to occur despite at least two trials of antiepileptic drugs at therapeutic levels.

Previous Submissions

Table 1 summarizes the EGI products relevant to both the Geodesic EEG System (GES) 400 and the GTEN 100.

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.

Product Name	Clearance Status	Description; Any Changes for GTEN
GES 400	K131882	Hardware is identical except for current generation, which is upgraded from 100 μA to 2 mA.
Net Station 5.0	Letter to file	The GTEN Interface Control allows selection of current source/sink electrodes and time course of current (DC, AC, pulse).
Geodesic Sensor Nets	K131882	No change.
Geodesic Photogrammetry System	K043309	No change.
Dermal Iontophoretic Bond	Not cleared; a component of the present product	Protocol for Direct Current delivery to decrease impedance of electrode-skin contact with iontophoresis, and to apply topical lidocaine.
GeoSource 2.0	K092844	Electrical Source Imaging (ESI) with atlas model, no change.
GeoSource 3.0	Not cleared; to be submitted separately.	ESI with individual head model created by MIE.
Model Image Engine (MIE)	Not cleared; to be submitted separately.	Software framework for image processing.
MIE GTEN Planning Module	Not cleared; a component of the present product	Plans source/sink electrode pattern to deliver current to specific brain target.

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

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 μA) to test contact impedance of the electrodes with the scalp.

The GTEN 100 uses the same hardware as the GES 400, the Geodesic Sensor Nets, and Net Station, with the exception that the current injection capability of the GES 400 hardware has been upgraded. It now allows 2 mA total. In addition, an independent hardware limit to that current has been added through an integral safety circuit monitoring the injected current (the *Sentinel Circuit*®). To assure patient comfort, the impedances of all current delivery electrodes (anode or cathode) are monitored such that the target current level per electrode is maintained at about 200 μA (and the total is never more than 2 mA total). In addition, the GTEN 100 uses two other cleared accessories: the Geodesic Photogrammetry System (K043309) and GeoSource 2.0 (K092844), which will soon be upgraded to GeoSource 3.0.

Rationale for the GTEN 100 for Suppressing Seizures

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 limited, roughly on a par with that of antiepileptic drugs (Bergey, 2013).

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 medial temporal lobe structures, potentially worsening epilepsy. If we can successfully control seizures in adults and adolescents with GTEN therapy, then in the future we will extend this noninvasive therapy to control seizures in children, and greatly improve the quality of life for millions of people. Even if seizures are only partially suppressed, the reduction may be clinically significant. For the present trial, we defined the clinically significant suppression as a 50% reduction. For those whose seizures continue chronically after two trials with antiepileptic drugs, it seems clear that a 50% reduction, even if temporary (over a few months) would be a meaningful improvement in quality of life.

In addition, there is considerable evidence now that cognitive development is impaired in children with frequent spikes, even if seizures are controlled (Ebus et al., 2012; Rudzinski &

Meador, 2013). It seems likely that brain function will be similarly impaired by spikes in adolescents and adults.

In the proposed safety and feasibility study, we now set the primary endpoint for demonstrating feasibility as a statistically significant suppression of epileptic spikes.

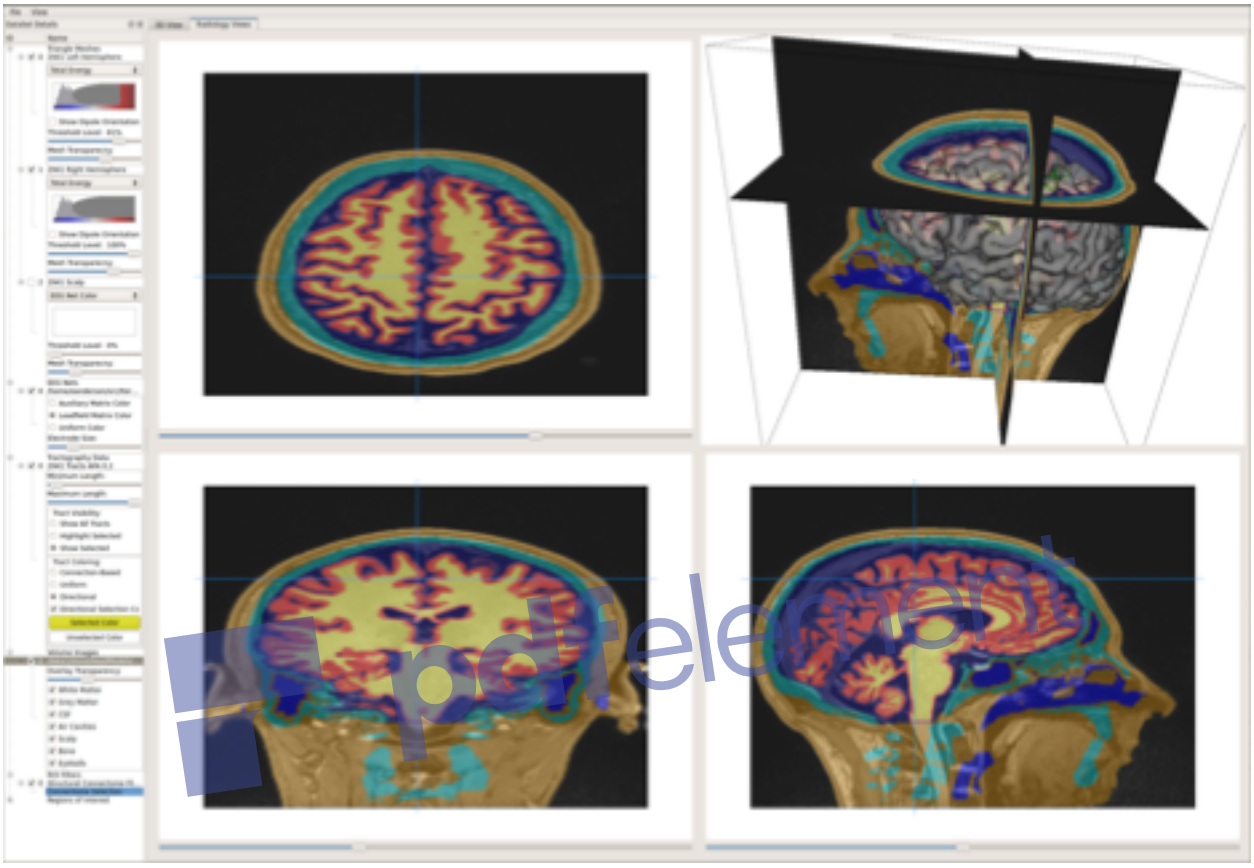

Figure 1. EGI's Modal Image Engine software provides segmentation of each major head tissue type, to allow a high resolution electrical (finite difference) model that simulates how electrical currents, both natural and impressed, propagate through the head. The extraction of the cortical surface (upper right) is important for specifying the location and orientation of cortical sources in Electrical Source Imaging (ESI). The cortical surface geometry is also needed for modeling the modulation current that is normal to the cortex and presumably therefore effective in altering the activity of neurons in the laminar cortex.

GTEN 100 Treatment Planning

A software accessory for the GTEN 100 is the GTEN Planning Module, a component of EGI's Modal Image Engine software. The Modal Image Engine is a set of software modules that allow processing of MRI, CT, images and sensor positions in preparation for Electrical Source Imaging ESI with the individual's MRI data, as well as for GTEN 100 treatment. Key features of the Modal Image Engine are automated tissue segmentation (scalp, skull, cerebrospinal fluid, gray and white matter) and cortical surface extraction (**Figure 1**). The Modal Image Engine (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 later in 2015. 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. The atlas models have been validated by comparison with intracranial recordings and by surgical outcome, as described below.

Geodesic Transcranial Electrical Neuromodulation in Epilepsy

The GTEN 100 and the GTEN Planning Module software have been developed under EGI's Quality System, with design controls and hazard review documented at each stage. Testing of the GTEN 100 with normal subjects has been conducted under human subjects review by EGI's Institutional Review Board, which has Multiple Project Assurance authority recognized by the US National Institute of Health.

The GTEN 100 is similar to conventional transcranial direct or alternating current stimulation (tDCS, tACS) systems that are now widely used in research, with three major differences. The first difference is using 256 electrodes to deliver current rather than

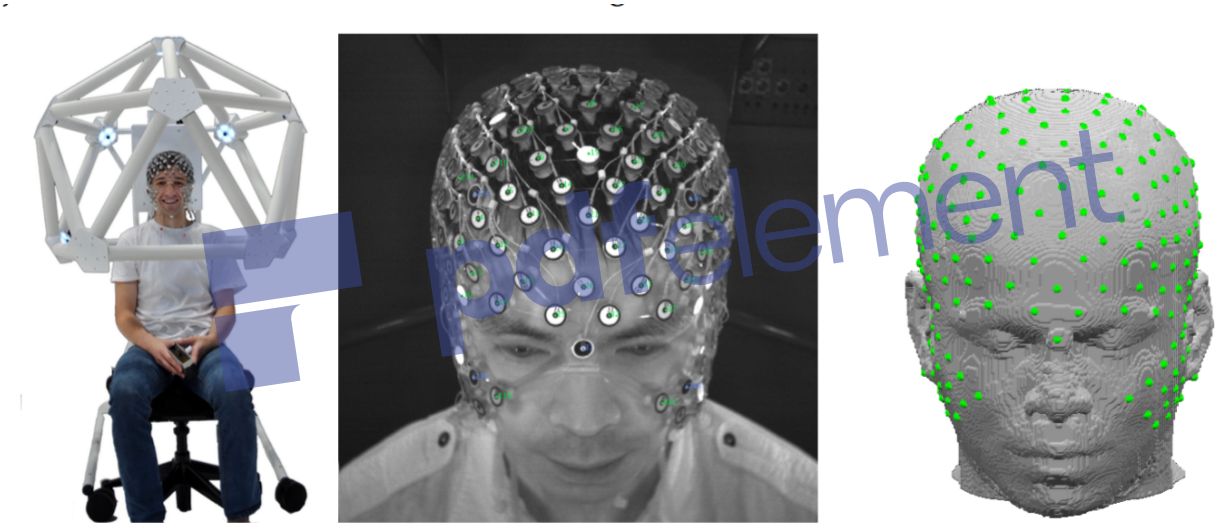

Figure 2. Left: With 11 video cameras, the exact 3D sensor positions are captured with EGI's Geodesic Photogrammetry System (GPS). **Middle:** the infrared images allow computer vision detection of all sensors in the Geodesic Sensor Net. **Right:** The 3D sensor coordinates are then registered with the individual's MRI or an atlas to allow precise planning of current delivery in relation to the person's head tissues.

2 large sponge electrodes. The second difference is that the same 256 electrodes that deliver current are also used in the localization of the epileptiform EEG (primarily spikes) generated by the epileptogenic zone. The third difference is that GTEN current delivery is computed with an accurate physics simulation of the tissue conductivity of the person's head.

