METHODS AND SYSTEMS FOR FACILITATING CLINICAL TRIALS

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ABSTRACT
The present invention provides methods and systems for improving clinical trials of experimental therapies. The present invention uses minimally invasive, leadless implantable devices that facilitate long term monitoring of a physiological signal (e.g., neural signals) from a patient population which may provide an indication of the effect of the experimental therapy on the patient population. In preferred embodiments, neural signals are sampled from the patients in the patient population with an externally powered, leadless implanted device and are transmitted to an external device for further processing.

11 START

Generate radiofrequency signal(s) 13

Receive radiofrequency signal to illuminate/energize an implantable device 15

Use the radiofrequency signal to interrogate the implantable device 17

Sample a physiological signal from the patient (EEG signal) with the implantable device 19

Communicate the measured physiological signal from the implantable device to an external device 21

Store the measured physiological signal in a memory 23

Analyze the sampled physiological signal to estimate brain state and estimate a propensity for a neurological event (e.g., seizure, migraine headache, episode of depression) 25

Generate an output in response to the estimated brain state and/or propensity 27

END
FIG. 1A
START

Generate radiofrequency signal(s) 13

Receive radiofrequency signal to illuminate/energize an implantable device 15

Use the radiofrequency signal to interrogate the implantable device 17

Sample a physiological signal from the patient (EEG signal) with the implantable device 19

Communicate the measured physiological signal from the implantable device to an external device 21

Store the measured physiological signal in a memory 23

Analyze the sampled physiological signal to estimate brain state and estimate a propensity for a neurological event (e.g., seizure, migraine headache, episode of depression) 25

Generate a output in response to the estimated brain state and/or propensity 27

END

FIG. 1B
START

Create an incision in the patient's scalp 102

Insert introducer assembly into incision and position introducer assembly at target area 104

Actuate introducer assembly to inject implantable device at target area 106

Remove introducer assembly 108

Sample EEG signals from the patient's brain with the implantable device 110

Wirelessly transmit the sampled EEG signals from the implantable device to an external device 112

Store the sampled EEG signals in a memory 114

END

FIG. 7
START

Implant a set of implantable devices beneath at least one layer of the patient's scalp and above the patient's cranium 122

Sample EEG signals with the set of implantable devices 124

Analyze the sampled EEG signals to lateralize the seizure focus 126

Identify a subset of the implantable devices that are lateralized to the seizure focus 128

Store the sampled EEG signals in a memory 130

Process the EEG signals from the subset of implantable devices to analyze the patient's epilepsy 132

END

FIG. 8
Minimally invasively inject one or more implantable devices in a patient 142

Sample EEG signals from the patient's brain with the implantable device(s) 144

Wirelessly transmit the sampled EEG signals from the implantable device to an external device 146

Store the sampled EEG signals in a memory 148

Analyze the EEG signals to derive statistics for the clinical and/or sub-clinical seizures for the patient 150

Generate a report regarding the statistics 152

END

FIG. 9
Minimally invasively implant one or more implantable devices in a patient 162

Use the one or more implantable devices to monitor the patient's EEG to obtain a baseline seizure activity data for the patient 164

Commence therapy 166

Use the one or more implantable devices to monitor the patient's EEG to obtain follow up seizure activity data for the patient 168

Compare the baseline data and the follow up data to evaluate the efficacy of the therapy 170

Change at least one parameter of the therapy 172 (Optional)

END

FIG. 10
Minimally invasively implant one or more implantable devices in a patient

Commence first efficacious therapy with first parameters

Monitor and process the patient's EEG to obtain a first patient data for the patient

Stop first efficacious therapy and commence therapy with second parameters

Monitor and process the patient's EEG to obtain second patient data for the patient

Stop therapy with second parameters

Commence therapy with nth parameters

Monitor and process the patient's EEG to obtain nth patient data for the patient

Analyze first patient data, second patient data, ...nth patient data to determine optimal parameters for therapy

END

FIG. 11
Enroll participants in a clinical trial

Implant the participants with one or more implantable devices

Use the one or more implantable devices to monitor the EEG of the participants in the patient population to obtain a baseline seizure activity data for the participants

Commence experimental therapy

Use the one or more implantable devices to monitor the participants' EEG to obtain follow up seizure activity data for the participants

Compare the baseline data and the follow up data to evaluate the efficacy of the experimental therapy for the patient population

FIG. 12
Enroll participants in a clinical trial

Implant the participants with one or more implantable devices

Use the one or more implantable devices to monitor the EEG of the participants in the patient population to obtain a baseline seizure activity data or other baseline data measurement for the participants

Commence experimental therapy in an intervention group of the patient population

Commence placebo therapy in an control group of the patient population

Use the one or more implantable devices to monitor the EEG of the intervention group to obtain follow up seizure activity data for the intervention group

Use the one or more implantable devices to monitor the EEG of the control group to obtain follow up seizure activity data for the control group

Compare the baseline data and the follow up data for both the intervention group and the control group to evaluate the efficacy of the experimental therapy for the patient population

FIG. 13
METHODS AND SYSTEMS FOR FACILITATING CLINICAL TRIALS
CROSS-REFERENCED TO RELATED APPLICATIONS

[0001] The present application claims benefit of U.S. Provisional Patent Application Ser. No. 60/805,710, filed Jun. 23, 2006, to Harris et al., entitled "Implantable Ambulatory Brain Monitoring System," the complete disclosure of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] The present invention relates generally to methods for sampling one or more physiological signals from a patient. More specifically, the present invention relates to long term, ambulatory monitoring of one or more neurological signals from a patient using a minimally invasive methods and systems in a clinical trial.

[0003] Epilepsy is a disorder of the brain characterized by chronic, recurring seizures. Seizures are a result of uncontrolled discharges of electrical activity in the brain. A seizure typically manifests itself as sudden, involuntary, disruptive, and often destructive sensory, motor, and cognitive phenomena. Seizures are frequently associated with physical harm to the body (e.g., tongue biting, limb breakage, and burns), a complete loss of consciousness, and incontinence. A typical seizure, for example, might begin as spontaneous shaking of an arm or leg and progress over seconds or minutes to rhythmic movement of the entire body, loss of consciousness, and voiding of urine or stool.

[0004] A single seizure most often does not cause significant morbidity or mortality, but severe or recurring seizures (epilepsy) results in major medical, social, and economic consequences. Epilepsy is most often diagnosed in children and young adults, making the long-term medical and societal burden severe for this population of patients. People with uncontrolled epilepsy are often significantly limited in their ability to work in many industries and usually cannot legally drive an automobile. An uncommon, but potentially lethal form of seizure is called status epilepticus, in which a seizure continues for more than 30 minutes. This continuous seizure activity may lead to permanent brain damage, and can be lethal if untreated.

[0005] While the exact cause of epilepsy is often uncertain, epilepsy can result from head trauma (such as from a car accident or a fall), infection (such as meningitis), or from neoplastic, vascular or developmental abnormalities of the brain. Most epilepsy, especially most forms that are resistant to treatment (i.e., refractory), are idiopathic or of unknown causes, and is generally presumed to be an inherited genetic disorder.

[0006] While there is no known cure for epilepsy, the primary treatment for these epileptic patients are a program of one or more anti-epileptic drugs or "AEDs." Chronic usage of anticonvulsant and antiepileptic medications can control seizures in most people. An estimated 70% of patients will respond favorably to their first AED monotherapy and no further medications will be required. However, for the remaining 30% of the patients, their first AED will fail to fully control their seizures and they will be prescribed a second AED—often in addition to the first—even if the first AED does not stop or change a pattern or frequency of the patient’s seizures. For those that fail the second AED, a third AED will be tried, and so on. Patients who fail to gain control of their seizures through the use of AEDs are commonly referred to as "medically refractory."

[0007] For those patients with infrequent seizures, the problem is further compounded by the fact that they must remain on the drug for many months before they can discern whether there is any benefit. As a result, physicians are left to prescribe AEDs to these patients without clear and timely data on the efficacy of the medication. Because these drugs are powerful neural suppressants and are associated with undesirable side-effects and sedation, it is important to minimize the use and dosage of these drugs if the patient is not experiencing benefit.

[0008] A major challenge for physicians treating epileptic patients is gaining a clear view of the effect of a medication or incremental medications. Presently, the standard metric for determining efficacy of the medication is for the patient or for the patient’s caregiver to keep a diary of seizure activity. However, it is well recognized that such self-reporting is often of poor quality because patients often do not realize when they have had a seizure, or fail to accurately record seizures. In addition, patients often have "sub-clinical" seizures where the brain experiences a seizure, but the seizure does not manifest itself clinically, and the patient has no way of making note of such seizures.

[0009] The "patient diary" problem similarly plagues companies that are developing new, experimental AEDs or electrical stimulation therapies. The current standard that is used to determine the effectiveness of the experimental AEDs and electrical stimulation therapy is through the self-reporting of seizure count using a patient diary. Because such a metric is so unreliable, clinical trials for experimental AEDs and stimulation therapies require very large sample populations, which increase the cost of development of the AEDs and stimulation therapies and increases the time it takes to bring the new AEDs and stimulation therapies to the market. Furthermore, such clinical trials typically enroll patients who have high a high frequency of seizure occurrence so as to provide a sufficient number of seizures so that it is possible to determine the efficacy of the experimental therapy. However, such a patient population is not necessarily reflective of target patient population who will be actually using the experimental therapy when the therapy reaches the market.

[0010] Consequently, what are needed are methods and systems that are capable of long-term, out-patient monitoring of epileptic patients. It would further be desirable if the long-term monitoring could be processed into appropriate metrics that can quantify the clinical benefit of the medication or other therapies. It would also be desirable to have system that could record seizure activity, to enable the meaningful study of patients with infrequent seizures. It would further be desirable if such methods and systems were minimally invasive so as to be appropriate for use in monitoring patients in a clinical trial.

SUMMARY OF THE INVENTION

[0011] The present invention provides methods and systems for monitoring one or more physiological signals from the patient. In preferred embodiments, the present invention
provides minimally-invasive systems that provide for the long-term, ambulatory monitoring of patient’s brain activity. The systems of the present invention will typically include one or more implantable devices that are capable of sampling and transmitting a signal that is indicative of the patient’s brain activity to a data collection device that is external to the patient’s body. The ambulatory systems of the present invention provide for substantially continuous sampling of brain wave electrical signals (e.g., electroencephalography or “EEG” and electrocorticogram “ECoG”, which are hereinafter referred to collectively as “EEG”).

[0012] A patient could wear their external data collection device at all times of the day (except while showering, etc.). At the physician’s office, the data from the external data collection device could be uploaded into a physician’s computer, which could then automatically analyze the stored EEG data and calculate certain metrics that would provide insight into the patient’s condition. For example, such metrics may allow the epileptologist to assess seizure frequency, monitor for sub-clinical seizures, determine the efficacy of the experimental treatment, determine the effect of any adjustments of the dosage of the experimental AED, determine the effects of adjustments of parameters of the electrical stimulation, assess the toxicity, long-term side-effects, dosing requirements of the AED, or the like.

[0013] The methods of the present invention typically make use of one or more low power implantable devices for minimally invasively sampling the patient’s EEG signal. The implantable devices are in communication with a device that is external to the patient’s body. The external device is typically configured to transmit power into the implantable device and to store the EEG signal that is sampled by the implantable device. The implantable device and the external device will be in communication with each other through a wireless communication link. While any number of different wireless communication links may be used, in preferred embodiments the systems of the present invention use a high-frequency communication link. Such a communication link enables transmission of power into the implantable device and facilitates data transfer to and from the implantable device.

[0014] In one aspect, the present invention provides a method of evaluating an experimental therapy for a patient population in a clinical trial. The method comprises minimally invasively implanting patients with one or more devices that are configured to measure a physiological signal from the patients. The physiological signals from the patients for a first time period are processed to obtain a first patient data. The physiological signals are measured from the patients after the patients have commenced the experimental therapy. Thereafter, the physiological signals that were measured after the commencement of the experimental therapy are processed to obtain a second patient data. The experimental therapy may be evaluated by analyzing the first patient data with the second patient data.

[0015] In some embodiments, the experimental therapy comprises a pharmacological agent, such as an AED. The methods of the present invention may be used to evaluate the efficacy, dosing requirements, toxicity and side effects of the experimental therapy on the patient population (and subgroups of the patient population). In other embodiments, the experimental therapy may comprise electrical stimulation. The electrical stimulation may comprise cortical stimulation, deep brain stimulation, cranial nerve stimulation, peripheral nerve stimulation (e.g., vagus nerve), or the like.

[0016] In some embodiments, the one or more devices are leadless and are implanted between at least one layer of the scalp and the skull. The one or more leadless devices may be in wireless communication with an external device and may transcutaneously transmit a data signal that is encoded with data that is indicative of the sampled physiological signal. Thereafter, the data may be stored in memory (of the external device or some other device).

[0017] The physiological signal is typically an EEG signal, but could be any other type of physiological signal that is measurable from the patient, such as temperature, body movement acceleration, chemical concentration in blood or tissue, or the like.