Whereas tDCS and tACS typically use large sponge electrodes, GTEN achieves improved targeting of cerebral currents through flexible selection of patterns of source and sink electrodes with the 256-electrode Geodesic Sensor Net (**Figure 2**). The geodesic partitioning of the head

surface with the Geodesic Sensor Net provides optimal electrode coverage of the head, including the face and neck. Whole head coverage is required for both effective measurement and effective targeting, particularly for basal brain surfaces. Exact sensor positions are registered with the computational electrical head model (either the patient's MRI or an MRI atlas) with the Geodesic Photogrammetry System (**Figure 2)**. The neuromodulation (source-sink electrode) pattern is designed to target the epileptogenic zone through computational modeling with a high resolution electrical volume conduction simulation of the person's head tissues (with the GTEN Planning Module). The Modal Image Engine software (**Figure 1**) segments the tissues of the head, allowing estimation of each tissue's conductivity with bounded Electrical Impedance Tomography (bEIT; described below). In addition, cortical surface extraction (**Figure 1 upper right**) followed by dipole tessellation (for example, 1 cm sq patches) allows estimation of both the electrically active cortex in Electrical Source Imaging (ESI) and the cortical target for GTEN manipulation of cortical activity.

Coping with Tissue Abnormalities

We have had considerable experience in modeling the cortex and head tissues of patients with epilepsy, including those with malformations of cortical development (MCD), which are rather subtle anomalies, as well as those with cortical resections, which are typically large anomalies. The image segmentation and electrical conductivity modeling works well, with careful review of the results, in both cases. There are indeed abnormal anatomical conditions, such as the extensive demyelination of advanced cases of progressive multifocal leukoencephalopathy (PML), where we have found that our tissue segmentation (gray-white separation) and cortical surface reconstruction break down. Nonetheless, we are confident that the head modeling (and thus GTEN targeting) workflow will be robust for the great majority of patients with epilepsy in the proposed trial. Patients with previous resections and thus skull defects will be excluded. We will carefully evaluate any abnormal cerebral anatomy that may be inconsistent with our assumptions about head tissue impedance. The bEIT scan, described below, provides an independent in vivo test of the head conductivity model developed for each patient.

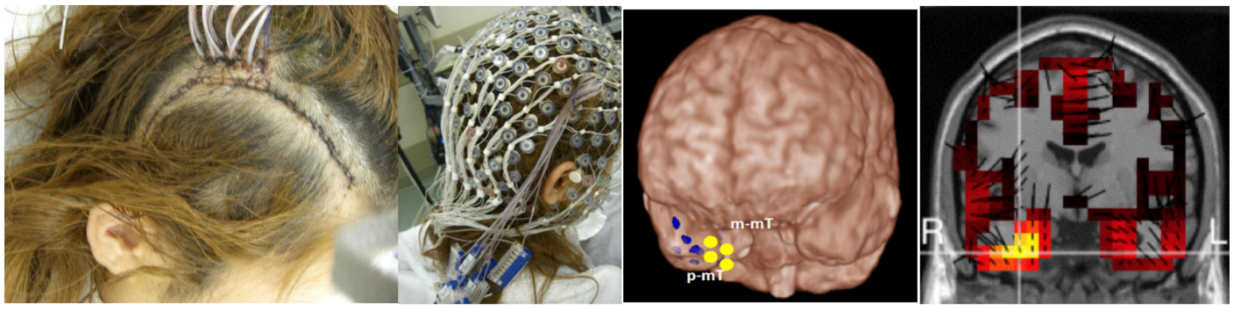

Figure 3. Intracranial recordings in epilepsy have provided independent validation of the localization accuracy of ESI with 256 dEEG. After the wound of the intracranial placement heals (left), the Geodesic Sensor Net is applied, and simultaneous intracranial recordings and 256 dEEG recordings confirm that the intracranial localization of epileptic spikes (yellow dots) are in the right anterior temporal pole. This localization was predicted by the preoperative (noninvasive) dEEG source localization with EGI's GeoSource 2 software (yellow voxels at right).

Localizing the Epileptogenic Zone

In the application of GTEN to suppress seizures, Electrical Source Imaging (ESI) is first conducted with the dense array EEG (dEEG) to localize epileptiform events (primarily spikes) with EGI's GeoSource software. As illustrated in **Figure 3**, dense array ESI 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. D. Holmes et al., 2008; M. Holmes et al., 2010; Yamazaki, Terrill, Fujimoto, Yamamoto, & Tucker, 2012; Yamazaki, Tucker, et al., 2012; Yamazaki, Tucker, Terrill, Fujimoto, & Yamamoto, 2013). Furthermore, we rely on the reciprocity between potentials generated by the epileptic discharge source and the current applied by optimal GTEN targeting. EGI's Geodesic Reciprocity Inverse Process (GRIP) technology (US Pats. No. 6,330,470 and 6,594,521) identifies the head surface potentials (lead field) of the epileptic discharge (spike or seizure), then uses that lead field to select the pattern of the source and sink electrodes from the 256 array for optimal targeting of the epileptogenic zone (identified by 256 dEEG ESI). This GRIP technology is the primary targeting method in the GTEN Planning Module of EGI's Modal Image Engine software.

Targeting the Epileptogenic Zone with the Geodesic Reciprocity Inverse Process

The second difference of GTEN from conventional tDCS (and tACS) is that the identification of the epileptogenic zone is achieved through Electrical Source Imaging (ESI) with dense array electroencephalography (dEEG) collected with the same 256channel Geodesic Sensor Net that is used for the GTEN targeting. This allows precise targeting of the epileptogenic zone with EGI's patented Geodesic Reciprocity Inverse Process (GRIP) in the GTEN Planning Module.

The basic idea of GRIP is that, by the principle of Lorentz reciprocity, the pattern of dipolar positive and negative potentials (EEG) created by an active area of cortex (effective current dipole) is also the optimal pattern of source and sink electrodes for current delivery to the neurons that generated that EEG. Intuitively, electricity goes in the same way that it comes out.

The physics of Lorentz reciprocity are clear. What is more speculative is the rationale that the way that the aligned neurons of the cortex generate far fields (EEG) provides a guide for how induced current alters the activity and polarization of cortical columns and their pyramidal neurons to affect ongoing function and thus long term plasticity. By careful analysis of therapeutic efficacy in relation to the estimation of dosage delivered normal to the cortical surface of the epileptogenic zone, we can test this rationale.

This oriented targeting is not possible for the majority of the cortex with TMS. To estimate this effective surface normal targeting with GTEN, we compute the dot product of the cortical surface normal (perpendicular) vector and the estimated current flow vector at the epileptogenic cortical site induced by the selected source-sink electrode configuration (**Figure 4**). This factor becomes a covariate in the statistical analysis of treatment efficacy, testing whether oriented targeting is indeed important or not.

Minimizing Effects on Nontarget Cortex: Discriminative Cortical Surface Vector Targeting

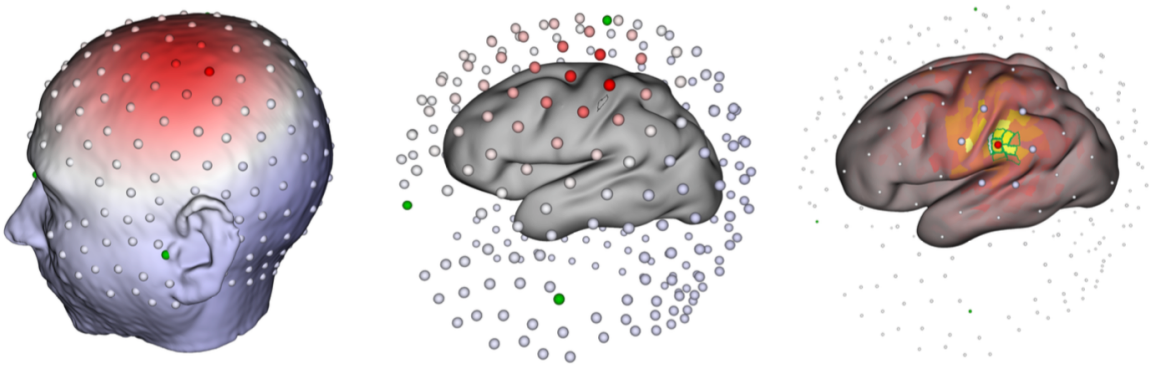

Figure 4. The GTEN Planning Module of the Modal Image Engine implements EGI's patented Geodesic Reciprocity Inverse Process (GRIP) technology. **Left:** The "forward" projection of the electrical field of the brain to the head surface (red is positive; blue is negative; white is the zero crossing), measured with EGI's 256-channel Geodesic Sensor Net. In assessing epilepsy, this would reflect the surface potentials generated by an epileptic spike or seizure. **Middle:** By the GRIP technology, the same pattern of electrodes that measures the field at the head surface can be used to impress current to target the cortical source site. **Right:** a focal pattern of stimulating a specific cortical target with a small set of sensors from the dense array. Considerable accuracy in targeting can be achieved by the combination of an adequate number of sensors and adequate computational power.

The third difference of GTEN from conventional tDCS is that we achieve precise targeting with a high resolution head model, with knowledge of the position and surface of the cortex. This allows knowledge of electrical stimulation of non target brain tissue. Even though we can model it accurately, and configure its delivery with the dense (256 channel) electrode array, the electrical current cannot be focused, and instead follows the path of least resistance between source and sink electrodes, influencing all tissues in its path. The GTEN Planning Module provides an estimation of the current delivery to non-target as well as target regions of cortex. In response to the FDA's concerns over current delivered to subcortical structures, such as the basal ganglia, we have now included a subcortical atlas, registered to the subject's MRI (and to the atlas brain models), so that computation of current delivered to each major subcortical structure is now estimated by the GTEN Planning Module.

For the subcortical nuclei, which are non-laminar, the orientation of the current flow is not expected to be relevant, so the total current is computed. For the non target cortex, we also consider the effect of the unintended current in relation to its orientation to the cortex surface. As described above, the source-sink configuration of the GRIP targeting is optimal for delivering cortical surface normal currents to the target region (which, by reciprocity, is collinear to the equivalent dipole vector in the electrical source estimation). However, other source-sink configurations can also be evaluated for their effective (dot product with the cortical surface vector) current flow.

The GTEN Planning Module incorporates a (patent pending) Discriminative Cortical Surface Vector (DCSV) targeting algorithm. This method maintains effective (surface normal) current in the target region for each pulse, but it alters the source-sink configuration to minimize the electrical current delivered at each pulse or interval to non target brain regions. Imagine that the normal surface vector of target patch of cortex is rotated for each interval (or pulse) of stimulation, with the center at the target: the target patch is still the centroid of current flow, but

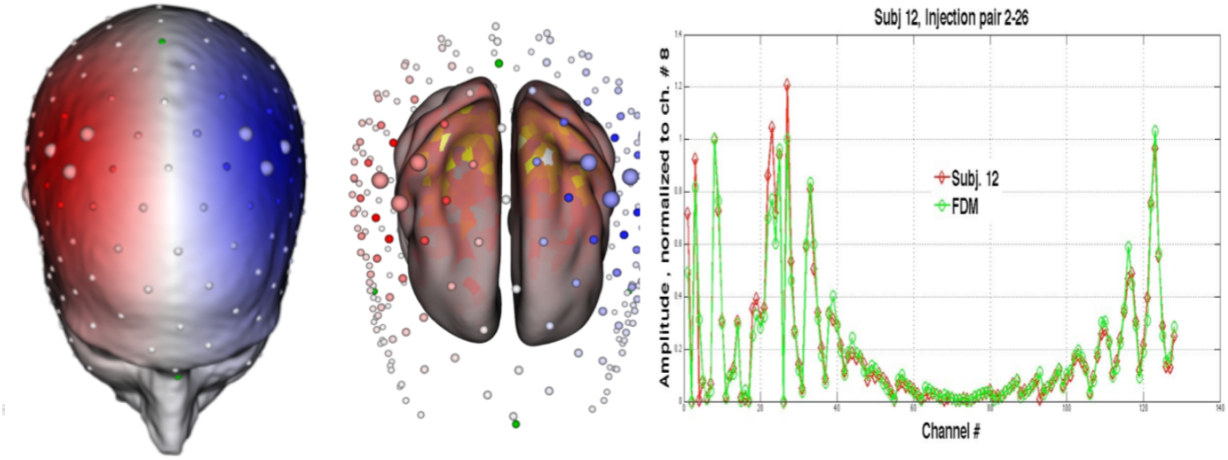

Figure 6. The GTEN Planning Module is designed to provide bEIT validation of the paths of the injected current through head tissues. **Left:** Illustration of the selection of three source electrodes (red) and 3 sink electrodes (blue). **Middle:** The forward projection of the electrical currents that 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 model (FDM, green) is compared to the measured potentials created by the injected currents between channels 2 and 26 for Subject 12 (red). If the potentials created at the head surface are within 10% of the prediction by the electrical head model, then we consider the accuracy of the currents impressed on the cortical surface to be verified.

Figure 5. A simple illustration of Discriminative Cortical Surface Vector targeting with two electrodes. From left to right: the red source (anode) is held constant and the blue sink (cathode) is moved from front to right to posterior right to posterior left. The cumulative charge delivered normal to each cortical patch is shown at each stage.

somewhat different non target regions receive current during each interval or pulse. Through computational optimization (in which the cost function is minimal non target current as well as maximal target current), the DCSV algorithm generates a set of source-sink electrode configurations that consistently deliver effective pulsed current flow to the target region but that create different (and thus minimized) current flow patterns in non-target regions over time (**Figure 5**).

Because digital switching of the GTEN 100 is fast, the treatment planning can establish multiple electrode configurations for multiple current paths, and each pulse of current can then be delivered through a different electrode configuration. With this flexible manipulation of the current flow, for either pulsed or sustained protocols, it is possible to minimize current delivery to non-target cortex, and thereby optimize effective therapy (hypothesized to be mediated by long-term depression) only in the target (epileptogenic) region. For the Pulsed GTEN protocol, the therapy involves 100 ms pulses of surface cathodal current at 0.5 Hz, emulating the effect of slow repetitive TMS (rTMS). In both cases, the goal is long-term depression of cortical excitability and thus suppression of seizures.

Validation of Targeting with bounded Electrical Impedance Tomography (bEIT)

Effective computational targeting with the GTEN Planning Module requires an accurate electrical head model. We have tested the GRIP estimation with the FDM electrical head model with independent estimation of current density impressed in the volume with the L2

computation. In addition, prior to beginning treatment, we test the validity of the electrical head model used for each patient (the with patient's own MRI or an atlas MRI) with the bounded Electrical Impedance Tomography (bEIT) protocol (**Figure 6**) that we have optimized and validated over the last decade (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 (**Figure 1**), 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 GTEN Planning Module, the bEIT validation (**Figure 6**) can be completed through impressing high frequency (200 Hz) low power (10 μA) signals between the source and sink electrodes that were selected to optimize cortical targeting in the GTEN Planning Module. If the measured potentials (from the non-targeting electrodes, demodulated at the current delivery frequency) fit the prediction, then the delivered currents, the electrical head model, and the distribution of currents throughout the volume used in the GTEN Planning Module are verified as accurate.

Software Life Cycle and Risk Management

The GTEN 100 software, including the Net Station GTEN Control Interface and the GTEN Planning Module, 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 VDE. 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 GTEN Treatment and Mitigation of Risks

The goal of GTEN treatment is to safely decrease the excitability of the cortex in order to suppress seizures. Whereas conventional tDCS (with large sponge electrodes) involves weak currents (and is well within limits for safety), it may not be as effective as rTMS, which induces larger currents in the brain. Furthermore, the higher current levels induced by rTMS are well within safety limits for tissue damage, and there is now fairly extensive evidence that slow rTMS (which we emulate with our protocol) has a very low risk of causing seizures. We therefore increased the GTEN current to 2 mA total, added lidocaine to increase comfort at this level.

We recognize the FDA's determination that, in epileptic patients, the GTEN 100 may present significant risk of worsening seizures or inducing cerebral discharges (possibly leading to kindling). We therefore request an Investigational Device Exemption. In addition, we detail the

strategy of mitigating the risk of inducing seizures, or inducing kindling, as well as other possible risks.

Risk of Tissue Damage with Electrical Fault

In the present proposed design of the GTEN 100, in order to achieve therapeutic efficacy more similar to TMS than tDCS, we have increased the power supply of the current delivery circuit to 10V (it was 5V in the previous presubmission).

In the worst case scenario where electrode-skin contact impedances are all intentionally reduced by the user (through severe scalp abrasion *against EGI's explicit instructions and training*), total circuit impedance could conceivably be as low as 1 kOhm. This would assume 1 kOhm source electrode impedance, and 0 kOhm sink impedance assuming that many sinks in parallel are all low and thus contribute an overall negligible impedance in parallel, and disregarding other head tissue contributions. This failure mode is highly unlikely in practice, but is relevant for worst case analysis.

Historical evidence may help to calibrate the risk of this failure mode. In the history of EGI's products, a circuit failure allowing current to be delivered to the subject (at a painless but perceptible level) has been detected and documented in one amplifier channel in the Net Amps product series (200, 300, and 400) with over 1000 systems in the field. About 70% of EGI systems sold have been 128 and 256 channels. Assuming equal numbers of 128 and 256 channels, we can estimate one failure in over 134,000 channels in use. The likelihood of *more* than one channel failing, in the same amplifier at the same time, is thus astronomically low. Nonetheless, even though the probability of even one failed channel is low, there is always a risk of electrical fault.

Tissue damage has been detected at a minimum total charge of 216 C/cm2 (2,160,000 C/m2) (Yuen, Agnew et al. 1981). In a study for epicranial tDCS stimulation in rats, (Liebetanz, Koch et al. 2009), Liebetanz and colleagues report that brain lesions were observed at a minimum cathodal electrode current density of 142.9 A/m2 for durations greater than 10 min.

Mitigating the Risk of Tissue Damage with Electrical Fault

Even with current applied in a TEN protocol, without scalp abrasion (*which is prohibited in EGI laboratories*) the electrode-scalp impedances almost never drop below 10k Ohms. Nonetheless, assuming the worst case of a user scraping the scalp to achieve a very low impedance of 1 kOhm for the source electrode (and using multiple sinks in parallel to create a near zero sink impedance), a single fault failure of the constant current circuit could apply a full, unregulated 10 V to the circuit. This would result in a current flow at a single source electrode that is 10 V/1 kOhm = 10 mA, resulting in a current density of ~10 mA/cm2 at that electrode/scalp interface in the electrical fault mode.

A first mitigation is created by the fact that this current level would be painful, even with the topical lidocaine electrolyte, leading to cessation of the treatment. In general, a practical mitigation is that the levels of current that would damage the brain would cause pain at the

scalp and skin. We instruct patients how to take the chin strap and pull the Geodesic Sensor Net off the head whenever they need to, such as in a fire or other emergency.

A second mitigation is the high reliability of the Net Amps electronics. Note that with a base rate of one failure in 134,000 channels, in hundreds if not thousands of hours of operation per channel, the odds of two channels failing at the same time are astronomically low.

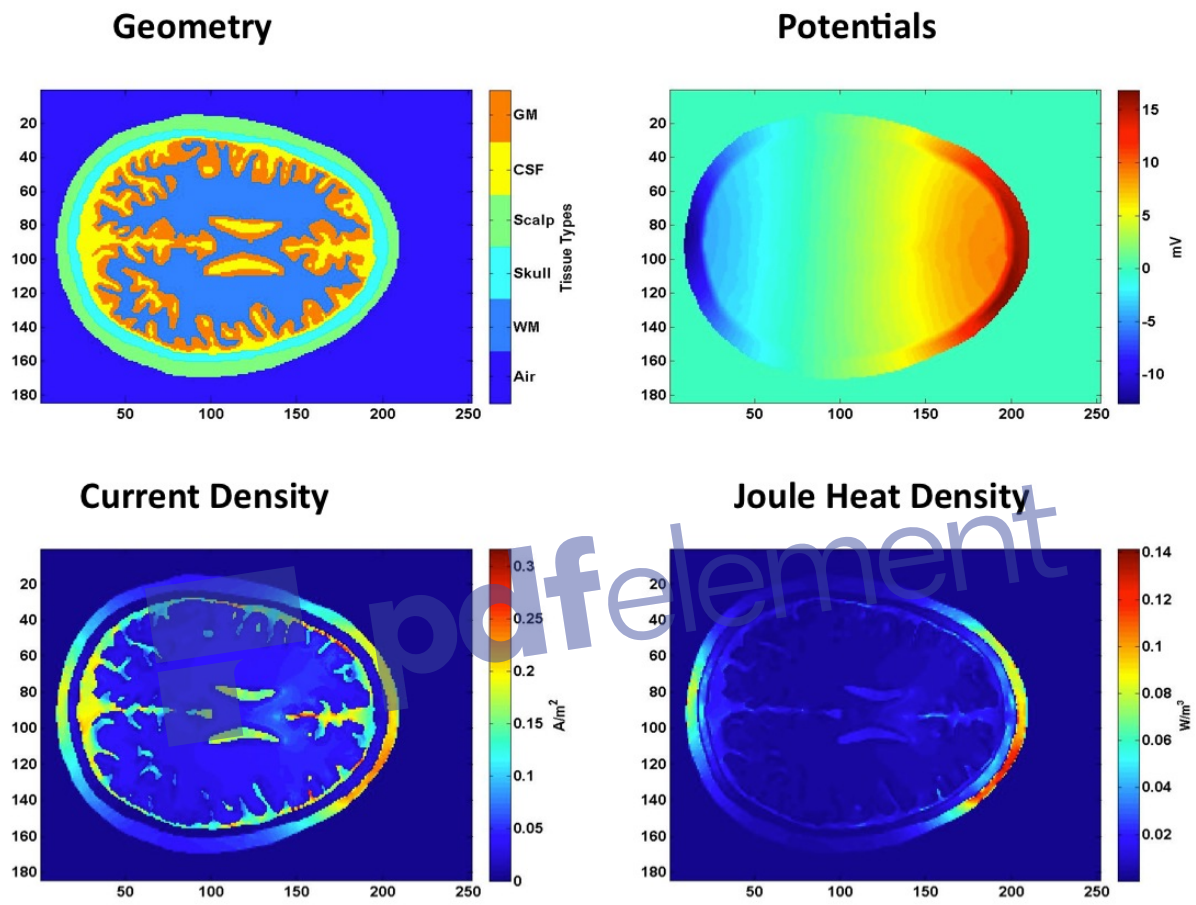

Figure 7. Finite Difference Model simulation with the EGI high resolution electromagnetic head model (Salman et al., 2005) showing (clockwise) one axial slice with the scalp, skull, cerebral spinal fluid and cortex geometry, the electrical potentials induced by simulated tDCS (6 anterior sources x 6 posterior sinks configuration; 1 mA total current injection), the power (Joule heat) density and the current density (strongly influenced by CSF). However, for purposes of examining the safety of the electrical current delivery in case of the worst case fault (for example assuming the pulsed TEN protocol were delivered to an unconscious patient for whom the scalp had been scraped), there are 3 pulse trains of 500 pulses of 0.1 second duration each. The total charge density would be 0.010 A/cm2 * 1 C/(A * s) * (1500 * 0.1) seconds = 1.5 C/cm2 (or 15000 C/m2) at the source electrode.