[0018] One particular usage of the methods of the present invention is for assessing therapies for epileptic patients. In such uses, the physiological signal is typically the EEG and the first patient data and second patient data comprise seizure statistics for the patients in the clinical trial. For example, the first patient data is typically considered to be the patient’s “baseline” activity. The second patient data (which is obtained after the patient has commenced the therapy) is used to determine if there were any quantifiable (e.g., statistically significant) changes to the baseline activity data. Because the system is able to substantially continuously monitor each of the patient’s EEG signals for the baseline time period and during the therapy time period, instead of relying on the patient diaries, the present invention is able to monitor and record actual data from the patient and provide quantifiable measurements to the physicians running the clinical trial. Some examples of the quantifiable seizure activity information that may be recorded and statistically analyzed include, but is not limited to, a number of clinical seizures during the time period, a number of subclinical seizures during the time period, seizure duration, seizure patterns, seizure frequency, and time of seizure occurrence. Such seizure activity information may be calculated for the first time period and second time period and statistically compared.

[0019] In some cases, it may be desirable to change at least one parameter of the therapy after the second time period has finished. In such embodiments, the parameter may be changed and the physiological signals may be monitored for a third time period. The physiological signals obtained during the third time period may be processed to obtain a third patient data. The experimental therapy may thereafter be evaluated by comparing the third patient data with the second patient data and/or the first patient data.

[0020] The parameter change may be any desired parameter. For pharmacological therapy, the parameter may be dosage, formulation, dosing frequency, form, or the like. For electrical stimulation, the parameter change may include frequency, pulse amplitude, pulse width, pulses per burst, burst frequency, burst/no-burst, duty cycle, etc.

[0021] In another aspect, the present invention provides a method of evaluating efficacy of an experimental pharmacological agent on a patient population in a clinical trial. The method comprises enrolling a patient population in the clinical trial and implanting the patient population with one
or more leadless devices between a patient’s skull and scalp that are configured to measure brain activity signals. Brain activity signals are measured for a baseline time period and the brain activity signals for the baseline time period are processed to obtain baseline data of the patient population. The patient population is then instructed to commence a treatment regimen of the pharmacological agent and brain activity signals are measured in the patient population for a desired time period after the patient population has commenced the pharmacological agent treatment regimen and the brain activity signals in the patient population for the desired time period are processed to obtain follow-up data of the patient population. The pharmacological agent is evaluated by comparing the baseline data and the follow-up data.

[0022] The methods of the present invention may be used to evaluate the efficacy, dosing requirements, toxicity and side effects of the experimental therapy on the patient population (and sub-groups of the patient population).

[0023] In some embodiments, the methods of the present invention are for evaluating pharmacological agents that are for managing seizures. The leadless devices may be configured to transcutaneously transmit the measured brain activity signals through a wireless communication link to a device that is external to the patient’s body. The brain activity signals may be stored in the external device. The stored data may be processed to extract seizure activity data from the brain activity signals. The seizure activity data includes, but is not limited to: clinical seizures during the time period, a number of sub-clinical seizures during the time period, average seizure duration, seizure patterns, seizure frequency, and time of seizure occurrence, etc. Once the data has been extracted, the baseline seizure activity data may be compared with the follow-up seizure activity data to evaluate the therapy.

[0024] In some cases, it may be desirable to change at least one parameter of the pharmacological agent therapy after the follow up time period has finished. In such embodiments, the parameter may be changed and the brain activity signals may be monitored for a desired time period. The brain activity signals obtained during the subsequent time period may be processed to obtain a subsequent patient data. The pharmacological agent therapy may thereafter be evaluated by comparing the subsequent patient data with the follow-up patient data and/or the baseline data. The parameter change may be any desired parameter of the pharmacological agent. For pharmacological therapy, the parameter may be dosage, formulation, dosing frequency, form, or the like.

[0025] In a further aspect, the present invention provides a method of evaluating an experimental therapy for a patient population in a clinical trial. The method comprises minimally invasively implanting the patient population with one or more devices (e.g., between the skull and at least one layer of the scalp) that are configured to measure a physiological signal from a patient and processing the physiological signal from the patient population for a baseline period to obtain a first patient data. A placebo therapy is commenced in a control group of the patient population and the experimental therapy is commenced in an intervention group of the patient population. The physiological signal from the control group and the intervention group are measured for a second time period after the patients’ have commenced the placebo therapy and experimental therapy, respectively. The physiological signals obtained during the second time period are processed to obtain a second patient data. The experimental therapy is evaluated by analyzing the first patient data and the second patient for both the control group and the intervention group.

[0026] In yet another aspect, the present invention provides a method of evaluating an experimental anti-epileptic drug (AED) therapy for a patient population in a clinical trial. The method comprises enrolling a patient population in the clinical trial and minimally invasively implanting one or more devices between the patient’s skull and scalp that are configured to substantially continuously sample an EEG signal from the patient for a baseline period. A signal encoded with the sampled EEG signals is wirelessly transmitted to a portable device that is external to the patient. The EEG signal from the patients is processed to obtain a seizure activity baseline for the patients in the patient population. The patient population are separated into a control group and an intervention group and a placebo AED therapy is commenced in the control group of the patient population and the experimental AED therapy is commenced in the intervention group of the patient population. The EEG signals from the control group and the intervention group are substantially continuously sampled with the implanted one or more devices for a selected time period after the patients have commenced the placebo therapy and experimental therapy, respectively. The EEG signals from the patients from the selected time period are processed to obtain a seizure activity outcome data. The experimental AED therapy is evaluated by comparing the baseline seizure activity data with the seizure activity outcome data for both the control group and the intervention group.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0028] FIG. 1A illustrates a simplified system embodying the present invention which comprises one or more implantable devices in communication with an external device.

[0029] FIG. 1B illustrates simplified methods of operating the system of the present invention.

[0030] FIG. 2A illustrates a bottom view of one embodiment of an active implantable device that is encompassed by the present invention.

[0031] FIG. 2B illustrates a cross-sectional view of the active implantable device of FIG. 2A along lines B-B.

[0032] FIG. 2C is a linear implantable device that comprises a plurality of electrode contacts in which at least one electrode contact comprises the active implantable device of FIG. 2A.

[0033] FIG. 2D is a cross sectional view of the implantable device of FIG. 2C along lines D-D.

[0034] FIG. 2E is a 4×4 electrode array that comprises a plurality of electrode contacts in which at least one electrode contact comprises the active implantable contact of FIG. 2A.
FIG. 3A is a cross-sectional view of another embodiment of an implantable device that is encompassed by the present invention.

FIG. 3B is a cross-sectional view of another embodiment of the implantable device in which a conductive layer forms a housing around the electronic components and acts as an electrode.

FIG. 3C illustrates a simplified plan view of an embodiment that comprises four electrodes disposed on the implantable device.

FIG. 4 illustrates one embodiment of the electronic components that may be disposed within the implantable device.

FIG. 5 is a block diagram illustrating one embodiment of electronic components that may be in the external device.

FIG. 6 illustrates a simplified trocar or needle-like device that may be used to implant the implantable device beneath the patient’s skin.

FIG. 7 illustrates a method of inserting an implantable device in the patient and wirelessly sampling EEG signals from a patient.

FIG. 8 illustrates a method of lateralizing a seizure focus.

FIG. 9 illustrates a method of measuring seizure activity data for clinical and/or sub-clinical seizures.

FIG. 10 illustrates a method of evaluating efficacy of a therapy.

FIG. 11 illustrates a method of titrating an efficacious therapy.

FIG. 12 illustrates a simplified method of performing a clinical trial.

FIG. 13 illustrates a more detailed method of performing a clinical trial.

FIG. 14 is a kit that is encompassed by the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Certain specific details are set forth in the following description and figures to provide an understanding of various embodiments of the invention. Certain well-known details, associated electronics and devices are not set forth in the following disclosure to avoid unnecessarily obscuring the various embodiments of the invention. Further, those of ordinary skill in the relevant art will understand that they can practice other embodiments of the invention without one or more of the details described below. Finally, while various processes are described with reference to steps and sequences in the following disclosure, the description is for providing a clear implementation of particular embodiments of the invention, and the steps and sequences of steps should not be taken as required to practice this invention.

The term “condition” is used herein to generally refer to the patient’s underlying disease or disorder—such as epilepsy, depression, Parkinson’s disease, headache disorder, etc. The term “state” is used herein to generally refer to calculation results or indices that are reflective of or indicate a particular point along a trajectory or state space that reflects the patient’s condition. The estimation of the patient’s state is of significant interest and may be used to determine the efficacy of a therapy or the need to adjust a treatment regimen.

The estimation of the patient’s state is also of significant interest and may be used to determine the onset of a seizure or other neurological event. The estimation of the patient’s state may be used to identify the onset of a seizure or other neurological event by comparing the estimated state to a threshold value. The estimation of the patient’s state may also be used to determine the efficacy of a therapy or the need to adjust a treatment regimen.

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patient’s brain activity. In one preferred embodiment, the system of the present invention may be used to monitor and store one or more substantially continuously sampled EEG signals from the patient, while providing a minimal inconvenience to the patient. Attempts at developing ambulatory monitoring systems in the past have relied on an array of electrodes being placed on the patient’s head and scalp with adhesive. Unfortunately, such systems are poorly tolerated by patients and are impractical for the duration of time needed for the accurate evaluation of the patient’s EEG and evaluation of the efficacy of the treatment the patients are undergoing. Unlike conventional ambulatory EEG systems, the ambulatory monitoring systems of the present invention typically include one or more devices that are implanted in a minimally invasive fashion in the patient and will be largely unnoticed by a patient as they go about their day-to-day activities. The implantable devices may be in wireless communication with an external device that may be carried by the patient or kept in close proximity to the patient. Consequently, the ambulatory monitoring systems of the present invention are conducive to longer, more effective monitoring of the patient (e.g., one week or longer, one month or longer, two months or longer, three months or longer, six months or longer, one year or longer, etc.).

[0056] The methods, devices and systems of the present invention may also find use in an emergency room or neurological intensive care units (ICU). For example, the systems may be used to monitor patients who have complex, potentially life-threatening neurological illnesses or brain injuries. Neuro ICUs may monitor patients who have suffered (or thought to have suffered) a stroke (e.g., cerebral infarction, transient ischemic attack, intracerebral hemorrhage, aneurysmal subarachnoid hemorrhage, arteriovenous malformations, dural sinus thrombosis, etc.), head trauma, spinal cord injury, tumors (e.g., spinal cord metastases, paraplegic syndromes), infections (e.g., encephalitis, meningitis, brain abscess), neuromuscular weaknesses (e.g., Guillain-Barre syndrome, myasthenia gravis), eclampsia, neuropathic malignant syndrome, CNS vasculitis, migraine headaches, or the like.

[0057] The neuro-ICUs require the ability to monitor the patient’s neurological condition for a long period of time to identify issues and diagnose the patient before permanent neurological damage occurs. Because the systems of the present invention are able to provide real-time monitoring of a patient’s EEG and many embodiments have the ability to detect or predict neurological events, such systems will be beneficial to patients and the staff of the ICU to allow the neurologist and support staff to detect and/or prevent complications that may arise from the patient’s neurological condition, before the patient’s condition deteriorates.

[0058] For example, a patient who is suffering from head trauma may be outfitted with a system of the present invention and because the implantable portions are MRI safe, the patient’s may still undergo MRI sessions. Furthermore, the systems of the present invention may also be used to continuously monitor a patient’s response to a drug therapy while the patient is in the neuro-ICU and when the patient leaves the neuro-ICU.

[0059] For epilepsy patients in particular, the monitoring systems of the present invention may be used in conjunction with, or as an alternative to, the in-patient video-EEG monitoring that occurs in the EMU. If used as an alternative to in-patient video-EEG monitoring, in some embodiments it may be desirable to provide one or more video recorders in the patient’s home to provide time-synced video recording of the patient as they live with their ambulatory monitoring system. In some embodiments, it may be desirable to provide a patient-mounted video system so as to allow video-monitoring of the patient outside of their home. Such a video system may or may not be in communication with the ambulatory monitoring system of the present invention; but both the video and the monitored EEG signals should be time-synced and analyzed together by the physician to assess the patient’s condition and/or efficacy of any therapy that the patient may be undergoing.

[0060] The systems and methods of the present invention may incorporate EEG analysis software to estimate and monitor the patient’s brain state substantially in real-time. The EEG analysis software may include a safety algorithm, a seizure prediction algorithm and/or a seizure detection algorithm that uses one or more extracted features from the EEG signals (and/or other physiological signals) to estimate the patient’s brain state (e.g., predict or detect the onset of a seizure). Additionally, some systems of the present invention may be used to facilitate delivery of a therapy to the patient to prevent the onset of a predicted seizure and/or abort or mitigate a seizure after it has started. Facilitation of the delivery of the therapy may be carried out by outputting a warning or instructions to the patient or automatically delivering a therapy to the patient (e.g., pharmacological, electrical stimulation, etc.). The therapy may be delivered to the patient using the implanted devices that are used to collect the ambulatory signals, or it may be delivered to the patient through a different implanted device. A description of some systems that may be used to deliver a therapy to the patient are described in commonly owned U.S. Pat. Nos. 6,366,313 and 6,819,956, U.S. Patent Application Nos. 2005/0021103 (published Jan. 27, 2005), 2005/0119603 (published Jan. 27, 2005), 2005/0021104 (published Jan. 27, 2005), 2005/0240242 (published Oct. 27, 2005), 2005/0222626 (published Oct. 6, 2005) and U.S. patent application Ser. No. 11/282,317 (filed Nov. 17, 2005), Ser. Nos. 11/321,897, 11/321,898, and 11/322,150 (all filed Dec. 28, 2005), the complete disclosures of which are incorporated herein by reference.