Furthermore, we assume that the the current source may have failed in a rail mode, with continuous 10 V output (instead of a 0.1 sec on duty cycle), the energy deposition might be considerably higher, 0.010 A/cm2 * 1 C/(A * s) * (1500 * 2) seconds = 30 C/cm2 (or 300,000 C/m2) at the source electrode.

Tissue damage has been detected at a minimum total charge of 216 C/cm2 (2,160,000 C/m2) (Yuen, Agnew et al. 1981). Thus, even assuming the worst case circuit failure with the 10V power supply and an unconscious patient with an abraded scalp, the single fault charge density at the source electrode is never more than 0.14 (30/216) of the charge density that causes tissue damage.

A separate question is the likelihood of damage to brain tissue with the worst case circuit failure. In a study for epicranial tDCS stimulation in rats, (Liebetanz, Koch et al. 2009), Liebetanz and colleagues report that brain lesions were observed at a minimum cathodal electrode current density of 142.9 A/m2 for durations greater than 10 min. For current densities between 142.9 and 285.7 A/m2, lesion size increased linearly with charge density (current density × time); with an extrapolated zero lesion size intercept of 52400 C/m2. If an EGI electrode were placed directly on the brain and a worst case electrical fault were to occur, the single fault charge density could exceed by a factor of 5.7 (300,000/52400) the zero lesion tissue safety limit at the source electrode, if it is allowed to exist for a full stimulation protocol.

However, the GTEN 100 electrodes are placed on the scalp (and face and neck). By careful modeling of head tissue conductivities (Gabriel, Peyman, & Grant, 2009; Turovets, Poolman, Salman, Malony, & Tucker, 2008) (**Figures 7 and 8**), we can determine that the current delivered at the scalp surface is attenuated by a factor of 100 or so at the brain. With an attenuation confidently estimated to range from 80 to 120, the total charge density of the proposed GTEN protocol to the brain would range from 0.07 (3750/52400) to .05 (2500/52400) of the lower bound of tissue damage of 52400 C/m2.

Figure 7 shows the fall off in current level when 1 mA of current is applied to 6 source electrodes and 6 sink electrodes (Salman, Turovets, Malony, Eriksen, & Tucker, 2005). Note that in this simulation, although the average current density is 167 μA per each of the six electrodes, this simulation models the current injection as a point source (with the FDM and palette showing the diffused current in the nearby scalp), whereas the simulation in **Figure 8** provides finite element modeling of the current density at the electrode-skin boundary (illustrating the effect of the specific electrode surface area and conductivity pattern).

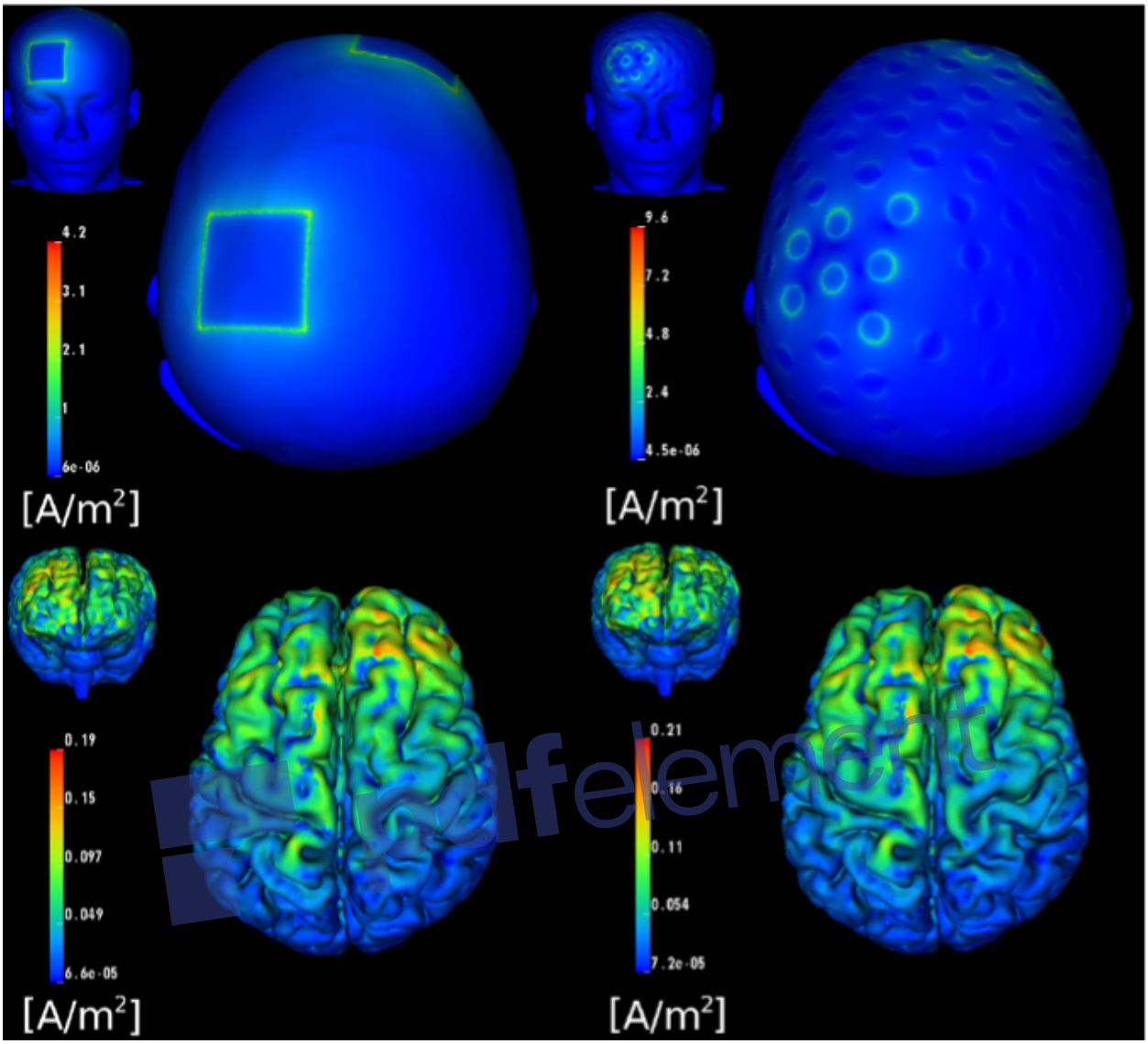

Figure 8. Finite element computations by Moritz Dannhauer and Rob McLeod at the University of Utah with EGI's electromagnetic head model and realistic conductivity values for the skull. Here the scalp current density (at the perimeter of the 1 sq cm electrodes, right) is about 4 A/m2 at the edges, and the maximum current density at the cortex is estimated as about 0.2 A/m2, an attenuation factor of about 20.

Risk of Pain in Normal Operation

In normal operation, the circuit for current delivery is a constant current circuit. It is important to emphasize that the worst case calculations with the power supply voltage are therefore not relevant to the controlled current delivered in normal operation (we apologize if our previous presubmission material was unclear on this point).

In normal operation, the delivery of electric current through small (1 cm2) scalp electrodes causes itching and then pain as the current density is increased. This was a major motivation for the development of TMS, which uses the magnetic field of the electromagnetic coil to induce the

mirror image electrical current in the cranial space without electrical current flow through the scalp (which has extensive nerve endings). With the GTEN 100, we observe there are considerable individual differences in the pain that is experienced. As a result, we train the experimenter to encourage reports of itching or pain, and then to cease treatment with any reports of discomfort. Because there is no observed tissue damage at any of the levels used in our preclinical studies, and only minor reddening of the skin, the pain reflects the electrical stimulation of the scalp nerves rather than tissue damage.

Mitigating the Risk of Pain in Normal Operation

As mentioned above, estimations of safe and painless operation with conventional (large square sponges) tDCS (Bikson, Datta, & Elwassif, 2009) have suggested charge densities range from 343-960 C/m2 (.0343-.0960 C/cm2). However, this calculation makes the common assumption in the tDCS literature that current is distributed evenly over the surface of the sponge. Instead, as would be consistent with classical physics model of the flow of current in a conductor, the current is distributed at the edge of the sponge, such that much higher current (and charge) densities have actually been delivered to the scalp at these perimeter locations in the conventional tDCS studies.

The same tendency for current to flow at the perimeter of the conductor is observed in simulations with the small (1 sq cm) electrodes of the GTEN 100 (Figure 8). However, the larger number of electrodes leads to greater perimeter distribution of the total current (Figure 8, right).

The first step to minimize the risk of pain is informing subjects that they can stop the procedure at any time just by letting us know they want to stop. This sensitivity to the patient's communications is an integral part of GTEN technician training. In addition, we tell each patient how, in case of emergency, they can take the chin strap and pull the Net off their head.

However, patients with epilepsy need an effective treatment, which may require brain current levels that are as close as possible to those induced by TMS. The present GTEN 100 protocol targets a current density at each electrode of 200 μA/cm2. We therefore minimize the risk of pain through iontophoretic (current induced) delivery of lidocaine that is mixed with the electrolyte. After a few minutes of iontophoretic application of lidocaine, our preliminary studies suggest 200 μA/cm2 is painless. If the subject detects any pain or discomfort, the current will be reduced so that the GTEN protocol (pulsed or sustained) is in fact painless.

In normal operation, the total current of the GTEN 100 is limited to 2 mA, and the current at each electrode is limited to 200 μA. Recognizing that increased current density ("hot spots") may be observed, we will mitigate this risk through careful inspection of the patient's skin and scalp after each session. A recent report of skin lesions after high current levels with tDCS electrodes (on the arm) showed that the first effect was reddening (erythemia) and that lasting redness (lasting several days) only occurred with repeated stimulation over multiple sessions (Khadka et al., 2015). Interestingly, the senior author of that study (Marom Bikson) reports that the erythemia does not suggest hot spots as suggested by FEM simulations, but rather that the current is fairly evenly distributed over the surface of the electrodes. Nonetheless, by careful monitoring after each session, we will assure that any reddening is not allowed to progress to a

lasting lesion. In many sessions with the GTEN 100 prototype with a range of skin types and current levels varying from 100 to 200 μA, we have not seen any evidence of lasting lesions.

Risk of Lidocaine Toxicity

In order to achieve effective therapeutic current level of 200 μA/electrode (closer to those of TMS) while minimizing patient discomfort due to painful electrical stimulation of skin/scalp nerves, we have developed the procedure of adding lidocaine to the electrolyte, and then applying current to achieve iontophoretic delivery of the lidocaine to the scalp and skin. Our preliminary experiments suggest this will allow painless delivery current densities of 200 μA per electrode (200 μA/cm2), even with rapid switching of current levels in the pulsed TEN (rTMS emulation) protocol.