[0061] For patients suspected or known to have epilepsy, the systems of the present invention may be used to provide data and other metrics to the patients and physicians that heretofore have not been accurately measurable. For example, the data may be analyzed to (1) determine whether or not the patient has epilepsy, (2) determine the type of epilepsy, (3) determine the types of seizures, (4) localize or lateralize one or more seizure foci, (5) assess baseline seizure statistics and/or change from the baseline seizure statistics (e.g., seizure count, frequency, duration, seizure pattern, etc.) (6) monitor for sub-clinical seizures, assess a baseline frequency of occurrence, and/or change from the baseline occurrence, (7) measure the efficacy of AED treatments, (8) assess the effect of adjustments of the dosage of the AED, (9) determine the effects of adjustments of the type of AED, (10) determine the effect of, and the adjustment to parameters of, electrical stimulation (e.g., vagus nerve stimulation (VNS), deep brain stimulation (DBS), cortical stimulation, etc.), (11) determine “triggers” for the patient’s seizures, (12) assess outcomes from surgical procedures,
(13) provide immediate biofeedback to the patient, (14) screen patients for determining if they are an appropriate candidate for a seizure advisory system or other neurological monitoring or therapy system, or the like.

[0062] The systems of the present invention typically include one or more implantable devices that are in wireless communication with an external data collection device, typically with a high frequency communication link. The implantable devices of the present invention are typically implanted in a minimally invasive fashion beneath at least one layer of the scalp, above the patient’s skull/calvarium, and over one or more target area of the patient’s brain. As will be described in more detail below, the implantable devices are typically injected underneath the skin/scalp using an introducer, trocar or syringe-like device using local anesthesia. It is contemplated that such a procedure could be completed in 20 to 30 minutes by a physician or neurologist in an out-patient procedure.

[0061] The implantable devices are typically used to continuously sample the physiological signals for a desired time period so as to be able to monitor fluctuations of the physiological signal over substantially the entire time period. In alternative embodiments, however, the implantable devices may be used to periodically sample the patient’s physiological signals or selectively/a periodically monitor the patient’s physiological signals.

[0064] The implantable devices may be permanently or temporarily implanted in the patient. If permanently implanted, the devices may be used for as long as the monitoring is desired, and once the monitoring is completed, because the implanted devices are biocompatible they may remain permanently implanted in the patient without any long term detrimental effects for the patient. However, if it is desired to remove the implanted devices, the devices may be explanted from the patient under local anesthesia. For ease of removal, it may be desirable to tether or otherwise attach a plurality of the implantable devices together (e.g., with a suture or staple) so that a minimal number of incisions are needed to explant the implantable devices.

[0065] Exact positioning of the implanted devices will usually depend on the desired type of monitoring. For patients who are being monitored for epilepsy diagnosis, the suspected type of epilepsy may affect the positioning of the implantable devices. For example, if the patient is thought to have temporal lobe epilepsy, a majority of the implantable devices will likely be located over the patient’s temporal lobe. Additionally, if the focus of the seizure is known, it may be desirable to place a plurality of implantable devices directly over the focus. However, if the focus has not been localized, a plurality of implantable devices may be spaced over and around the target area of the patient’s brain (and one or more implantable devices contralateral to the target area) in an attempt to locate or lateralize the seizure focus.

[0066] The number of implantable devices that are implanted in the patient will depend on the number of channels that the physician wants to concurrently monitor in the patient. Typically however, the physician will implant 2 or less, and preferably between about 2 and about 16 implantable devices, and most preferably between about 4 and about 8 implantable devices. Of course, in some instances, it may be desirable to implant more or less, and the present invention is not limited to the aforementioned number of implanted devices.

[0067] While the remaining discussion focuses on methods of using the systems and devices of the present invention for ambulatory monitoring of EEG signals of patients and patient populations for the diagnosis of epilepsy and/or evaluation of the efficacy and dosing of the patient’s AEDs, it should be appreciated that the present invention is not limited to sampling EEG signals for epilepsy or for monitoring the efficacy of AEDs. For example, the implanted devices may be implanted under the skin of the patient’s face, within the muscle of the patient’s face, within the skull, above the jaw (e.g., sphenoidal implant that is placed under the skin just above the jaw to monitor the brain activity in the temporal lobes), or any other desired place on the patient’s body. Furthermore, in addition to or as an alternative to monitoring EEG signals from the patient, it may be desired to monitor other physiological signals from a patient. For example, the system of the present invention may be used to monitor one or more of a blood pressure, blood oxygenation, temperature of the brain or other portion of the patient, blood flow measurements in the brain or other parts of the body, ECG/EKG, heart rate signals and/or change in heart rate signals, respiratory rate signals and/or change in respiratory rate signals, chemical concentrations of medications, pH in the blood or other portions of the body, other vital signs, other physiological or biochemical parameters of the patient’s body, or the like.

[0068] Furthermore, the systems of the present invention may be useful for monitoring and assisting in the analysis of treatments for a variety of other neurological conditions, psychiatric conditions, episodic and non-episodic neurological phenomenon, or other non-neurological and non-psychiatric maladies. For example, the present invention may be useful for patients suffering from sleep apnea and other sleep disorders, migraine headaches, depression, Alzheimer’s, Parkinson’s Disease, eating disorders, dementia, attention deficit disorder, stroke, cardiac disease, diabetes, cancer, or the like. Likewise, the present invention may also be used to assess the symptoms, efficacy of pharmacological and electrical therapy on such disorders.

[0069] Referring now to the Figures, FIG. 1A illustrates a simplified system 10 embodied by the present invention. System 10 includes one or more implantable devices 12 that are configured to sample electrical activity from the patient’s brain (e.g., EEG signals). The implantable devices may be active (with internal power source), passive (no internal power source), or semi-passive (internal power source to power components, but not to transmit data signal). The implantable devices 12 may be implanted anywhere in the patient, but typically one or more of the devices 12 may be implanted adjacent a previously identified epileptic focus or a portion of the brain where the focus is believed to be located. Alternatively, the devices 12 themselves may be used to help determine the location of the epileptic focus.

[0070] The physician may implant any desired number of devices in the patient. As noted above, in addition to monitoring brain signals, one or more additional implanted devices 12 may be implanted to measure other physiological signals from the patient.

[0071] While it may be possible to implant the implantable devices 12 under the skull and in or on the brain, it is preferred to implant the implantable devices 12 in a minimally invasive fashion under at least one layer of the
patient’s scalp and above the skull. Implantable devices 12 may be implanted between any of the layers of the scalp (sometimes referred to herein as “sub-galeal”). For example, the implantable devices may be positioned between the skin and the connective tissue, between the connective tissue and the epicranius aponeurosis/galea aponeurotica, between the epicranius aponeurosis/galea aponeurotica and the loose aerolar tissue, between the loose aerolar tissue and the pericranium, and/or between the pericranium and the calvarium. In some configurations, it may be useful to implant different implantable devices 12 between different layers of the scalp.

Implantable devices 12 will typically be configured to substantially continuously sample the brain activity of the groups of neurons in the immediate vicinity of the implanted device. In some embodiments, if placed below the skull and in contact with the cortical surface of the brain, the electrodes may be sized to be able to sample activity of a single neuron in the immediate vicinity of the electrode (e.g., a microelectrode). Typically, the implantable device 12 will be interrogated and powered by a signal from the external device to facilitate the substantially continuous sampling of the brain activity signals. Sampling of the brain activity is typically carried out at a rate above about 200 Hz, and preferably between about 200 Hz and about 1000 Hz, and most preferably at about 400 Hz, but it could be higher or lower, depending on the specific condition being monitored, the patient, and other factors. Each sample of the patient’s brain activity will typically contain between about 8 bits per sample and about 32 bits per sample, and preferably between about 12 bits per sample and about 16 bits per sample. Thus, if each return communication transmission to the external device includes one EEG sample per transmission, and the sample rate is 400 Hz and there are 16 bits/sample, the data transfer rate from the implantable devices 12 to the external device 14 is at least about 6.4 Kbits/second. If there are 32 implantable devices, the total data transfer rate for the system 10 would be about 205 Kbits/second. In alternative embodiments, it may be desirable to have the implantable devices sample the brain activity of the patient in a non-continuous basis. In such embodiments, the implantable devices 12 may be configured to sample the brain activity signals periodically (e.g., once every 10 seconds) or a periodically.

Implantable device 12 may comprise a separate memory module for storing the recorded brain activity signals, a unique identification code for the device, algorithms, other programming, or the like.

A patient instrumented with the implanted devices 12 will typically carry a data collection device 14 that is external to the patient’s body. The external device 14 would receive and store the signal from the implanted device 12 with the encoded EEG data (or other physiological signals). The external device is typically of a size so as to be portable and carried by the patient in a pocket or bag that is maintained in close proximity to the patient. In alternative embodiments, the device may be configured to be used in a hospital setting and placed alongside a patient’s bed. Communication between the data collection device 14 and the implantable device 12 typically takes place through wireless communication. The wireless communication link between implantable device 12 and external device 14 may provide a communication link for transmitting data and/or power.

External device 14 may include a control module 16 that communicates with the implanted device through an antenna 18. In the illustrated embodiment, antenna 18 is in the form of a necklace that is in communication range with the implantable devices 12. It should be appreciated however, that the configuration of antenna 18 and control module 16 may be in a variety of other conventional or proprietary forms. For example, in another embodiment control module 16 may be attached around an arm or belt of the patient, integrated into a hat, integrated into a chair or pillow, and/or the antenna may be integrated into control module 16.

In order to facilitate the transmission of power and data, the antenna of the external device and the implantable devices must be in communication range of each other. The frequency used for the wireless communication link has a direct bearing on the communication range. Typically, the communication range is between at least one foot, preferably between about one foot and about twenty feet, and more preferably between about six feet and sixteen feet. As can be appreciated, however, the present invention is not limited to such communication ranges, and larger or smaller communication ranges may be used. For example, if an inductive communication link is used, the communication range will be smaller than the aforementioned range.

In some situations, it may be desirable, to have a wire running from the patient-worn data collection device 14 to an interface (not shown) that could directly link up to the implanted devices 12 that are positioned below the patient’s skin. For example, the interface may take the form of a magnetically attached transducer, as with cochlear implants. This could enable power to be continuously delivered to the implanted devices 12 and provide for higher rates of data transmission.

In some configurations, system 10 may include one or more intermediate transponder (not shown) that facilitates data transmission and power transmission between implantable device 12 and external device 14. The intermediate transponder may be implanted in the patient or it may be external to the patient. If implanted, the intermediate transponder will typically be implanted between the implantable device 12 and the expected position of the external device 14 (e.g., in the neck, chest, or head). If external, the transponder may be attached to the patient’s skin, positioned on the patient’s clothing or other body-worn assembly (e.g., eyeglasses, cellular phone, belt, hat, etc.) or in a device that is positioned adjacent the patient (e.g., a pillow, chair headrest, etc.). The intermediate transponder may be configured to only transmit power, only transmit data, or it may be configured to transmit both data and power. By having such intermediate transponders, the external device 14 may be placed outside of its normal communication range from the implanted devices 12 (e.g., on a patient’s belt or in a patient’s bag), and still be able to substantially continuously receive data from the implantable device 12 and/or transmit power to the implantable device 12.

Transmission of data and power between implantable device 12 and external device 14 is typically carried out through a radiofrequency link, but may also be carried out through magnetic induction, electromagnetic link, Bluetooth® link, Zigbee link, sonic link, optical link, other types of wireless links, or combinations thereof.

One preferred method 11 of wirelessly transmitting data and power is carried out with a radiofrequency link,
similar to the link used with radiofrequency identification (RFID) tags. As illustrated in FIGS. 1A and 1B, in such embodiments, one or more radio frequency signals are emitted from the external device 14 through antenna 18 (step 13). If the external device 14 is in communication range of the implantable devices, at step 15 the radiofrequency (RF) energy signal illuminates the passive, implantable devices 12.

[0080] At step 17 the same RF signal interrogates the energized implantable device 12 to allow the implantable device to sample the desired physiological signal from the patient (such as an EEG signal). At step 19, the implantable device samples the instantaneous EEG signal (or other physiological signal) from the patient.

[0081] At step 21, the implantable device 12 then communicates a return RF signal to the external device 14 that is encoded with data that is indicative of the sampled EEG signal. Typically, the return RF signal is based on the RF signal generated by the external device and includes detectable modifications which indicate the sampled EEG signal. For example, the return signal is typically a backscattering of the RF signal from the external device with the detectable modifications that indicate the sampled EEG signal. Advantageously, such backscattering does not require generation of a separate radiating signal and would not require an internal power source. The return RF signals may also include the identification code of the implanted device so as to identify which device the data is coming from. At step 23, the return RF signal emitted by the internal device 12 is received by the antenna 18, and the RF signal is decoded to extract the sampled EEG signal. The sampled EEG signal may thereafter be stored in a memory of the external device 14. For embodiments in which the method is used to collect data, such data will be stored until accessed by the patient. Typically, such data will be analyzed on a separate device (e.g., physician’s computer workstation).