There is a risk that, with multiple electrodes conditioned for source and sinks, the total iontophoretic lidocaine delivery will result in toxic systemic levels.

Mitigating the Risk of Lidocaine Toxicity

As pointed out by the FDA reviewer, there are multiple mechanisms for the infusion of topical lidocaine in the presence of electrical current, including iontophoretic, electroosmosis, and passive diffusion. To minimize the risk of toxicity, we will assure that the total dose of lidocaine applied to the skin, even if all of it were absorbed, will be below the toxic level.

Over the counter lidocaine cream (5% concentration, for example: RectoCare®) is mixed in equal parts with Elefix electrolyte paste. This is done before each treatment session.

To calculate the amount of electrolyte/ lidocaine cream under one electrode, the space available under EGI's electrode cup is about 150 cubic mm. The total amount of paste under one cap is 150 mg. Half of this is an over-the-counter 5% lidocaine cream (and half is Elefix gel). The total amount of lidocaine is therefore 3.75 mg. If we assume 10 high current electrodes are treated, then if all were absorbed, the dose would be 10 times smaller than the systemic toxic threshold for a average patient weight of 70 kg (5mg/kg x 70 = 370 mg). Of course , the amount absorbed is a fraction of what is present at the skin. For example, lidocaine patches, even after 12 hours on the skin, still contain about 95 % of initial amount of drug and are recommended to be disposed with appropriate care.

Risk of Tissue Damage in Normal Operation

Tissue damage must be considered separately from pain. Pain is noticeable with changes in current density, including the offset of the current, apparently through stimulating scalp nerves. Furthermore, pain decreases to become unnoticeable with constant direct current (DC) in the typical tDCS paradigm. Tissue damage, however, is a function of current density over time, or charge density. Estimations of both safe and painless operation with conventional (large square sponges) tDCS (Bikson et al., 2009) have suggested that safe charge densities in the typical tDCS experiments with large wet sponge electrodes range from 343-960 C/m2 (.0343-.0960 C/cm2). Nonetheless, there are reports of skin lesions when hard tap water (containing calcium carbonate) was used instead of saline (Palm et al., 2014). Furthermore, there have been reports

of skin lesions at the corners of large sponge electrodes, even though the estimation of charge density over the surface area of the electrode is lower than the safety limit (Rodriguez, Opisso, Pascual-Leone, & Soler, 2014). As shown in by the FEM simulation in **Figure 8**, the charge density is unlikely to be distributed evenly over the surface of the electrode, but rather is concentrated at the perimeter (and particularly the corners of square electrodes).

In a study for epicranial tDCS stimulation in rats, Liebetanz and colleagues report that brain lesions were observed at a minimum cathodal electrode current density of 142.9 A/m2 for durations greater than 10 min (Liebetanz, Koch et al. 2009). For current densities between 142.9 and 285.7 A/m2, lesion size increased linearly with charge density (current density × time); with an extrapolated zero lesion size intercept of 52400 C/ m2.

Mitigating the Risk of Tissue Damage in Normal Operation

In normal operation, the total current of the GTEN 100 is limited to 2 mA, and the electrode-scalp impedances are measured continually to assure that each electrode (for example 10 cathodes and many anodes) is maintained at or less than a current level of 200 μA (current density of 200 μA/cm2).

In the pulsed GTEN protocol, over 0.1 seconds (for example, a single pulse injected over 10 channels) in normal operation, the total charge density per electrode would be 0.0002 A/cm2 * 1 C/(A * s) * 0.1 seconds = 0.00002 C/cm2 (i.e. 0.2 C/m2) at the source electrode. Over the full pulsed GTEN session protocol of 3 pulse trains of 500 pulses of 0.1 second duration each, the total charge density would be 0.0002 A/cm2 * 1 C/(A * s) * (1500 * 0.1) seconds = 0.03 C/cm2 (i.e. 300 C/m2) at the source electrode.

Tissue damage has been detected at a minimum total charge of 216 C/cm2 (2,160,000 C/m2) (Yuen, Agnew et al. 1981). The normal GTEN 100 current flow at the source electrode is .001 (. 204/216) of that limit. We have never seen skin damage, or any effects other than temporary reddening of the skin (erythemia) with the GTEN protocols and the Geodesic Sensor Net electrodes, even when current density varies from 200 to 400 μA over many minutes.

We also consider the risk of tissue damage in the brain. In a study for epicranial tDCS stimulation in rats, (Liebetanz, Koch et al. 2009), Liebetanz and colleagues report that brain lesions were observed at a minimum cathodal electrode current density of 142.9 A/m2 for durations greater than 10 min. For current densities between 142.9 and 285.7 A/m2, lesion size increased linearly with charge density (current density × time); with an extrapolated zero lesion size intercept of 52400 C/m2.

Figure 8 shows an attenuation factor of about 20 X from the current level for multiple scalp electrodes (each at about 4 A/m2) to the cortical surface (peaking at about 0.2 A/m2). A similar calculation from one electrode (the worst case failure situation under less than astronomical odds for creating charge density of 2040 C/m2) shows an attenuation of about 100 X, from about 20 A/m2 at the scalp to achieve 0.2A/m2 on the cortex. With the attenuation of scalp charge density (2040 C/m2) by head tissues ranging from a factor of 80 to 120, the GTEN 100

normal mode charge density at the brain ranges from 26 C/m2 to 17 C/m2 or a factor of .0005 (26/52400) to .0003 (17/52400) of the safe limit for current to the brain.

The FDA reviewer cited earlier studies suggesting that the attenuation may be a factor of 30 rather than 100. Our modeling, with accurate skull conductivity from CT and with validation through bEIT studies, provides more accurate justification for the values than these early literature values. Nonetheless, we agree with the FDA that caution is warranted in assuming attenuation. As a result, we propose to mitigate the worst case failure through an additional layer of fault protection circuitry.

Note that (although it was not clearly explained in the previous submission), the GTEN 100 includes circuitry to limit the current per channel to 200 μA. The fault protection is designed to limit total current assuming this circuit fails.

The GTEN 100 design has now been revised to include a second Sentinel Circuit®, in series with the first one, to insure that failure requires a triple fault (the circuit fault, and failure of both Sentinel Circuits). The Sentinel Circuit is a separate electronic monitor circuit that detects if the current level exceeds the planned 2 mA value (such as if there is a fault in the electronics circuit). In that event, the Sentinel Circuit disconnects the current generator.

Risk of Seizures in Normal Operation

An important risk of the GTEN treatment is the risk of causing seizures. This risk may not be simply related to the level of current, but rather involves the more complex and poorly understood neurophysiology of epilepsy. The evidence on treating epilepsy with both tDCS and rTMS is relevant to assessing the risk of seizures.

Mitigating the Risk of Seizures in Normal Operation

It should be emphasized that patients must agree to maintain their regular anti epileptic medication during the course of the study.

There are two studies we found that have examined the effects of a single session of tDCS treatment of the apparent epileptogenic zone (F. Fregni, Thome-Souza, et al., 2006; Rotenberg et al., 2008). Both showed beneficial short term effects of the treatment in suppressing epileptiform discharges, with no increase in seizure frequency.

For the pulsed GTEN protocol emulating the effects of slow rTMS, the literature on seizure risk with slow rTMS in epilepsy is relevant. An important caution is that there have been only a few studies of slow rTMS therapy in epilepsy. Nonetheless, a recent review of the literature for rTMS therapy suggests that there appears to be minimal risk of inducing seizures by the slow rTMS treatment (Bae et al., 2007). The seizures that have been recorded during the slow rTMS treatment session have been the patient's typical seizures in both duration and semiology, suggesting these were not induced by the treatment (Rotenberg et al., 2009).

Thus, for the present feasibility study, the literature suggests the risk of seizures is low. To mitigate the risk, we will monitor carefully for seizures during and after the treatment. During

the three-month pretreatment baseline evaluations, we will characterize the patient's interictal events, plus any ictal events that are recorded, during three two-hour dEEG evaluations. We will train the treatment technician to monitor the EEG for these events during the treatment session. Because the source site of the interictal events is also the presumed epileptogenic zone and the target of the GTEN 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 has a select montage (screen arrangement) for the channels that reflect the patient's spikes (and likely seizures).

During the 17 minute GTEN treatment intervals, the EEG channels that are not used for (source or sink) current delivery will be monitored. The 24 bit ADs of the NA 400 allow adequate dynamic range (+/200 mV) that even channels nearby the current delivery seldom clip. During the rest (resting EEG and break) intervals, all 256 channels will be monitored. For the first ten patients, we will monitor the EEG for three hours following the completion of the treatment; for the rest of the patients we will monitor the EEG for 30 minutes following the completion of treatment.

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 Inducing Kindling of Seizures

It is well known that repeated electrical stimulation of the normal mammalian brain may lead to augmenting or progressive kindling of discharges, leading to seizures. Persons with epilepsy may show enhanced cortical excitability that places them at increased risk. In the animal literature, kindling occurs when repeated electrical stimulation of the cortex elicits cortical after-discharges (continuing when the stimulation stops); in some reports the discharges not only lead to seizures, but may lead to epilepsy, with spontaneous discharges and/or seizures in the absence of stimulation (Bertram, 2007).

Mitigating the Risk of Inducing Kindling of Seizures

The same procedures of careful EEG monioring used to mitigate the risk of seizures will mitigate the risk of kindling. Specifically, the EEG of each patient will be monitored during and after the treatment session, including a specific inspection of the channels near the target site. If the GTEN treatment is observed to lead to any epileptiform discharges that are unlike the patient's typical discharges (spikes) in frequency or localization, the treatment will be discontinued. A specific warning for possible kindling is the observation of repeated discharges that are associated with the repeated application of stimulation, specifically the pulses of the pulsed GTEN protocol. If these are observed, treatment will be stopped.

Risk of Unwanted Plasticity

The short term effects of transcranial neuromodulation 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) as evidenced by learning effects that are mediated by NMDA (Monte-Silva et al., 2013). The rationale of the present interventions is that inducing long term depression 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 GTEN treatment may change other aspects of the patient's cortical function that may create unwanted changes in brain function or plasticity. The large general literatures for tDCS and slow rTMS suggest there are unlikely to be serious unwanted changes. Nonetheless, we will achieve more focal and potentially more effective current delivery than in previous research with tDCS, and we will achieve deeper current delivery than previous research with slow rTMS.

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, paying close attention to any changes from the expected improvement in performance with practice from the normative data. The patient's baseline performance with the CVLT is assessed during the pre-treatment baseline assessment. We will also 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. Finally, for each patient we will examine the effective dose delivered to non target brain regions as a function of the DCSV targeting recorded by the GTEN Planning Module to insure that the electrical dosage (and the presumed induction of long term depression) is appropriately limited to the target cortex.