[0082] In alternative embodiments, however, in which the external device may comprise software to analyze the data in substantially real-time, the received RF signal with the sampled EEG may be analyzed by the EEG analysis algorithms to estimate the patient’s brain state which is typically indicative of the patient’s propensity for a neurological event (step 25). The neurological event may be a seizure, migraine headache, episode of depression, tremor, or the like. The estimation of the patient’s brain state may cause generation of an output (step 27). The output may be in the form of a control signal to activate a therapeutic device (e.g., implanted in the patient, such as a vagus nerve stimulator, deep brain or cortical stimulator, implanted drug pump, etc.). In other embodiments, the output may be used to activate a user interface on the external device to produce an output communication to the patient. For example, the external device may be used to provide a substantially continuous output or periodic output communication to the patient that indicates their brain state and/or propensity for the neurological event. Such a communication could allow the patient to manually initiate therapy (e.g., wave band over implanted vagus nerve stimulator, cortical, or deep brain stimulator, take a fast acting AED, etc.) or to make themselves safe.

[0083] In preferred embodiments, the return RF signal is transmitted (e.g., backscattered) immediately after sampling of the EEG signal to allow for substantially real-time transfer (and analysis) of the patient’s EEG signals. In alternate embodiments, however, the return RF signal may be buffered in an internal memory and the communication transmission to the external device 14 may be delayed by any desired time period and may include the buffered EEG signal and/or a real-time sampled EEG signal. The return RF signal may use the same frequency as the illumination RF signal or it may be a different frequency as the illumination RF signal.

[0084] Unlike conventional digital implantable devices that send large packets of stored data with each return RF communication transmission, some embodiment of the methods and devices of the present invention substantially continuously sample physiological signals from the patient and communicate in real-time small amounts of data during each return RF signal communication. Because only small amounts of data (one or a small number of sampled EEG signals from each implantable device 12) are transmitted during each communication, a lower amount of power is consumed and the illumination of the implanted device from the incoming high-frequency RF signal will be sufficient to power the implantable device 12 for a time that is sufficient to allow for sampling of the patient’s EEG signal. Consequently, in most embodiments no internal power source, such as a battery, is needed in the implantable device 12—which further reduces the package size of the implantable device 12.

[0085] The implantable devices 12 and the external devices 14 of the present invention typically use an electromagnetic field/high frequency communication link to both illuminate the implantable device and enable the high data transfer rates of the present invention. Conventional devices typically have an internally powered implantable device and use a slower communication link (e.g., that is designed for long link access delays) and transmit data out on a non-continuous basis. In contrast, some embodiments of the present invention uses a fast access communication link that transmits a smaller bursts of data (e.g., single or small number of EEG sample at a time) on a substantially continuous basis.

[0086] The frequencies used to illuminate and transfer data between the implantable devices 12 and external device are typically between 13.56 MHz and 10 GHz, preferably between 402 MHz and 2.4 GHz, more preferably between 900 MHz and 2.4 GHz. While it is possible to use frequencies above 2.4 GHz, Applicants have found that it is preferred to use a frequency below 2.4 GHz in order to limit attenuation effects caused by tissue. As can be appreciated, while the aforementioned frequencies are the preferred frequencies, the present invention is not limited to such frequencies and other frequencies that are higher and lower may also be used. For example, it may be desirable to use the MICS (Medical Implant Communication Service band) that is between 402-405 MHz to facilitate the communication link in Europe, it may be desirable to use ETSI RFID allocation 869.4-869.65 MHz.

[0087] While not illustrated in FIG. 1B, the system 10 of the present invention may also make use of conventional or proprietary forward error correction (“FEC”) methods to control errors and ensure the integrity of the data transmitted from the implantable device 12 to the external device 14. Such forward error correction methods may include such...
conventional implementations such as cyclic redundancy check ("CRC"), checksums, or the like.

[0088] If desired, the data signals that are wirelessly transmitted from implantable device 12 may be encrypted prior to transmission to the control module 16. Alternatively, the data signals may be transmitted to the control module 16 as unencrypted data, and at some point prior to the storage of the data signals in the control module 16 or prior to transfer of the data signals to the physician’s office, the EEG data may be encrypted so as to help ensure the privacy of the patient data.

[0089] FIGS. 3A and 3B illustrate two embodiments of the externally powered leadless, implantable device 12 that may be used with the system 10 of the present invention. The implantable devices 12 of the present invention are preferably passive or semi-passive and are "slaves" to the "master" external device 14. The implantable devices will typically remain dormant until they are interrogated and possibly energized by an appropriate RF signal from the external device 14. As will be described below, the implantable device 14 may have minimal electronic components and computing power, so as to enable a small package size for the implantable device.

[0090] Advantageously, the embodiment illustrated in FIGS. 3A and 3B is minimally invasive and may be implanted with an introducer, trocar or syringe-like device under local anesthesia by a physician or potentially even a physician’s assistant. Typically, the implantable device of FIG. 3A may have a longitudinal dimension 20 of less than about 3 cm, and preferably between about 1 cm and about 10 cm, and a lateral dimension 22 of less than about 2 mm, and preferably between about 0.5 mm and about 10 mm. As can be appreciated, such dimensions are merely illustrative, and other embodiments of the implantable device may have larger or smaller dimensions.

[0091] FIG. 3A illustrates an embodiment that comprises a first electrode 24 and a second electrode 26 that are disposed on opposing ends of housing 28. The first and second electrodes 24, 26 may be composed of platinum, platinum-iridium alloy, stainless steel, or any other conventional material. The electrodes may include a coating or surface treatment such as platinum-iridium or platinum-black in order to reduce electrical impedance. The first and second electrodes 24, 26 will typically have a smooth or rounded shape in order to reduce tissue erosion and may have a surface area of about 3 mm², but other embodiments may be smaller or larger. Since electrodes 24, 26 are typically adapted to only sense physiological signals and are not used to deliver stimulation, the surface area of the electrodes may be smaller than conventional implantable devices. The smaller electrodes have the advantage of reducing the overall device size which can be beneficial for improving patient comfort and reducing the risk of tissue erosion.

[0092] Housing 28 is typically in the form of a radially symmetrical, substantially cylindrical body that hermetically seals electronic components 30 disposed within a cavity 32. Housing 28 may be composed of a biocompatible material, such as glass, ceramic, liquid crystal polymer, or other materials that are inert and biocompatible to the human body and able to hermetically seal electronic components. Housing 28 may have embedded within or disposed thereon one or more X-ray visible markers 33 that allow for X-ray localization of the implantable device. Alternatively, one or more X-ray visible markers may be disposed within the cavity 32. Cavity 32 may be filled with an inert gas or liquid, such as an inert helium nitrogen mixture which may also be used to facilitate package leakage testing. Alternatively, it may be desirable to fill the cavity 32 with a liquid encapsulant (not shown) that hardens around the electronic components. The liquid encapsulant may comprise silicone, urethane, or other similar materials.

[0093] While housing 28 is illustrated as a substantially cylindrical body with the electrodes 24, 26 on opposing ends, housing may take any desired shape and the electrodes may be positioned at any position/orientation on the housing 28. For example, housing 28 may taper in one direction, be substantially spherical, substantially oval, substantially flat, or the like. Additionally or alternatively, the body may have one or more substantially planar surfaces so as to enhance the conformity to the patient's skull and to prevent rotation of the implantable device 12. While not shown, housing 28 may optionally include a conductive electromagnetic interference shield (EMI) that is configured to shield the electronic components 30 in housing 28. The EMI shield may be disposed on an inner surface of the housing, outer surface of the housing, or impregnated within the housing.

[0094] If desired, housing 28 may optionally comprise an anchoring assembly (not shown) that improves the anchoring of the implantable device 12 to the skull or the layers within the scalp. Such anchoring may be carried out with adhesive, spikes, barbs, protruberances, suture holes, sutures, screws or the like.

[0095] In the illustrated embodiment, first electrode 24 is disposed on a first end of housing 28 and is in electrical communication with the electronic components 30 through a hermetic feedthrough 34. Feedthrough 34 may be the same material as the first electrode 24 or it may be composed of a material that has a similar coefficient of thermal expansion as the housing 28 and/or the first electrode 24. Feedthrough 34 may make direct contact with a pad (not shown) on a printed circuit board 36, or any other type of conventional connection may be used (e.g., solder ball, bond wire, wire lead, or the like) to make an electrical connection to the printed circuit board 36.

[0096] Second electrode 26 may be spaced from a second, opposing end of the housing 28 via an elongated coil member 38. In the illustrated embodiment, the second electrode 26 typically comprises a protruberance 39 that is disposed within and attached to a distal end of the coil member 38. Coil member 38 acts as an electrical connection between second electrode and the electronic components 30 disposed within housing 28.

[0097] Coil member 38 will typically be composed of stainless steel, a high strength alloy such as MP35N, or a combination of materials such as a MP35N outer layer with silver core.

[0098] The illustrated embodiment shows that coil member 38 has a largest lateral dimension (e.g., diameter) that is less than the largest lateral dimension (e.g., diameter) of housing 28, but in other embodiments, the coil may have the same lateral dimension or larger lateral dimension from housing 28.
Coil member 38 may also be used as an antenna to facilitate the wireless transmission of power and data between the implantable device 12 and the external device 14 (or other device). In preferred embodiments, coil member 38 may be used to receive and transmit radiofrequency signals. In alternative embodiments, however, coil member 38 may be inductively coupled to an external coil to receive energy from a modulating, alternating magnetic field. Unlike other conventional implantable devices, the RF antenna is disposed outside of the housing 28 and extends from one end of housing 28. It should be appreciated however, that the present invention is not limited to a substantially cylindrical antenna extending from an end of the housing 28 and various other configurations are possible. For example, it may be desirable to wind the antenna around or within the housing 28. Furthermore, it may be desirable to use a substantially flat antenna (similar to RFID tags) to facilitate the transmission of power and data. To facilitate implantation, such antennas may be rolled into a cylindrical shape and biased to take the flat shape upon release from the introducer.

While not shown, it may also be desirable to provide a second antenna between the first electrode 24 and the housing 28. The second antenna may be used for power and downlink using a first frequency, e.g., 13.56 MHz, while the first antenna may be used for uplink using a second frequency, e.g., 902-928 MHz. In such embodiments, however, the implantable devices would need to have an internal timebase (e.g., oscillator and a frequency synthesizer). For the embodiments that use only a single frequency for the downlink and uplink, an internal timebase or frequency synthesizer is not needed—and the timebase established by the master (e.g., external device 14) can be used.

Coil member 38 may be in electrical communication with the electronic components 30 with a hermetic feedthrough 42 that extends through a via 44 in housing 28. Feedthrough 42 is typically composed of a material that has a coefficient of thermal expansion that is substantially similar to the material of housing 40. Because the coil member 38 is outside of the housing 28 the length of the implantable device 12 will be increased, but the flexible coil will be better exposed to the RF signals and will be allowed to conform to the shape of the patient’s skull.

Coil member 38 is typically disposed outside of the housing 28 and disposed within an elongate, substantially flexible housing 40. Compared to the more rigid housing 28, the flexible housing 40 is better able to conform to the shape of an outer surface of the patient’s skull, more comfortable for the patient and reduces the chance of tissue erosion. Flexible housing 40 may comprise silicone, polyurethane, or the like. In the illustrated embodiment, flexible housing 40 extends along the entire length of coil member 38, but in other embodiments, flexible housing 40 may extend less than or longer than the longitudinal length of coil member 38. Flexible housing 40 will typically have a substantially cylindrical shape, but if desired a proximal end 46 of the cylindrical housing may be enlarged or otherwise shaped to substantially conform to a shape of the housing 28. The shaped proximal end 46 may be adhered or otherwise attached to the end of the housing 40 to improve the hermetic seal of the housing and may reduce any potential sharp edge or transition between the housings 28, 40. While FIG. 3A only illustrates a single layered flexible housing, if desired, the flexible housing 40 may comprise a plurality of layers, and the different layers may comprise different types of materials, have embedded X-ray markers, or the like.

A longitudinal length of flexible housing 40 and the longitudinal length of the rigid housing 28 may vary depending on the specific embodiment, but a ratio of the longitudinal length of the flexible housing 40 to the longitudinal length of the more rigid housing 28 is typically between about 0.5:1 and about 3:1, and preferably between about 1:1 and about 2:1. By having the longitudinal length of the flexible housing longer than the longitudinal length of the rigid housing, advantageously the implantable device will be more comfortable and better able to conform to the outer surface of the patient’s skull. In alternative embodiments, it may also be desirable to have a longitudinal length of the rigid housing 28 be longer than the longitudinal length of the flexible housing 40, or in any other desired configuration.

Because the implantable devices 12 of the present invention consume a minimal amount of energy and use a high frequency RF coupling to power the device and communicate the EEG signals to the external device, unlike other conventional devices, some of the implantable devices 12 of the present invention will not need a ferrite core to store energy, and the electronic components 30 of the present invention will typically include aluminum or other MRI-safe material. Consequently, the patient’s implanted with the implantable device 12 may safely undergo MRI imaging.

FIG. 3B illustrates another embodiment of implantable device 12 that is encompassed by the present invention. The embodiment of FIG. 3B shares many of the same components as the embodiment of FIG. 3A, and such components are noted with the same reference numbers as FIG. 3A. There are, however, a few notable exceptions. Specifically, instead of having a hermetically sealed housing, the embodiment of FIG. 3B provides a conductive body 48 that acts as both the housing for the electronic components 30 and as the second electrode. Conductive body 48 may be composed of a metallized polymer, one or more metal or metal alloys, or other conductive material. Because body 48 is conductive, it may act as an electromagnetic interference (EMI) shield to the electronic components disposed within the cavity 32. Electrical connections to the printed circuit board 36 may be carried out with one or more conductive spring connectors 50 or other conventional lead connectors.

Feedthrough 42 that is connected to the coil member 38 extends from the end of coil member 38 and makes an electrical connection with a lead on the printed circuit board 36. The feedthrough 42 works in conjunction with one or more dielectric seals or spacers 52 to hermetically seal the cavity 32. Similar to above, the cavity 32 may be filled with an inert gas or an encapsulant. The proximal end 46 of flexible body 40 may be coupled to the seals 52 and/or coupled to the conductive body 48.

As shown in the embodiment of FIG. 3B, the surface area of conductive body 48 (e.g., the first electrode) may be larger than the surface area of the second electrode 26. In other embodiments, however, the surface area of the second electrode 26 may have the substantially same surface area and/or shape as the conductive body 48.

In most embodiments, the implantable devices shown in FIGS. 3A and 3B function completely independent
of the other implantable devices 12 and there is no physical connection or communication between the various devices. If desired, however, the implantable devices 12 may be physically coupled to each other with a connecting wire or tether and/or in communication with each other. If the plurality of implanted devices 12 are in communication with one another, it may be desired to use a communication frequency between the implanted devices 12 that is different from the frequency to communicate between the implanted devices and the external device 14. Of course, the communication frequency between the implanted devices 12 may also be the same frequency as the communication frequency with the external device 14.

[0109] While FIGS. 3A and 3B illustrate a first and second electrode 24, 26, the implantable devices 12 of the present invention are not limited to only two electrodes. Any number of electrodes may be coupled to the implantable device in any orientation. For example, the electrodes do not have to extend from ends of the housing, but may be positioned anywhere along a portion of the housings 28, 40. Furthermore, a plurality of electrodes and their leads may be disposed along the length of the flexible housing 40 and/or rigid housing 28 so as to provide more than two electrodes per implantable device. For example, FIG. 3C illustrates a simplified embodiment in which there are two additional electrode 24, 26 positioned on the rigid housing 28 and flexible housing 40, respectively. The spacing between the various contacts 24, 24, 26, 26 may vary or be the same distance between each other. The spacing between electrodes will likely depend on the overall length of the implantable device, but will typically be between about 2 mm and about 20 mm and preferably be between about 5 mm and about 10 mm. In addition to the embodiment shown in FIG. 3C, it may be desirable to have the additional electrodes only on the flexible housing 40 or only on the rigid housing 28. While only four electrodes are shown on the implantable device, it should be appreciated that any number of electrodes (e.g., anywhere between two electrodes and about sixteen electrodes) may be coupled to the implantable device.

[0110] While FIGS. 3A-3B illustrate some currently preferred embodiments of the implantable device 12, the present invention further encompasses other types of minimally invasive implantable devices 12 that can monitor the brain activity and other physiological signals from the patient. For example, a plurality of electrodes might reside on a single lead that could be tunneled under the scalp from a single point of entry. Examples of such embodiments are shown in FIGS. 2A-2E.

[0111] Such implantable devices 12 include an active electrode contact 400 that is in communication with one or more passive electrode contacts 401. The active electrode contact 400 may be used to facilitate monitoring of the physiological signals using the array of active and passive electrode contacts. The arrays of electrode contacts may be arranged in a linear orientation (FIG. 2C) or in a grid pattern (FIG. 2F), or any other desired pattern (e.g., circular, star pattern, customized asymmetric pattern, etc.) For example, if the implantable device comprises two electrode contacts (e.g., one active contact and one passive contact), such an embodiment would have a similar configuration as the embodiment of FIG. 3A. Similarly, if the implantable device were to have four substantially linearly positioned electrode contacts (e.g., one active contact and three passive contacts), such an embodiment would be substantially similar to the configuration shown in FIG. 3C.

[0112] FIG. 2A illustrates a bottom view of an active electrode contact 400 that may be part of the implantable device 12 of the present invention. The active electrode contact comprises a base 402 that is coupled to a contact portion 404. The base 402 and contact portion may be composed of any number of different types of materials, such as platinum, platinum-iridium alloy, stainless steel, or any other conventional material. In preferred embodiments, both the base 402 and contact portion 404 are formed to their desired shape. The base 402 may comprise a plurality of hermetic feedthroughs 413 that is implemented using conventional glass metal seal technology (e.g., pins 408, glass seal 414, and via 406). The hermetic feedthroughs 413 may be used to connect to an antenna (not shown) for communication with the external device 14 or to make an electrical connection with an adjacent passive electrode contact 401 in the implantable device 12. In the illustrated embodiment, base 402 comprises four hermetic feedthroughs 413. But as can be appreciated the base 402 may comprise any desired number of feedthroughs 413 (e.g., anywhere between two and sixty four feedthroughs).

[0113] FIG. 2B illustrates a cross-sectional view of the active electrode contact 400 along lines B-B in FIG. 2A. As shown in FIG. 2B, the contact portion 404 is shaped to as to align the base 402 along a bottom surface defined by flanges 409. Base 402 may be coupled to the contact portion 404 with a laser weld, glass metal seal, or other conventional connector 410 along an outer perimeter of the base 402 to hermetically seal components of the active electrode contact within a cavity 412 defined by the base 402 and contact portion 404. If desired, the cavity 412 may be backfilled with nitrogen and/or helium to facilitate package leak testing.

[0114] A thin or thick filled microcircuit or a printed circuit board (“PCB”) 416 may be mounted onto an inner surface of the base 402. PCB 416 may have active components 418 (e.g., integrated circuits, ASIC, memory, etc.) and passive components 420 (e.g., resistors, capacitors, etc.) mounted thereto. Leads or bond wires 422 from the active and passive components may be electrically attached to pads on the PCB (not shown) which make electrical connections to leads or bond wires 424 that are attached to the hermetic feedthroughs 413. While not shown in FIG. 2B, the active electrode contact 400 may comprise a rechargeable or non-rechargeable power supply (e.g., batteries), and/or x-ray visible markers (not shown).

[0115] As noted above, the active contacts may be used in conjunction with one or more passive contacts to form an active implantable device 12 to facilitate monitoring of the patient’s physiological signals and to communicate with the external device 14. FIGS. 2C and 2D illustrate an embodiment of the implantable device 12 in which one active contact 400 is housed in a body 426 along with a plurality of passive contacts 401 to form a multiple contact implantable device 12. The contact portion of the active contact 400 is exposed through an opening in the body 426 to allow for sampling of the physiological signals (e.g., EEG) from the patient. The body 426 may be substantially flexible or rigid and may have similar dimensions and/or shapes as the embodiments shown in FIGS. 3A-3C. Body 426 may be
composed of a biocompatible material such as silicone, polyurethane, or other materials that are inert and biocompatible to the human body. Body 426 may also be composed of a rigid material such as polycarbonate. The implantable device may be injected into the patient using the introducer assembly shown in FIG. 6 and methods shown in FIG. 7.

[0116] As shown in FIG. 2D wire leads 427 may extend from the passive contacts 401 and be electrically and physically coupled to one of the hermetic feedthroughs 413 of the active contact 400 to facilitate sampling of the physiological signals using all four electrode contacts. For embodiments which use a wireless link (e.g., RF) to wirelessly transmit data to the external device 14 and optionally to power the device, one of the feedthroughs may be coupled to an antenna 428 that is configured to wirelessly communicate with the external device. It should be appreciated, that while not described herein, the embodiments of FIGS. 2C–2E may have any of the components or variations as described above in relation to FIGS. 3A–3B.

[0117] FIG. 2E illustrates an alternative embodiment of the implantable device 12 in which the implantable device 12 is in the form of a 4x4 grid array of active and passive contacts. At least one of the electrode contacts may be an active contact 400 so as to facilitate monitoring of the patient’s physiological signals with the array. In the illustrated embodiment, the contacts in the leftmost column (highlighted with cross-hatching) are active electrode contacts 400, and the contacts in remaining columns are electrically connected to one of the active contacts 400. Of course, any number of active contacts 400 and passive contacts 401 may be in the grid array and the active contact(s) 400 may be positioned anywhere desired. For example, if the active electrode contact 400 has sixteen or more hermetic feedthroughs, only one of the contacts in the array needs to be active and the remaining fifteen contacts could be passive contacts.

[0118] FIG. 4 illustrates one simplified embodiment of the electronic components 30 (e.g., active components 418 and passive components 420 in FIG. 2D) that may be disposed in the implantable devices 12 as shown in FIGS. 2A–3C. It should be appreciated, however, that the electronic components 30 of the implantable device 12 may include any combination of conventional hardware, software and/or firmware to carry out the functionality described herein. For example, the electronic components 30 may include many of the components that are used in passive RF integrated circuits.

[0119] The first and second electrodes will be used to sample a physiological signal from the patient—typically an EEG signal 53, and transmit the sampled signal to the electronic components 30. While it may be possible to record and transmit the analog EEG signal to the external device, the analog EEG signal will typically undergo processing before transmission to the external device 14. The electronic components typically include a printed circuit board that has, among others, an amplifier 54, one or more filters 56 (e.g., bandpass, notch, lowpass, and/or highpass) and an analog-to-digital converter 58. In some embodiments, the processed EEG signals may be sent to a transmit/receive sub-system 60 for wireless transmission to the external device via an antenna (e.g., coil member 38). Additional electronic components that might be useful in implantable device 12 may be found in U.S. Pat. Nos. 5,193,539, 5,193,540, 5,312,439, 5,324,316, 5,405,367 and 6,051,017.

[0120] In some alternative embodiments of the present invention, the electronic components 30 may include a memory 64 (e.g., RAM, EEPROM, Flash, etc.) for permanently or temporarily storing or buffering the processed EEG signal. For example, memory 64 may be used as a buffer to temporarily store the processed EEG signal if there are problems with transmitting the data to the external device. For example, if the external device’s power supply is low, the memory in the external device is removed, or if the external device is out of communication range with the implantable device, the EEG signals may be temporarily buffered in memory 64 and the buffered EEG signals and the current sampled EEG signals may be transmitted to the external device when the problem has been corrected. If there are problems with the transmission of the data from the implantable device, the external device may be configured to provide a warning or other output signal to the patient to inform them to correct the problem. Upon correction of the problems, the implantable device may automatically continue the transfer the temporarily buffered data and the real-time EEG data to the memory in the external device.

[0121] The electronic components 30 may optionally comprise dedicated circuitry and/or a microprocessor 62 (referred to herein collectively as “microprocessor”) for further processing of the EEG signals prior to transmission to the external device. The microprocessor 62 may execute EEG analysis software, such as a seizure prediction algorithm, a seizure detection algorithm, safety algorithm, or portions of such algorithms, or portions thereof. For example, in some configurations, the microprocessor may run one or more feature extractors that extract features from the EEG signal that are relevant to the purpose of monitoring. Thus, if the system is being used for diagnosing or monitoring epileptic patients, the extracted features (either alone or in combination with other features) may be indicative of or predictive of a seizure. Once the feature(s) are extracted, the microprocessor 62 may send the extracted feature(s) to the transmit/receive sub-system 60 for the wireless transmission to the external device and/or store the extracted feature(s) in memory 64. Because the transmission of the extracted features is likely to include less data than the EEG signal itself, such a configuration will likely reduce the bandwidth requirements for the communication link between the implantable device and the external device. Since the extracted features do not add a large amount of data to the data signal, in some embodiments, it may also be desirable to concurrently transmit both the extracted feature and the EEG signal. A detailed discussion of various embodiments of the internal/external placement of such algorithms are described in commonly owned U.S. patent application Ser. No. 11/322,150, filed Dec. 28, 2005 to Bland et al., the complete disclosure of which is incorporated herein by reference.

[0122] While most embodiments of the implantable device 12 are passive and do not need an internal power source or internal clock, in some embodiments, the electronic components 30 may include a rechargeable or non-rechargeable power supply 66 and an internal clock (not shown). The rechargeable or non-rechargeable power supply may be a battery, a capacitor, or the like. The rechargeable
power supply 66 may also be in communication with the transmit/receive sub-system 60 so as to receive power from outside the body by inductive coupling, radiofrequency (RF) coupling, etc. Power supply 66 will generally be used to provide power to the other components of the implantable device. In such embodiments, the implanted device may generate and transmit its own signal with the sampled EEG signal for transmission back to the external device. Consequently, as used herein “transmit” includes both passive transmission of a signal back to the external device (e.g., backscattering of the RF signal) and internal generation of a separate signal for transmission back to the external device.

[0123] FIG. 5 is a simplified illustration of some of the components that may be included in external device 14. Antenna 18 and a transmit/receive subsystem 70 will receive a data signal that is encoded with the EEG data (or other physiological data) from the antenna 38 of the implantable device 12 (FIG. 4). As used herein, “EEG data” may include a raw EEG signal, a processed EEG signal, extracted features from the EEG signal, an answer from an implanted EEG analysis software (e.g., safety, prediction and/or detection algorithm), or any combination thereof.

[0124] The EEG data may thereafter be stored in memory 72, such as a hard drive, RAM, permanent or removable Flash Memory, or the like and/or processed by a microprocessor 74 or other dedicated circuitry. Microprocessor 74 may be configured to request that the implantable device perform an impedance check between the first and second electrodes and/or other calibrations prior to EEG recording and/or during predetermined times during the recording period to ensure the proper function of the system.