Pre-Clinical Testing with Normal Volunteers

We have studied the comfort and safety of the GTEN protocols, and evaluated their efficacy in manipulating cortical excitability, with normal volunteers. A preliminary report was presented at the June 2014 Organization for Human Brain Mapping (Tucker, Turovets, Anderson, & Luu, 2014). In the first series of experiments, we limited the GTEN current delivery to 1 mA total, and applied this through 7 to 10 of the electrodes of the Geodesic Sensor Net for the anodal current and 7 to 10 electrodes for the cathodal current. Both saline and gel (Elefix) electrolytes were used. Typical tDCS protocols were evaluated, with head surface anodal current predicted to increase cortical excitability, and head surface cathodal current predicted to decrease cortical excitability (T. Wagner et al., 2007). Using typical tDCS procedures including ramping up the DC stimulation over several seconds, the 1 mA current levels were generally comfortable for the subjects, when distributed over 7 to 10 electrodes. The motor cortex was identified anatomically by the hand knob, and a typical tDCS targeting of the motor cortex was achieved with the GTEN Planning Module. The effect on cortical excitability was tested through TMS stimulation of the hand area to create a thumb Motor Evoked Potential (MEP), with the TMS strength (% of

initial motor threshold) defining cortical excitability. **Figure 9** shows the TMS and GTEN targeting.

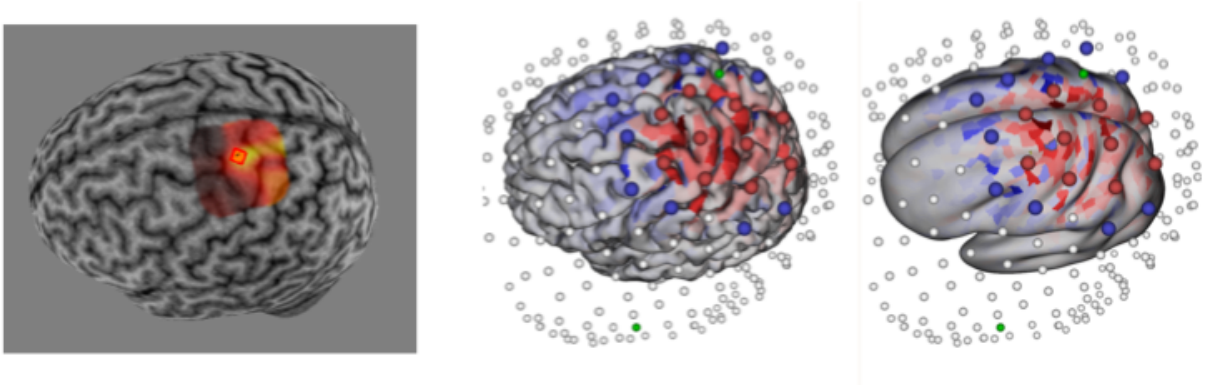

Figure 9. Left: targeting of Motor Evoked Potential (MEP) with TMS (the red bulls eye is the TMS target). The cortex is rendered with a convex hull slice. Middle: GTEN source (red = anodal) and sink (blue = cathodal) pattern for a radial current flow pattern targeting the hand knob of motor cortex. Right: inflated brain to show sulcal current delivery.

Consistent with the tDCS literature, head surface anodal current generally increased cortical excitability as indexed by the TMS MEP, and head surface cathodal current generally decreased cortical excitability. Also consistent with the literature, individual responses varied considerably.

In the next series of experiments (now in preparation for publication), we tested the comfort level with higher current levels (200 μA for each 1 cm2 electrode), using the typical tDCS protocol. Iontophoretic impedance conditioning was used to lower typical electrode-scalp impedances to 20 to 40K Ohms. There were large individual differences with comfort as well, but with the Geodesic Sensor Net 1 cm2 electrodes and 7 to 10 with the primary cathodal or anodal current, most subjects reported minimal or no sensation at 50 μA, feelings of itching or minor pain at 100 μA, and noticeable itching and painful irritation at 200 μA. We then mixed lidocaine with the gel electrolyte, applied anodal current for iontophoretic delivery (see above for dose analysis) during the iontophoretic impedance conditioning, and then repeated the experiments at 200 μA. Subjects consistently reported this was a painless procedure. Only when we asked them to feel the scalp with their fingers did they notice the slight numbing of the scalp under the active (7 to 10 focal anodal or cathodal) electrodes.

We have now completed testing with normal volunteers with the Pulsed GTEN protocol. Initial tests (with the investigators) without lidocaine confirm that the pulsed stimulation is more painful than ramped and sustained tDCS, even at 100 μA. However, with the lidocaine iontophresis, the 200 μA per electrode results in no noticeable sensation with the pulsed protocol. These pulsed experiments will be completed and submitted for publication, with the requirement that safety and comfort are both verified with normal volunteers prior to initiating clinical feasibility trials with the Pulsed GTEN protocol.

Therapeutic Mode of Action

In addition to insuring safety, we want to suppress seizures effectively. The literature on electrical neuromodulation in epilepsy suggests that tDCS typically has only a short term therapeutic effect in suppressing epileptiform discharges or EDs (Auvichayapat et al., 2013; Faria, Fregni, Sebastiao, Dias, & Leal, 2012). However, other evidence (Monte-Silva et al., 2013; Monte-Silva, Kuo, Liebetanz, Paulus, & Nitsche, 2010) suggests that repeated blocks of tDCS can induce lasting changes in cortical excitability (even though these studies were not with epilepsy).

In addition, the literature on epilepsy treatment suggests that slow (1 Hz or 0.5 Hz) repetitive transcranial magnetic stimulation (slow rTMS) has a lasting effect, including seizure suppression, assuming that the epileptogenic zone is accurately targeted (F. Fregni, Otachi, et al., 2006; Sun et al., 2012). Considering these several lines of evidence, we propose to implement a Pulsed TEN protocol to emulate the brain currents induced by slow rTMS to induce LTD and decrease cortical excitability.

Both tDCS and TMS achieve neurophysiological effects through creating electrical currents in the brain. Whereas the induction of current by the magnetic field of the TMS coil has the advantage of delivering higher brain currents while minimizing painful current flow through the scalp, the current flow is almost exclusively tangential to the head surface (because of the mechanical constraints of the coil), and the current is limited to roughly two centimeters of depth from the head surface, depending on the coil design (Pascual-Leone, Davey, Rothwell, Wassermann, & Puri, 2002)). As a result, even if the epileptogenic zone is localized correctly, effective targeting (current flow normal to the cortical surface) is difficult (and often impossible) with TMS. This conclusion is supported by the finding that TMS is often successful with neocortical foci, but may not be successful with deep medial temporal foci (F. Fregni, Otachi, et al., 2006; Sun et al., 2012).

The initial, single treatment session application of cathodal tDCS in epilepsy has suggested there is a suppression of epileptiform activity, but only over days or weeks (Auvichayapat et al., 2013; Faria et al., 2012). Our goal is suppression over several months. Several recent lines of evidence have suggest that the effects of tDCS stimulation can be made more lasting in two ways: (1) separating the repeated blocks of stimulation by short intervals of no stimulation, and (2) by repeating treatment over successive days.

In a cathodal tDCS study, Monte-Silva et al. (2010) showed that two, 9-minute tDCS sessions separated by brief (3 or 20 minute interval) breaks (i.e., no stimulation)

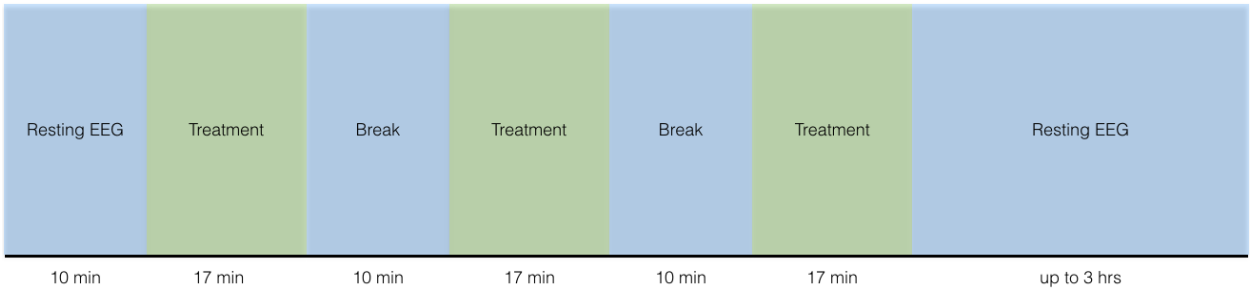

Figure 10. The protocol for interleaving GTEN treatment (either Blocked Sustained tDCS or Pulsed GTEN) and dEEG assessment (recorded and evaluated during the breaks as well as the resting EEG intervals).

enhanced the inhibitory after effect as well as prolonged it (up to two hours). They also showed that 9-minute sessions separated by 3 or 24 hours reduced the immediate aftereffects, but within 25 minutes after tDCS was completed the aftereffects were then enhanced and sustained for up to 2 hours. In a more recent study, Monte-Silva et al. (2013) showed that 13-minute anodal stimulation sessions separated by 3 or 20 minute intervals extended the aftereffects beyond 24 hours post-stimulation. From both studies, when tDCS is applied within the aftereffect window of the first tDCS session, it has the ability to enhance the lasting aftereffects (i.e., inhibit or facilitate neuronal function depending on cathodal vs anodal polarity) as well as to prolong these effects in time.

Two studies have found that tDCS applied over multiple days produces learning effects that last for weeks to several months. Reis et al. applied 20-minute anodal tDCS over five consecutive sessions (each separated by 24 hours) as subjects performed a visuomotor task (Reis et al., 2009). The effect of anodal tDCS on task performance was measured at five intervals, the longest interval being 85 days after tDCS. Reis et al. found that tDCS enhanced motor learning and that this enhancement persisted for up to 85 days post tDCS treatment. More recently, Olma et al. applied anodal tDCS to the visual cortex over five consecutive days (each separated by 24 hours) as subjects performed a visual motion perception task (Olma et al., 2013). Anodal tDCS in this paradigm resulted in an improvement in motion perception that lasted up to 28 days.

Of course these are not just direct neurophysiological effects of tDCS, but rather learning changes in the brain where the process of learning has been augmented by tDCS. Treating epilepsy may be more challenging because there is no systematic or deliberate learning regimen, but rather a more simple attempt to suppress cortical excitability.

With these effects in mind, n each treatment session there are three 17 minute blocks of sustained TEN, separated by 10 minute breaks or rest periods, with pre-session and post-session resting EEG as shown in **Figure 10**. This treatment session is administered each day for five days in one week. The successful Sun, et al., protocol included slow rTMS treatment 5 days per week for two weeks and suppressed seizures for up to 6 months. However, for the present feasibility study, we propose to treat for 5 days in one week, with feasibility and targeting accuracy demonstrated through observing spike suppression at weeks 2, 8, 16, and 24. Seizure suppression will also be evaluated each month in the seizure diary.

Relative Strengths of TMS and TEN

It is generally assumed that TMS induces large electrical currents in the brain, and indeed these are sufficient to stimulate neuronal discharges, such as evidenced by the motor evoked potential. In contrast, TEN (tDCS and tACS) generally induces much smaller currents in the brain, and there may be concern that the proposed TEN protocols cannot be as effective as the slow rTMS treatment protocols in the literature (F. Fregni, Otachi, et al., 2006; Sun et al., 2012).