[0125] The EEG data may be transmitted from memory 72 to microprocessor 74 where the data may optionally undergo additional processing. For example, if the EEG data is encrypted, it may be decrypted. The microprocessor 74 may also comprise one or more filters that filter out high-frequency artifacts (e.g., muscle movement artifacts, eye blink artifacts, chewing, etc.) so as to prevent contamination of the high frequency components of the sampled EEG signals. In some embodiments, the microprocessor may process the EEG data to measure the patient’s brain state, detect seizures, predict the onset of a future seizure, generate metrics/measurements of seizure activity, or the like. A more complete description of seizure detection algorithms, seizure prediction algorithms, and related components that may be implemented in the external device 14 may be found in pending, commonly owned U.S. patent application Ser. Nos. 11/321,897 and 11/321,898, filed on Dec. 28, 2005, to Leyde et al. and DiLorenzo et al., and 60/897,551, filed on Jan. 25, 2007, to Leyde et al., the complete disclosures of which are incorporated herein by reference.

[0126] It should be appreciated, however, that in some embodiments some or all of the computing power of the system of the present invention may be performed in a computer system or workstation 76 that is separate from the system 10, and the external device 14 may simply be used as a data collection device. In such embodiments, the personal computer 76 may be located at the physician’s office or at the patient’s home and the EEG data stored in memory 72 may be uploaded to the personal computer 76 via a USB interface 78, removal of the memory (e.g., Flash Memory stick), or other conventional communication protocols, and minimal processing may be performed in the external device 14. In such embodiments, the personal computer 76 may contain the filters, decryption algorithm, EEG analysis software, such as a prediction algorithm and/or detection algorithm, report generation software, or the like. Some embodiments of the present invention may take advantage of a web-based data monitoring/data transfer system, such as those described in U.S. Pat. Nos. 6,471,645 and 6,824,512, the complete disclosures of which are incorporated herein by reference.

[0127] External device 14 may also comprise an RF signal generator 75 that is configured to generate the RF field for interrogating and optionally powering the implanted devices 12. RF generator 75 will be under control of the microprocessor 74 and generate the appropriate RF field to facilitate monitoring and transmission of the sampled EEG signals to the external device.

[0128] External device 14 will typically include a user interface 80 for displaying outputs to the patient and for receiving inputs from the patient. The user interface typically comprise outputs such as auditory devices (e.g., speakers) visual devices (e.g., LCD display, LEDs to indicate brain state or propensity to seizure), tactile devices (e.g., vibratory mechanisms), or the like, and inputs, such as a plurality of buttons, a touch screen, and/or a scroll wheel.

[0129] The user interface may be adapted to allow the patient to indicate and record certain events. For example, the patient may indicate that medication has been taken, the dosage, the type of medication, meal intake, sleep, drowsiness, occurrence of an aura, occurrence of a seizure, or the like. Such inputs may be used in conjunction with the recorded EEG data to improve the analysis of the patient’s condition and determine the efficacy of the medications taken by the patient.

[0130] The LCD display of the user interface 80 may be used to output a variety of different communications to the patient including, status of the device (e.g., memory capacity remaining), battery state of one or more components of the system, whether or not the external device 14 is within communication range of the implantable devices 12, brain state indicators (e.g., a warning (e.g., seizure warning), a prediction (e.g., seizure prediction), unknown brain state, safety indication, a recommendation (e.g., “take drugs”), or the like). Of course, it may be desirable to provide an audio output or vibratory output to the patient in addition to or as an alternative to the visual display on the LCD. In other embodiments, the brain state indicators may be separate from the LCD display to as to provide a clear separation between the device status outputs and the brain state indicators. In such embodiments, the external device may comprise different colored LEDs to indicate different brain states. For example, a green LED may indicate a safe brain state, a yellow light may indicate an unknown brain state, and a red light may indicate either a seizure detection or seizure prediction.

[0131] External device 14 may also include a medical grade power source 82 or other conventional power supply that is in communication with at least one other component of the external device 14. The power source 82 may be rechargeable. If the power source 82 is rechargeable, the power source may optionally have an interface for communication with a charger 84. While not shown in FIG. 5, external
device 14 will typically comprise a clock circuit (e.g., oscillator and frequency synthesizer) to provide the time base for synchronizing external device 14 and the internal device(s) 12. In preferred embodiments, the internal device(s) 12 are slaves to the external device and the implantable devices 12 will not have to have an individual oscillator and a frequency synthesizer, and the implantable device(s) 12 will use the “master” clock as its time base. Consequently, it may be possible to further reduce the size of the implantable devices.

[0132] In use, one or more of the implantable devices are implanted in the patient. The implanted device is interrogated and powered so that the EEG signals are sampled from the patient’s brain. The EEG signals are processed by the implanted device and the processed EEG signals are wirelessly transmitted from the implanted device(s) to an external device. The EEG signals are stored for future or substantially real-time analysis.

[0133] As noted above, in preferred embodiments, the implantable devices are implanted in a minimally invasive fashion under the patient’s scalp and above an outer surface of the skull. FIG. 6 illustrates a simplified introducer assembly 90 that may be used to introduce the implantable devices into the patient. The introducer assembly 90 is typically in the form of a cannula and stylet or a syringe-like device that can access the target area and inject the implantable device under the skin of the patient. As noted above, the implantable devices 12 are preferably implanted beneath at least one layer of the patient’s scalp and above the patient’s skull. Because of the small size of the implantable devices 12, the devices may be injected into the patient under local anesthesia in an out-patient procedure by the physician or neurologist. Because the implantable devices are implanted entirely beneath the skin, the infection risk would be reduced and there would be minimal cosmetic implications. Due to the small size of the implantable devices 12, it may be desirable to have a plurality of implantable devices pre-loaded into a sterile introducer assembly 90 or into a sterile cartridge (not shown) so as to minimize the risk of contamination of the implantable devices 12 prior to implantation.

[0134] FIG. 7 schematically illustrates one example of a minimally invasive method 100 of implanting the implantable devices for ambulatory monitoring of a patient’s EEG signals. At step 102, an incision is made in the patient’s scalp. At step 104, an introducer assembly is inserted into the incision and a distal tip of the introducer assembly is positioned at or near the target site. Of course, the introducer assembly itself may be used to create the incision. For example, if the introducer assembly is in the form of a syringe, the syringe tip may be made to create the incision and steps 102 and 104 may be consolidated into a single step. At step 106, the introducer assembly is actuated to inject the implantable device 12 to the target site. If desired, the introducer may be repositioned to additional target sites underneath the patient’s skin and above the skull. If needed, additional incisions may be created in the patient’s skin to allow for injection of the implantable device 12 at the additional target sites. After a desired number of implantable devices are placed in the patient, at step 108 the introducer assembly is removed from the target site. At step 110, the implantable devices are activated and used to perform long term monitoring of the patient’s EEG signals from each of the target sites. At step 112, the sampled EEG signals are then wirelessly transmitted to an external device. At step 114, the sampled EEG signals may then be stored in a memory in the external device or in another device (e.g., personal computer). If desired, the EEG signals may then be processed in the external device or in a personal computer of the physician.

[0135] While not shown in FIG. 7, it may also be desirable to anchor the implantable devices to the patient to reduce the likelihood that the implantable devices are dislodged from their desired position. Anchoring may be performed with tissue adhesive, barbs or other protrusions, sutures, or the like.

[0136] Advantageously, the implantable devices are able to monitor EEG signals from the patient without the use of burr holes in the skull or implantation within the brain—which significantly reduces the risk of infection for the patient and makes the implantation process easier. While there is some attenuation of the EEG signals and movement artifacts in the signals, because the implantable devices are below the skin, it is believed that there will be much lower impedance than scalp electrodes. Furthermore, having a compact implantable device 14 below the skin reduces common-mode interference signals which can cause a differential signal to appear due to any imbalance in electrode impedance and the skin provides some protection from interference caused by stray electric charges (static).

[0137] While FIG. 7 illustrates one preferred method of implanting the implantable devices in the patient and using the implantable devices to monitor the patient’s EEG, the present invention is not limited to such a method, and a variety of other non-invasive and invasive implantation and monitoring methods may be used. For example, while minimally invasive monitoring is the preferred method, the systems and devices of the present invention are equally applicable to more invasive monitoring. Thus, if it is desired to monitor and record intracranial EEG signals (e.g., ECoG), then it may be possible to implant one or more of the implantable devices inside the patient’s skull (e.g., in the brain, above or below the dura mater, or a combination thereof) through a burr hole created in the patient’s skull.

[0138] Once implanted in the patient, the monitoring systems 10 of the present invention may be used for a variety of different uses. For example, in one usage the systems of the present invention may be used to diagnose whether or not the patient has epilepsy. Patients are often admitted to video-EEG monitoring sessions in an EMU to determine if the patient is having seizures, pseudo-seizures, or is suffering from vaso-vagal syncope, and the like. Unfortunately, if the patient has infrequent “seizures,” it is unlikely that the short term stay in the EMU will record a patient’s seizure and the patient’s diagnosis will still be unclear. Consequently, in order to improve the patient’s diagnosis, in addition to the in-hospital video-EEG monitoring or as an alternative to the in-hospital video-EEG monitoring, the patient may undergo an ambulatory, long term monitoring of the patient’s EEG using the system of the present invention for a desired time period. The time period may be one day or more, a week or more, one month or more, two months or more, three months or more, six months or more, one year or more, or any other desired time period in between. The patient may be implanted with the system 10 using the method described above, and after a predetermined time
period, the patient may return to the physician’s office where the EEG data will be uploaded to the physician’s personal computer for analysis. A conventional or proprietary seizure detection algorithm may be applied to the EEG data to determine whether or not a seizure occurred in the monitoring time period. If it is determined that one or more seizures occurred during the monitoring period, the seizure detection algorithm may be used to provide an output to the physician (and/or generate a report for the patient) indicating the occurrence of one or more seizures, and various seizure activity metrics, such as spike count over a period of time, seizure count over a period of time, average seizure duration over a period of time, the pattern of seizure occurrence over time, and other seizure and seizure related metrics. In addition, the software may be used to display the actual EEG signals from specific events or selected events for physician confirmation of seizure activity. Such data may be used as a “baseline” for the patient when used in assessing efficacy of AEDs or other therapies that the patient will undergo.

If the patient has been diagnosed with epilepsy (either using the system of the present invention or through conventional diagnosis methods), the present invention may also be used to determine the epilepsy classification and/or seizure type. To perform such methods, a desired number of implantable devices may be implanted in the patient for the long term monitoring of the patient’s pattern of electrical activity in the different portions of the patient’s brain. Such monitoring will be able to provide insight on whether or not the patient has partial/focal seizures or generalized seizures. The seizure detection algorithm may be used to determine the desired placement for the implantable devices in the patient. For patients suspected or known to have temporal lobe epilepsy, the implantable devices will likely be focused over the temporal lobe and adjacent and/or over the regions of epileptiform activity. Likewise, for patient’s suspected or known to have partial lobe epilepsy, some or all of the implantable devices will be positioned over the aural and adjacent and/or over the regions of epileptiform activity. Furthermore, if the seizure focus or foci are known, at least some of the implantable devices may be positioned over the seizure focus or foci and some may be positioned contralateral to the known seizure focus or foci.

If a seizure focus in the patient has not been lateralized, the present invention may be used to lateralize the seizure focus. FIG. 8 illustrates one method 120 of lateralizing a seizure focus in a patient. At step 122, a set of implantable devices are implanted on the patient’s skull. The set of implantable devices are positioned to localize the seizure focus. Preferably, the electrode devices will comprise more than one electrode to improve the ability to localize the seizure focus. For embodiments that include two electrodes, a very large number of implantable devices may be required to actually localize the seizure focus. In one embodiment, implantation may be carried out using the method steps 102-108 illustrated in FIG. 7. At step 124, the set of implantable devices are used to sample the patient’s EEG signals. At step 126, each of the EEG signals from the implantable devices are analyzed over a period of time (e.g., with EEG analysis software, such as a seizure detection algorithm) to monitor the patient’s seizure activity and once a seizure has occurred try to lateralize the seizure focus. At step 128, if the seizure focus is lateralized, a subset of the implantable devices that are lateralized to the seizure focus are identified. At steps 130 and 132, the EEG signals from the subset of implantable may continue to be sampled, and such EEG signals may thereafter be stored and processed to analyze the patient’s brain activity. The implantable devices that are not lateralized to the focus may be removed from the patient, disabled, or the EEG signals from such implantable devices may be ignored or not captured/stored. However, if desired, such EEG signals may continue to be stored and processed. The location and/or lateralization of the seizure focus may thereafter be used by the physicians to determine whether or not the patient is a candidate for resective surgery or other procedures.