The earlier textbook models of the current density induced by TMS suggest that current densities induced in the cortex are on the order of 3000 μA/cm2 (30 A/m2) (T. A. Wagner, Zahn, Grodzinsky, & Pascual-Leone, 2004). However, Wagner, et al. (2004) point out that these textbook models of TMS used unrealistically high head tissue permittivity for the magnetic fields. With more realistic permittivity values, the estimate obtained in the Wagner et al. simulation was 300 μA/cm2 (3 A/m2) current density at the cortex.

In contrast, in the simulation of **Figure 8**, the total current of 2 mA was impressed at the 7 source scalp electrodes to create a current density of 286 μA/cm2 (0.2 A/m2) on the cortex. If we limit the scalp current density to 200 μA/cm2, as with the proposed protocol for the GTEN 100, then the cortical surface current density will be 0.13 A/m2, a factor of 23 less than TMS.

However, the effective modulation of brain activity may depend not on the absolute current density, but on the current flow that is normal to the cortical surface. This is because the neurons of the cortex are aligned perpendicular to the cortical surface, and the induced current serves to alter neuronal polarization along the apical dendrite to somatic axis of the cortical pyramidal neurons (Datta, Zhou, Su, Parra, & Bikson, 2013). Wagner et al (2004) point out that as little as 30% of the current induced by TMS may be oriented normal to the cortical surface. This implies that TEN, which can be directed from the 256 channel array to be oriented mostly normal to the cortical surface, may achieve effective dosage that is within a factor of 10 less than the magnitude of the effective TMS induced current.

Importantly, a major advantage of TEN over TMS is the ability to reach deep sources. In the simulations of TMS by Wagner, et al. (2004), the depth penetration of TMS was 2 cm into brain tissue, where it reached only the crown of the gyrus, and there the current was largely tangential to the gyral crown (rather than surface normal). We must assume, therefore, that the targeting in the existing studies of slow rTMS for epilepsy (Fregni, et al., 2006; Sun, et al., 2012) was highly approximate. Although Fregni et al. used focal cortical dysplasias to guide targeting, it is highly unlikely that these were all within 2 cm of the cortex, or that effective targeting of current direction was achieved.

Therefore, considering these several factors, we can reasonably expect that the electrical dosage of the GTEN 100, with the safety and comfort level set at 200 μA per electrode for the study protocol pulses (**Figure 10**), when targeted appropriately to the epileptogenic focus with the 256 array and the high resolution head model, will be an effective treatment for seizure suppression.

Clinical Feasibility Trial Design

The goal of this unblinded and uncontrolled ("open-label") feasibility study is to evaluate the safety, comfort, and preliminary efficacy of GTEN 100 treatment in achieving temporary suppression of epileptic activity, as assessed primarily by spikes and secondarily by seizures. The GTEN 100 applies small, electrical currents (up to 200 μA per electrode and up to 2 mA total) in a pattern that targets the cortical site of epileptiform discharges in order to decrease the excitability of the epileptogenic cortical tissue.

For this safety and feasibility study, two clinical sites are being planned in the US (Eugene, Seattle) and one in China (Shanghai). An expert epileptologist will provide medical guidance at each site. The Chair of the Study Monitoring Committee will not be associated with these sites or with EGI: Dr. Douglas Rose, Cincinnati Children's Hospital Medical Center. Racial and gender composition will be as it appears in each sample. Study protocols and safety procedures have been approved by IRBs in Eugene and Seattle, and are under review at Huashan Hospital in Shanghai.

Patient Recruitment

Adult and adolescent patients (12 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. All patients agree to maintain their current antiepileptic drug dose throughout the study, including the two month baseline and the two month follow-up period.

Inclusion Criteria

(1) Partial onset seizures (simple or complex) with failure of adequate seizure control after prior use of at least 2 anti-seizure drugs at effective doses.

(2) A clearly identified and localizable focus of epileptiform discharges, as defined by the discharges (typically epileptiform spikes) and as identified by dEEG assessment through one or more routine clinical dEEG evaluations.

(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. 33

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) 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.

(3) A history or condition of status epilepticus or psychogenic seizures.

(4) 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.

(5) Previous surgery involving opening the skull.

(6) Allergy to or condition contraindicating lidocaine.

(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 at stimulation currents of 200 uA.
(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.
(5) A two-fold increase of seizure frequency over the baseline seizure frequency. If the frequency of seizures is very low, then an apparent increase during treatment (not reliably quantified as a two-fold increase) will be discussed with the patient, family, physician and Study committee.

The entire study will terminate if 5 subjects meet escape criteria.

Baseline Evaluation

During a one-month pre-treatment baseline evaluation period, the patient (and/or family) will maintain the seizure diary, which will be reviewed by the study coordinator in a phone contact once per week. In addition, 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. Each baseline evaluation also includes the California Verbal Learning Test, and the Quality of Life in Epilepsy report.

Probe Treatment and Evaluation

The GTEN Plan is developed to apply current pulses to the epileptic focus, as it is identified from the dEEG source localization of the spike onset. The GTEN Plan will often include more than one treatment option, primarily depending on the orientation of the cortical region identified as the epileptic focus. To evaluate a treatment targeting option, a probe treatment may be conducted, consisting of one 17-min pulsed treatment block (Figure 10) followed by one hour of dEEG evaluation and spike counting. If multiple targeting options are evaluated, the one with the best evidence of spike suppression will be selected for the 5 session treatment intervention.

The probe treatment and evaluation protocol is thus a subset (one block instead of 3 blocks of 17-minute pulses) of the approved treatment protocol.

The same GTEN Planning Module is used to develop each probe treatment targeting plan, with the primary difference being the cortical region that is targeted. This is a judgment made by the scientists (Drs. Tucker and Luu at EGI) on the basis of the ability to target the cortical region, which is very difficult in medial temporal regions, and the epileptologist (Dr. Holmes at Harborview) on the basis of the likely relation of the spike development to seizure onset. Often there are multiple possible targets, and the probe treatments and evaluations may allow us to contrast their efficacies.

Treatment Protocol

A two hour GTEN treatment sessionthen targets the identified focal epileptogenic zone for 5 days during one week. For the first ten patients the post treatment monitoring is continued for 3 hours after the treatment session. For those patients whose spikes were more frequent during sleep during the baseline evaluation sessions, an effort will be made to have them fall asleep as the lidocaine takes effect and before the GTEN treatment begins, so that the treatment matches the excitable state during which spikes occur.

All sessions are conducted by personnel who are trained in the dEEG and GTEN 100 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.

Follow up Protocol

The one week treatment period is followed by a weekly seizure diary review by phone with the study coordinator for six months, plus a dEEG follow up evaluation session in weeks 2, 4, 8, 16, and 24. Each follow up session includes dEEG evaluation during the entire session, including during the review of seizure diary, cognitive function testing with the California Verbal Learning Test, and the Quality of Life in Epilepsy report, as well as a resting dEEG interval. If the patient has interictal events in sleep or drowsiness, the resting dEEG evaluation will include a quiet period for a nap.

Primary Endpoint and Study Success

The primary endpoint is a temporary suppression of epileptic spikes. With assessments of spike rates at weeks 2, 4, 8, 16, and 24, the study will allow estimation of how temporary a suppression is achieved by the one-week treatment. The routine dEEG sessions typically collect dEEG for over an hour, and spike rates per hour will be the standard metric. To be successful, and to warrant progression to a randomized clinical trial, this clinical feasibility study must demonstrate successful targeting and suppression of the epileptogenic zone, as evidenced by temporary but statistically significant spike suppression in contrast to the pre-treatment baseline. All spike rates (baseline, treatment, and follow-up) will be counted as spikes per hour and classified in relation to waking or sleep stage (N1, N2, N3).

Secondary Endpoints and Study Success

The secondary endpoint is monthly suppression of seizures, assessed by the seizure diary each month for six months following treatment, in comparison to the mean seizure frequency for the one-month pre-treatment evaluation baseline. It is clearly advantageous if there is seizure as well as spike suppression as we plan the design of the pivotal trial.

Additional secondary endpoints will be (1) any improvement of cognitive function testing beyond the practice effect (estimated from norms and the improvement in the sham control group); (2) any improvement in quality of life ratings.

Study Monitoring Committee

The safety and comfort decisions for each patient are made by the epileptologist at each site. The safety, comfort, and efficacy of each treatment protocol across sites are reviewed by the Study Monitoring Committee. Vigilance will be maintained throughout the pivotal study to insure safety (no provoked seizures and no adverse effect to non target brain regions). Treatment will be discontinued for any patient that shows treatment-induced seizures, defined as seizures that are not the patient's typical seizures or that occur twice as frequently as the patient's typical seizures, as assessed during baseline. If there are more than five patients with worsening seizures (meeting escape criteria as stated above), the treatment will be suspended at that site. The Study Monitoring Committee (and the FDA when possible) will decide if the trial with that treatment should be terminated at all sites.

At each site, careful attention will be given to the dosage that patients tolerate well, primarily in relation to maintaining adequate comfort with the treatment current and the lidocaine anesthetic. We are confident from the pre-clinical studies that these protocols are tolerated by normal volunteers, and should be comfortable patients with epilepsy. If the electrical dosage needs to be adjusted for individual patients, then the quantitation of cortical target dosage and the dose-response analysis will provide an indication of dosage efficacy (at varying dosage levels) across the entire trial.

Quantitating the Estimated Effective Dose

Because the effective (surface normal) targeting varies across patients according to the location of the epileptogenic zone, the data analysis will attempt to predict the criterion of seizure suppression from the quantitation of effective dosage for each patient. Eventually, this quantitative prediction may allow indications for use that are gauged in relation to the estimated targeting effectiveness in the pre-treatment GTEN planning process. If successful, the adaptive estimation of effective cortical dosage would allow the physician to (1) localize the epileptogenic zone with dEEG, (2) conduct an initial analysis GTEN Planning Module of the effective dose that can be delivered with the 256 array with the 2 mA dose level, (3) conduct a pilot session to determine if the patient is comfortable with the dose required for efficacy, and then (4) discuss with the patient whether GTEN treatment is a worthwhile option. Post hoc analysis of the effective targeting in the clinical feasibility trial will provide initial evidence of the importance of cortical surface normal targeting dosage in predicting seizure suppression.

Power Analysis and Missing Data Analysis

This clinical feasibility trial will test for a statistically significant suppression of epileptic spikes at several time points (weeks, 2, 4, 8, 16, and 24) following treatment in contrast to the average of two dEEG evaluations during the one-month baseline. Without previous results on the Pulsed GTEN treatment, it is difficult to estimate effect sizes for power analysis for this one-week treatment intervention.

As pointed out by the FDA reviewer, an extensive statistical plan may not be warranted for a feasibility study. Furthermore, although we have considered the results of the rTMS study of Sun et al (Sun et al., 2012) to provide some indication of effect size, we agree that we have little basis for estimating the power required for determining the significance of spike suppression with GTEN therapy. We do plan to follow the reviewer's suggestion to compare spike rates following treatment to those from the baseline assessment with a one-sided t-test with a significance level of 0.025.

At the same time, we recognize that we are proposing to evaluate two protocols (Sustained Blocked tDCS and Pulsed GTEN), and must have sufficient numbers of patients to demonstrate feasibility, and to examine the significance of spike suppression, for either treatment protocol. If one protocol is effective and the other is not, we propose to stop enrolling patients for the ineffective protocol and focus recruitment on the effective one to demonstrate efficacy for a pivotal study.