In another use, the present invention may be used to quantify seizure activity statistics for the patient. The most common method of quantifying a patient’s seizure activity is through patient self reporting using a seizure diary. Unfortunately, it has been estimated that up to 65% of all seizures are missed by patients. Patient’s missing the seizures are usually caused by the patient being amnesic to the seizures, unaware of the seizures, mentally incapacitated, the seizures occur during sleep, or the like. FIG. 9 illustrates a simplified method 140 of measuring and reporting a patient’s seizure activity statistics. At step 142, one or more implantable devices are implanted in a patient, typically in a minimally invasive fashion as shown in FIG. 7. At step 144, the implantable devices are used to substantially continuously sample EEG signals from the patient. At step 146, the sampled EEG signals are wirelessly transmitted from the implantable device to an external device. At step 148, the sampled EEG signals are stored in a memory. At step 150, the stored EEG signals are analyzed with EEG analysis software, typically using a seizure prediction and/or detection algorithm, to derive statistics for the clinical seizures and/or the sub-clinical seizures for the patient based on the long-term, ambulatory EEG data. For example, the following statistics may be quantified using the present invention:

Seizure count over a time period—How many clinical and sub-clinical seizures does the patient have in a specific time period?

Seizure frequency—How frequent does the patient have seizures? What is the seizure frequency without medication and with medication? Without electrical stimulation and with electrical stimulation?

Seizure duration—How long do the seizures last? Without medication and with medication? Without electrical stimulation and with electrical stimulation?

Seizure timing—When did the patient have the seizure? Do the seizures occur more frequently at certain times of the day?

Seizure patterns—Is there a pattern to the patient’s seizures? After certain activities are performed? What activities appear to trigger seizures for this particular patient?

Finally, at step 152, report generation software may be used to generate a report based on the statistics for the seizure activity. The report may include some or all of the statistics described above, an epilepsy/no epilepsy diagnosis, identification of a seizure focus, and may also include the EEG signal(s) associated with one or more of the
seizures. The report may include text, graphs, charts, images, or a combination thereof so as to present the information to the physician and/or patient in an actionable format. Advantageously, the systems may be used to generate a baseline report for the patient, and the system may be continuously used to record data over a long period of time and provide a quantification of the patient’s change in their condition and/or the efficacy of any therapy that the patient is undergoing (described in more detail below).

[0148] As noted above, the present invention enables the documentation and long-term monitoring of sub-clinical seizures in a patient. Because the patient is unaware of the occurrence of sub-clinical seizures, it is therefore the long-term monitoring of sub-clinical seizures was not possible. Documentation of the sub-clinical seizures may further provide insight into the relationship between sub-clinical seizures and clinical seizures, and medical practitioners, and provide important additional information relevant to the effectiveness of patient therapy, and may further enhance the development of additional treatments for epilepsy.

[0149] FIG. 10 illustrates one exemplary method of how the seizure activity data may be used to evaluate the efficacy or clinical benefit of a current or potential therapy and allow for the intelligent selection of an appropriate therapy for an individual patient and/or stopping the usage of ineffective therapies. Currently, effectiveness of the AED therapy is based on self-reporting of the patient, in which the patient makes entries in a diary regarding the occurrence of their seizure(s). If the entries in the patient diary indicate a reduction in seizure frequency, the AED is deemed to be effective and the patient continues with some form of the current regimen of AEDs. If the patient entries in the patient diary do not indicate a change in seizure frequency, the AEDs are deemed to be ineffective, and typically another AED is prescribed—and most often in addition to the AED that was deemed to be ineffective. Because AEDs are typically powerful neural suppressants and are associated with undesirable side-effects, the current methodology of assessing the efficacy of the AEDs often keeps the patient on ineffective AEDs and exposes the patient to unnecessary side-effects.

[0150] By way of example, a medically refractory patient coming to an epilepsy center for the first time might first have the system of the present invention implanted and then asked to collect data for a prescribed time period, e.g., 30 days. The initial 30 days could be used to establish a baseline measurement for future reference. The physician could then prescribe an adjustment to the patient’s medications and have the patient collect data for another time period, e.g., an additional 30 day period. Metrics from this analysis could then be compared to the previous analysis to see if the adjustment to the medications resulted in an improvement. If the improvement was not satisfactory, the patient can be taken off of the unsatisfactory medication, and a new medication could be tried. This process could continue until a satisfactory level of seizure control was achieved. The present invention provides a metric that allows physicians and patients to make informed decisions on the effectiveness and non-effectiveness of the medications.

[0151] FIG. 10 schematically illustrates one example of such a method. At step 162, one or more implantable devices are implanted in the patient, typically in a minimally-invasive fashion. At step 164, the one or more implantable devices are used to monitor the patient’s EEG to obtain a baseline measurement for the patient. The baseline measurement is typically seizure activity statistics for a specific time period (e.g., number of seizures, seizure duration, seizure pattern, seizure frequency, etc.). It should be appreciated however, that the baseline measurement may include any number of types of metrics. For example, the baseline metric may include univariate, bivariate, or multivariate features that are extracted from the EEG, or the like. In one preferred embodiment, the baseline measurement is performed while the patient is not taking any AEDs or any other therapy. In other embodiments, however, the patient may be taking one or more AEDs and the baseline measurement will be used to evaluate adjustments to dosage or efficacy of other add-on therapies.

[0152] At step 166, the therapy that is to be evaluated is commenced. The therapy will typically be an AED and the patient will typically have instructions from the neurologist, epileptologist, or drug-manufacturer regarding the treatment regimen for the AED. The treatment regimen may be constant (e.g., one pill a day) throughout the evaluation period, or the treatment regimen may call for varying of some parameter of the therapy (e.g., three pills a day for the first week, two pills a day for the second week, one pill a day for the third week, etc.) during the evaluation period. During the evaluation period, the implantable device(s) will be used to substantially continuously sample the patient’s EEG and assess the effect that the AED has on the patient’s EEG. The sampled EEG may thereafter be processed to obtain a follow-up measurement for the patient (Step 168). If the baseline measurement was seizure statistics for the baseline time period, then the follow-up measurement will be the corresponding seizure statistics for the evaluation period. At step 170, the baseline measurement is compared to the follow-up measurement to evaluate the therapy. If the comparison indicates that the therapy did not significantly change the patient’s baseline, the therapy may be stopped, and other therapies may be tried.

[0153] Currently, the primary metric in evaluating the efficacy of an AED is whether or not the AED reduces the patient’s seizure count. In addition to seizure count, the systems of the present invention would be able to track any reduction in seizure duration, modification in seizure patterns, reduction in seizure frequency, or the like. While seizure count is important, because the present invention is able to provide much greater detail than just seizure count, efficacy of an AED may be measured using a combination of additional metrics, if desired. For example, if the patient was having a large number of sub-clinical seizures (which the patient was not aware of) and the AED was effective in reducing or stopping the sub-clinical seizures, the systems of the present invention would be able to provide metrics for such a situation. With conventional patient diary "metrics", the patient and physician would not be aware of such a reduction, and such an AED would be determined to be non- efficacious for the patient. However, because the present invention is able to provide metrics for the sub-clinical seizures, the efficacious medication could be continued, if desired.

[0154] At step 172, the epileptologist or neurologist may decide to change one or more parameters of the therapy. For example, they may change a dosage, frequency of dosage,
form of the therapy or the like, and thereafter repeat the follow-up analysis for the therapy with the changed parameter. After the "second" follow-up measurement is complete, the second follow-up data may be obtained and thereafter compared to the "first" follow-up measurements and/or the baseline measurements. While not shown in FIG. 10, the method may also comprise generating a report that details the patient's metrics, change in metrics, recommendations, etc. 

[0155] In addition to evaluating an efficacy of a therapy for an individual patient, the metrics that are provided by the present invention also enable an intelligent titration of a patient's medications. As shown in FIG. 11, if the patient is on a treatment regimen of an efficacious therapy, the present invention may be used to reduce/titrate a dosage or frequency of intake of the AED or AEDs, or other pharmacological agents. At step 182, one or more implantable devices are minimally invasively implanted in the patient. Typically, the patient will already be on a treatment regimen of the efficacious therapy, but if not, the efficacious therapy is commenced with the prescribed parameters, e.g., "standard" dosage (Step 184). At step 186, the patient's EEG (and/or other physiological signal) is monitored for a desired time period to obtain a first patient data measurement for the patient (e.g., the baseline measurement). Similar to previous embodiments, the first patient data measurement may be any desired metrics, but will typically be clinical seizure frequency, clinical seizure duration, sub-clinical seizure frequency, sub-clinical seizure duration, medication side effects. At step 188, after the baseline measurement has been taken, the first efficacious therapy is stopped and a therapy with at least one changed parameter is started (referred to as "therapy with second parameters" in FIG. 11). Typically, the changed parameter will be a reduction in dosage, but it could be changing a frequency of the same dosage, a change in formulation or form of the same AED, or the like. 

[0156] At step 190, the patient's EEG is monitored and processed to obtain a second patient data measurement for the patient (e.g., follow-up data measurement). If the neurologist or epileptologist is satisfied with the results, the titration may end. But in many embodiments, the titration process will require more than one modification of parameters of the therapy. In such embodiments, the second therapy is stopped (step 192), and a therapy with Nth parameters (e.g., third, fourth, fifth . . . ) is commenced (step 194). Monitoring and processing of the patient's EEG signals are repeated (step 196), and the process is repeated a desired number of times (as illustrated by arrow 197). Once the desired numbers of modifications to the therapy have been made, the various patient data measurements may be analyzed (e.g., compared to each other) to determine the most desirable parameters for the therapy (step 198). As can be imagined, any number of different analyses or statistical methods may be performed. In one embodiment, seizure activity statistics (e.g., clinical seizure frequency, sub-clinical seizure frequency, seizure rate per time period, seizure duration, seizure patterns, etc.) may be used to assess the efficacy and differences between the therapies. 

[0157] With the instrumentation provided by the present invention, the process of selecting appropriate AEDs and the titration of dosages of such AEDs could occur much faster and with much greater insight than ever before. Further, the chance of a patient remaining on an incremental AED that was providing little incremental benefit would be minimized. Once a patient was under control, the patient could cease the use of the system, but the implantable device could remain in the patient. In the future, the patient might be asked to use the system again should their condition change or if the efficacy of the AED wane due to tolerance effects, etc. 

[0158] While FIGS. 10 and 11 are primarily directed toward assessing the efficacy of a pharmacological agent (e.g., AED), such methods are equally applicable to assessing the efficacy and optimizing patient-specific parameters of non-pharmacological therapies. For example, the present invention may also be used to evaluate and optimize parameters for the electrical stimulation provided by the Vagus Nerve Stimulator (sold by Cyberonics Corporation), Responsive Neurostimulator (RNS) (manufactured by NeuroPace Corporation), Deep Brain Stimulators (manufactured by Medtronic), and other commercial and experimental neural and spinal cord stimulators. 

[0159] Furthermore, the systems of the present invention will also be able to provide metrics for the effectiveness of changes to various electrical parameters (e.g., frequency, pulse amplitude, pulse width, pulses per burst, burst frequency, burst/no-burst, duty cycle, etc.) for the electrical stimulation treatments. Such metrics will provide a reliable indication regarding the effectiveness of such parameter changes, and could lead to optimization of stimulation for parameters for individual patients or the patient population as a whole. 

[0160] In addition to facilitating the selection of appropriate AEDs and titration of dosages of the AEDs for an individual patient, the present invention may have beneficial use in the clinical trials for the development of experimental AEDs and other therapies for the epileptic patient population (and other neurological conditions). One of the greatest barriers to developing new AEDs (and other pharmacological agents) is the costs and difficulties associated with the clinical trials. Presently, the standard metric for such clinical trials is patient seizure count. Because this metric is self-reported and presently so unreliable, to power the study appropriately clinical trials for AEDs must involve very large patient populations, in which the patient's must have a high seizure count. At an estimated cost of $20,000 per patient for pharmacological trials, the cost of developing a new drug for epilepsy is exceedingly high and may deter drug companies from developing AEDs. 

[0161] The minimally invasive systems of the present invention may be used to facilitate these clinical trials. Such systems could result in significantly more reliable data, which would result in much smaller sample patient populations, and could include a broader types of patients (e.g., patient’s who don’t have frequent seizures) for appropriately powering the study. Improved certainty in efficacy would also reduce (e.g., clinical company, as it moved from safety studies to efficacy studies. Significantly reducing risk and improving the economics of these studies by reducing the required number of study subjects could lead to an increase in the development of new therapies for this patient population, and other patient populations. 

[0162] It should be appreciated however, that the present invention is not limited to clinical trials for epilepsy therapies, and the present invention has equal applicability to
other clinical trials (e.g., cancer therapy, cardiac therapy, therapy for other neurological disorders, therapy for psychiatric disorders, or the like.)

[0163] FIGS. 12-13 illustrate some methods of performing clinical trials that are encompassed by the present invention. The present invention is applicable to any type of clinical trial, including but not limited to a randomized clinical trial, e.g., an open clinical trial, a single-blinded study, a double-blinded study, a triple-blinded study, or the like.

[0164] FIG. 12 illustrates a simplified method 200 of performing a clinical trial according to the present invention. At step 201 participants are enrolled in the clinical trial. At step 202, selected participants in the clinical trial are implanted with one or more leadless, implantable devices (such as those described above) in order to sample one or more physiological signal from the patient. Typically, the physiological signal is an EEG signal. In preferred embodiments, the EEG signal is sampled substantially continuously for the entire baseline period for each of the participants in the clinical trial. In alternative embodiments, it may be desirable to sample the EEG signals in a non-continuous basis.