Study Procedures

Informed Consent

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

• GTEN (Geodesic Transcranial Electrical Neuromodulation) is a method of applying small electrical currents through the head in order to achieve a lasting decrease in the neuronal activity of the epileptogenic (seizure-causing) zone of cortex. The experimental treatment protocols have been designed on the basis of previous scientific studies. For the Pulsed TEN, the studies have suggested suppression of epileptic seizures with Transcranial Magnetic Stimulation (in the Fregni, et al., 2006 and Sun, et al., 2012 trials). GTEN is used instead of TMS because of the ability to control the targeting of cortical sites more precisely, as guided by the dEEG fields of the epileptiform discharges. In addition, GTEN is able to target epileptogenic zones in deep as well as superficial cortical sites.

• There is minimal risk of the treatment. The slow pulsed electrical neuromodulation has been applied in several studies of epilepsy with the TMS procedure, and there is no evidence that it causes seizures. Transcranial electrical stimulation (tDCS) has been applied in several experimental studies of patients with epilepsy, with no evidence that it causes seizures. Nonethless, there is always a small risk of causing seizures, and medical procedures are in place both to monitor for seizures (with the EEG recording in each session) and to provide first aid if a seizure occurs.

• The primary feeling of the electrical current is a tingling sensation, and there is risk of minor itching and/or scalp pain. A small amount of lidocaine is mixed in the electrolyte to minimize the pain at the electrode site, and the procedures will be adjusted to assure that any discomfort is acceptable to the patient. 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.

Changes to the Harborview Informed Consent Form

The Informed Consent Document (ICD) approved with the GTEN IDE was the EGI Consent Form (GTEN) 12/29/2014. This was rewritten to conform to the format of the University of Washington IRB and approved by the UW IRB. It was then modified to include the probe test (as described in the present protocol) and approved in November 2015. A minor error (stating the probe test was 10 min rather than 17 min) was corrected and the correction was approved March 9, 2016.

The EGI Parental Consent Form approved with the IDE is unchanged, but is not in use because the only active trial site (UW Harborview) is not enrolling adolescents.

Both the EGI IRB Consent form of December 29, 2014 (approved with the IDE) and the UW IRB Consent Form (proposed for this trial with the present Supplement) are attached.

With the exception of the probe test, there are only minor differences in these consent forms, involving the change of format to the UW IRB Consent Form format. Following is a section-by-section summary of the revision, emphasizing where the same information from the (IDE approved) EGI IRB Consent Form is included in the UW IRB Consent Form.

Purpose of the Study: This was rewritten to be easier to read. It contains a similar description of treating epileptic discharges with small currents applied to the brain.

Study Summary: added to fit the UW format. This section gives an overview of the study. It describes the evaluation and treatment phases, including the probe test, as well as the follow ups sessions. This information is contained in **Study Procedures** in the EGI form.

Study Procedures: This describes the specifics of each baseline, treatment, and evaluation session, including the CVT and QOLIE.

Risk, Stress, or Discomfort: This was rewritten in the required UW format: it describes the same concerns covered in the EGI form: discomfort, skin irritation, adds risk of loss of privacy and psychological risk of ineffective treatment. This mentions the (very minimal) risk of silver allergy (from the AgCl electrodes) that was discussed in an EGI GTEN Hazard Review (since the IDE). It emphasizes risk of seizures and the procedures for seizure monitoring, in a very similar way as the EGI form.

Benefits of the Study: The important statement is that there may be no benefits, similar to the EGI form.

Source of Funding: This was added following the UW format, and explains EGI's financial support for the trial (equipment, 25% salary for Dr. Holmes, and full salary for Ms. Wise).

Confidentiality of Research Information: Emphasizes procedures to maintain, and possible limits, similar to the EGI form.

Alternative to Taking Part in This Study and **Other Information** cover the information that is described in the **Participation** section of the EGI form.

Localizing Epileptiform Discharges (EDs)

The cortical target for GTEN treatment will be determined from ESI applied to epileptiform discharges (spikes) observed during one or more 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. 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. A variant of the protocol is identification of the GTEN targeting through localization of seizure onset, such as with long term video dEEG monitoring.

The GTEN Planning Process

Given the selection of the epileptogenic treatment target from the pre-treatment 256 dEEG evaluation exam with electrical source imaging (ESI), and prior to the first treatment session, the source-sink electrode pattern for targeting is derived through reciprocity with the interictal epileptic focus site with the Geodesic Reciprocity Inverse Process (GRIP). First, the cortical site of spike onset is used to generate the forward projection, from an equivalent dipole at that cortex site to the 256 electrodes (**Figure 4**). By reciprocity, the inverse of this forward projection then defines the optimal sink pattern (from the negative potentials) and the source pattern (from the positive potentials) to be used for the current injection electrodes to achieve current flow normal to the cortical surface (in other words, in the same orientation as the ESI source dipole vector) at the target region.

Next, minimization of non-target current delivery is evaluated for variations of the GRIP pattern, with the Discriminative Cortical Surface Vector (DSCV) method. Typically five to ten different DCSV patterns are used, each with effective delivery to the target and maximal variation of current delivered to non-target areas compared to the other patterns. As described above, given the laminar arrangement of cortical neurons, the efficacy of electrical current in modulating membrane and synaptic activity appears to depend on the delivery of electrical current normal (perpendicular) to the cortical surface (along the dendritic-soma axis) at the site of the epileptogenic zone (as estimated by the site of spike onset). The effective dose computed by the dot product of the current delivery with the cortical surface vector, summed over the

treatment session, will serve as a measure of targeting efficacy and will be retained as a covariate for statistical analysis of treatment efficacy.

bEIT Validation of the Head Model

Once the GTEN Targeting is complete, the first treatment session is scheduled. At the beginning of that first session, the bounded Electrical Impedance Tomography (bEIT) procedure (**Figure 6)** is used with the selected sink-source electrode targeting configuration to test the prediction of the electric head model developed for that subject (with the individual's MRI or the atlas MRI and finite difference modeling). If the mean prediction of the recovered bEIT signal across recording electrodes is not within 10%, the model is judged to be flawed and the treatment is postponed until an accurate targeting model is created.

Once an accurate targeting model is achieved for the sink and source electrodes of the patient's GTEN Targeting of the presumed epileptogenic zone, it can be used for the subsequent treatment sessions, with the restriction that the placement of the Geodesic Sensor Net is replicated (within 2mm desired accuracy) in each session. Accurate placement is verified in each session with the Geodesic Photogrammetry System (**Figure 2**).

Iontophoretic Electrode-Skin Impedance Conditioning and Lidocaine Topical Anesthetic

Because scalp abrasion is prohibited, the electrode-to-skin impedance of the Geodesic Sensor Net typically begins at 50K to 100K Ohms. For consistent and effective delivery of electrical currents for neuromodulation, impedances of 20K Ohms are preferred. Furthermore, given the single current source of the GTEN 100, it is preferable to have all source (anodal) and sink (cathodal) electrodes at about the same impedance level (so that they divide the current evenly at about the 200 μA per electrode target).

Electrode-scalp impedances will be conditioned with the Dermal Iontophoretic Bond (DIB) protocol, a (patent pending) method of using iontophoresis to carry ions from the electrolyte across the stratum corneum (dead layer) of the skin with DC current, thereby decreasing impedance to the desired level. By including lidocaine in the electrolyte solution, we will anesthetize the scalp and skin under the electrode to minimize superficial nerve pain from the electrical stimulation. Similar to the iontophoresis that is widely used for drug delivery (for example for delivering pain relievers in sports medicine), the iontophoretic impedance conditioning is safe, can be adjusted to be painless for each subject, and can be carried out in parallel with impedance testing at the beginning of the dEEG or GTEN session. The lidocaine is delivered during the conditioning procedure through anode electrodes, with cathodes adjusted to minimize any current flow through the brain. Over several minutes of the 200 μA/electrode current level of GTEN 100 treatment, we typically observe the (non-abraded) electrode-scalp impedance to drop to 20K Ohms, and occasionally to 10K Ohms. These impedance levels will then be monitored at multiple points during the treatment session.

Setting Current Levels and Administering Treatment

The goal is to optimize the current delivered at the target epileptogenic site, while limiting overall current delivery to 2 mA, and limiting the current applied to each electrode to about 200

μA. Once the targeting is planned for each subject, the first session will evaluate the comfort level, and current levels adjusted to insure they are acceptable to the patient.

Treatment is applied in a two-hour session (including post session dEEG monitoring), 5 days per week for 1week. For the first ten patients with each treatment, the first treatment session is followed by 3 hours of dEEG monitoring to insure there are no seizures. After that the post-treatment dEEG monitoring is continued for 30 min.

Review of the EEG for Safety and for Spike Counts

The dEEG is reviewed after each treatment and follow up session, by visual inspection by a trained electroencephalographer and with an automated spike detection and clustering algorithm (EGI's Spike Beacon software), with the quantitation reported as a trial endpoint. 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 if there is an increase in spike frequency of over one standard deviation compared to the baseline sessions, 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.

The experimental procedures for each patient session are summarized in Table 2.

Monitoring of Risk

A daily diary with a count and description of seizures is reviewed at each session (treatment and follow up). If there is an increase in seizures of two-fold over the patient's baseline levels, the patient's treatment is suspended and the safety of the treatment is evaluated by the epileptologist, patient, and family. In the follow up sessions, routine dEEG evaluations, cognitive function assessments, and quality of life ratings are conducted once each week for three weeks following the treatment, and then week 8. 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), 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 2 presents an overview of the treatment protocol. An exception is that for the first ten patients the dEEG will be monitored for seizures for 3 hours after the first treatment session.

Session	Procedure
Pre-Treatment Evaluation	Review of seizure diary each week for one month. Two routine dEEG evaluations to capture epileptiform discharges (ED), including spikes and seizures. MRI when available to determine possible malformations of cortical development and build individual head model.

Session	Procedure
First Treatment Session	• Review of seizure diary. • Application of the Geodesic Sensor Net. • Geodesic Photogrammetry System (GPS) to localize sensors. • bEIT scan to verify electrical head model. Lidocaine iontophoresis conditioning during this scan. • 10 minutes resting dEEG. • GTEN treatment: 3 sets of 500 pulses (600s intervals between sets) or 3 sets of sustained tDCS with the same intervals. • 30 minutes resting dEEG (unless sleep EEG needed, then 2 hrs). • California Verbal Learning Test • Quality of Life Questionnaire
Treatment Sessions 2-5	• Review of seizure diary. • Application of the Geodesic Sensor Net. • Geodesic Photogrammetry System to localize sensors. • 10 minutes resting dEEG. Lidocaine iontophoresis conditioning during this time. • GTEN treatment, 3 sets of 500 pulses (600s intervals between sets) or 3 sets of sustained tDCS with the same intervals. • 30 minutes resting dEEG (unless sleep EEG needed, then 2 hrs). • California Verbal Learning Test • Quality of Life Questionnaire
Follow up routine dEEG, weeks 2, 4, 8, 16, and 24.	• Review of seizure diary. • Application of the Geodesic Sensor Net. • Geodesic Photogrammetry System to localize sensors. • 30 minutes resting dEEG (unless sleep EEG needed, then 2 hrs). • California Verbal Learning Test • Quality of Life Questionnaire

Table 2. Summary of treatments and assessments.

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