[0165] At step 204, the sampled EEG signals are processed for a desired time period to obtain a first patient data measurement, e.g., a baseline data measurement, for each of the participants in the clinical trial. After the participants have commenced the experimental therapy (typically by following a prescribed treatment regimen by the investigator or drug company), the same implantable devices are used to sample the EEG signals from the participant for an evaluation period, and the EEG signals are processed to provide a second patient data measurement, e.g., follow-up measurement (Step 206, 208). At step 210, the baseline data measurement and the follow-up data measurement may be compared using conventional statistical methods in order to evaluate the experimental therapy on the patient population.

[0166] While not shown in FIG. 12, it may be desirable to have a "second" evaluation period (and a second follow-up measurement) in which at least one parameter of the experimental therapy is changed and the changed experimental therapy is administered to the patient. Similar to the method of FIG. 11, such a method may provide guidance to finding the appropriate dosing, formulation, and/or form of delivery of the experimental therapy.

[0167] The baseline period and the evaluation period are typically the same time length. The time length may be any desired time, but is typically at least one week, and preferably between at least one month and at least three months.

[0168] Evaluation of the experimental therapy may be to evaluate dosing requirements, evaluate toxicity of the experimental therapy, evaluate long-term adverse effects of the experimental therapy or to determine efficacy of the experimental therapy. In one preferred embodiment, the comparison may simply determine whether there was a statistically significant change in a seizure count between the baseline period and the evaluation period. But as noted above, the baseline data measurement and follow-up data measurement may include any metric that is extracted from the EEG signals.

[0169] FIG. 13 illustrates a more detailed method of performing a clinical trial according to the present invention. At step 222 participants are enrolled in the clinical trial. At step 224, the participants in the clinical trial are implanted with one or more leadless, implantable devices (such as those described above) in order to sample one or more physiological signal from the patient. Typically, the physiological signal is an EEG signal. In preferred embodiments, the EEG signal is sampled substantially continuously for the entire baseline period for each of the participants in the clinical trial.

[0170] At step 226, the sampled EEG signals are processed to obtain a first patient data measurement, e.g., a baseline data measurement, for each of the participants in the clinical trial. If the patient’s do not have any seizures during the baseline period, then the patient’s will most likely be excluded from the remainder of the clinical trial. The remaining participants in the clinical trial are then broken into an intervention group and a control group. The experimental therapy is commenced in the intervention group of the patient population (step 228), and a placebo therapy is commenced in the control group of the patient population (step 230).

[0171] The implantable devices are used to substantially continuously sample the EEG signals of both the intervention group and the control group during an evaluation period. The EEG signals are processed to obtain follow-up seizure activity data (or some other metric) for both groups (step 232, 234). Thereafter, the baseline data and the follow-up data for both the intervention group and the control group are analyzed, (e.g., compared with each other) to evaluate the efficacy of the experimental therapy for the patient population (step 236). While not shown in FIG. 13, the method may further include changing one or more parameters of the experimental therapy and comparing the “second” follow up data to the baseline data and/or other follow up data.

[0172] While the preferred embodiments described above are directed toward evaluating experimental AEDs in the clinical trial, the present invention is equally applicable to clinical trials for other experimental pharmacological agents, biology, devices, and other non-pharmacological therapies. For example, the present invention may also be used to evaluate the Vagus Nerve Stimulator (sold by Cyberonics Corporation), Responsive Neurostimulator (RNS) (manufactured by NeuroPace Corporation), Deep Brain Stimulators manufactured by Medtronic, and other commercial and experimental neural and spinal cord stimulators. The minimally invasive systems of the present invention may be implanted in patients who are equipped with any of the above stimulators to provide metrics regarding the efficacy of the electrical stimulation treatments.

[0173] Furthermore, the systems of the present invention will also be able to provide metrics for the effectiveness of changes to various electrical parameters (e.g., frequency, pulse amplitude, pulse width, pulses per burst, burst frequency, burst/no-burst, etc.) for the electrical stimulation treatments. Such metrics will provide a reliable indication regarding the effectiveness of such parameter changes, and could lead to optimization of stimulation for parameters for individual patients or the patient population as a whole.

[0174] FIG. 14 illustrates a packaged system or kit 300 that is encompassed by the present invention. The packaged system 300 may include a package 302 that has one or more
compartments for receiving an introducer assembly 304 and one or more implantable devices 12. The introducer 304 is typically in the form of a syringe-like device or a cannula and stylet. The implantable device 12 may include any of the embodiments described herein. One or more of the implantable devices 12 may be pre-loaded within the introducer 304. In other embodiments, the implantable devices 12 may be loaded in its separate sterile packaging (shown in dotted lines) for easy loading into the introducer 304. The packaged system 300 may include instructions for use ("IFU") 306 that describe any of the methods described herein.

[0175] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. For example, the present invention also encompasses other more invasive embodiments which may be used to monitor the patient’s neurological system.

[0176] Alternative embodiments of the implantable device of the present invention may require a neurosurgeon to create a more invasive incision in the patient’s scalp. For example, it may be desirable to use a low profile device that is not substantially cylindrical, but instead is substantially planar or concave so as to conform to the curvature of the patient’s skull. Such embodiments would likely not be able to be implanted without general anesthesia and may require a surgeon to implant the device.

[0177] On the other hand, in some embodiments it may be desirable to be completely non-invasive. Such embodiments include “implantable” devices 12 that are not actually implanted, but instead are “wearable” and may be attached to the outer surface of the skin with adhesive or a bandage so as to maintain contact with the patient’s skin. For example, it may be possible to surface mount the device 12 behind the ears, in the scalp, on the forehead, along the jaw, or the like. Because the electrodes are wireless and are such a small size, unlike conventional electrodes, the visual appearance of the electrodes will be minimal.

[0178] Furthermore, in some embodiments, it may be desirable to modify the implantable device 12 to provide stimulation to the patient. In such embodiments, the implantable device 12 will include a pulse generator and associated hardware and software for delivering stimulation to the patient through the first and second electrodes 24, 26 or other electrodes coupled to the device. In such embodiments, the external device 14 will include the hardware and software to generate the control signals for delivering the electrical stimulation to the patient.

[0179] While the above embodiments describe that power to the implanted devices may be derived wirelessly from an external device and/or from a battery in the implanted device, it should be appreciated that the internal devices may derive or otherwise “scavenge” power from other types of conventional or proprietary assemblies. Such scavenging methods may be used in conjunction with the external power source and/or the internal power source, or it may be used by itself to provide the necessary power for the implanted devices. For example, the implanted devices may include circuitry and other assemblies (e.g., a microgenerator) that derive and store power from patient-based energy sources such as kinetic movement/vibrations (e.g., gross body movements), movement of organs or other bodily fluids (e.g., heart, lungs, blood flow), and thermal sources in the body (e.g., temperature differences and variations across tissue). As can be imagined, such technology could reduce or eliminate the need for recharging of an implanted battery, replacement of a depleted battery, and/or the creation of an external RF field—and would improve the ease of use of the devices by the patients.

[0180] Some embodiments of the monitoring system may include an integral patient diary functionality. The patient diary may be a module in the external device and inputs by the patient may be used to provide secondary inputs to provide background information for the sampled EEG signals. For example, if a seizure is recorded, the seizure diary may provide insight regarding a trigger to the seizure, or the like. The diary may automatically record the time and date of the entry by the patient. Entries by the patient may be a voice recording, or through activation of user inputs on the external device. The diary may be used to indicate the occurrence of an aura, occurrence of a seizure, the consumption of a meal, missed meal, delayed meal, activities being performed, consumption of alcohol, the patient’s sleep state (drowsy, going to sleep, waking up, etc.), mental state (e.g., depressed, excited, stressed), intake of their AEDs, medication changes, missed dosage of medication, menstrual cycle, illness, or the like. Thereafter, the patient inputs recorded in the diary may also be used by the physician in assessing the patient’s epilepsy state and/or determine the efficacy of the current treatment. Furthermore, the physician may be able to compare the number of seizures logged by the patient to the number of seizures detected by the seizure detection algorithm.

[0181] It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:
1. A method of evaluating an experimental therapy for a patient population in a clinical trial, the method comprising:
   - minimally invasively implanting patients with one or more devices that are configured to measure a physiological signal from the patients;
   - processing the physiological signal from the patients for a first time period to obtain a first patient data;
   - measuring the physiological signal from the patients after the patients have commenced the experimental therapy;
   - processing the physiological signal that was measured after the commencement of the experimental therapy to obtain a second patient data; and
   - evaluating the experimental therapy by analyzing the first patient data and the second patient data.

2. The method of claim 1 wherein the experimental therapy comprises a pharmacological agent.
3. The method of claim 1 wherein comparing is performed to evaluate the efficacy of the experimental therapy in the patient population.
4. The method of claim 1 wherein comparing is performed to evaluate dosing requirements of the experimental therapy for the patient population.
5. The method of claim 1 wherein comparing is performed to evaluate toxicity of the experimental therapy for the patient population.
6. The method of claim 1 wherein comparing is performed to evaluate long-term adverse effects of the experimental therapy on the patient population.
7. The method of claim 1 wherein the experimental therapy comprises vagus nerve stimulation.
8. The method of claim 1 wherein the experimental therapy comprises brain stimulation.
9. The method of claim 1 wherein minimally invasively implanting patients with one or more devices comprises implanting one or more leadless devices between at least one layer of the scalp and the skull.
10. The method of claim 1 further comprising:
    transcutaneously transmitting data that is indicative of the measured physiological signal through a wireless communication link to a device that is external to the patient’s body; and
    storing the data that is indicative of the measured physiological signal in a memory.
11. The method of claim 1 wherein the experimental therapy is for managing epilepsy and the physiological signal comprises an EEG signal.
12. The method of claim 11 wherein processing the physiological signal from the patient for a first time period comprises obtaining a baseline seizure activity that comprises at least one of a number a clinical seizures during the first time period, a number of sub-clinical seizures during the first time period, seizure duration, seizure patterns, seizure frequency, and time of seizure occurrence.
13. The method of claim 12 wherein evaluating the experimental therapy by comparing the first patient data with the second patient data comprises comparing baseline seizure activity with seizure activity after commencement of the experimental therapy.
14. The method of claim 1 further comprising:
    changing at least one parameter of the experimental therapy;
    measuring the physiological signal from the patients after the patients have commenced the experimental therapy with the at least one changed parameter for a third time period;
    processing the physiological signal that was measured during the third time period to obtain a third patient data; and
    evaluating the experimental therapy by comparing the third patient data with at least one of the first patient data and the second patient data.
15. A method of evaluating efficacy of an experimental pharmacological agent on a patient population in a clinical trial, the method comprising:
    enrolling a patient population in the clinical trial;
    implanting the patient population with one or more leadless devices between a patient’s skull and scalp that are configured to measure brain activity signals;
    measuring brain activity signals for a baseline time period;
    processing the brain activity signals for the baseline time period to obtain baseline data of the patient population;
    instructing the patient population to commence a treatment regimen of the pharmacological agent;
    measuring brain activity signals in the patient population for a desired time period after the patient population has commenced the pharmacological agent treatment regimen;
    processing the brain activity signals in the patient population for the desired time period to obtain follow-up data of the patient population; and
    evaluating the pharmacological agent by comparing the baseline data and the follow-up data.
16. The method of claim 15 wherein evaluating the pharmacological agent comprises assessing the efficacy of the pharmacological agent in the patient population.
17. The method of claim 15 wherein evaluating the pharmacological agent comprises assessing dosing requirements of the pharmacological agent for the patient population.
18. The method of claim 15 wherein evaluating the pharmacological agent comprises assessing toxicity of the pharmacological agent for the patient population.
19. The method of claim 15 wherein evaluating the pharmacological agent comprises assessing long-term adverse effects of the pharmacological agent on the patient population.
20. The method of claim 15 wherein the pharmacological agent is for managing seizures.
21. The method of claim 20 wherein processing the brain activity for the baseline time period to obtain baseline data of the patient population comprises:
    transcutaneously transmitting the measured brain activity signals through a wireless communication link to a device that is external to the patient’s body; and
    extracting seizure activity data from the brain activity signals.
22. The method of claim 21 wherein the seizure activity data comprises at least one of: a number a clinical seizures during the baseline time period, a number of sub-clinical seizures during the baseline time period, average seizure duration, seizure patterns, seizure frequency, and time of seizure occurrence.
23. The method of claim 20 wherein evaluating the pharmacological agent by comparing the baseline data with the follow-up data comprises comparing baseline seizure activity with seizure activity in the follow-up data.
24. The method of claim 15 further comprising:
    changing at least one parameter of the pharmacological agent;
    measuring the brain activity signals from the patients after the patients have commenced the treatment regimen with the pharmacological agent with the at least one changed parameter;
processing brain activity signals that were measured after the commencement of the treatment regimen with the pharmacological agent with the at least one changed parameter to obtain subsequent patient data; and

evaluating the pharmacological agent by comparing the subsequent patient data with at least one of the baseline data and the follow-up data.

25. A method of evaluating an experimental therapy for a patient population in a clinical trial, the method comprising:

minimally invasively implanting the patient population with one or more devices that are configured to measure a physiological signal from a patient;

processing the physiological signal from the patient population for a baseline time period to obtain a first patient data;

commencing a placebo therapy in a control group of the patient population;

commencing the experimental therapy in an intervention group of the patient population;

measuring the physiological signal from the control group and the intervention group for a second time period after the patients have commenced the placebo therapy and experimental therapy, respectively;

processing the physiological signal obtained during the second time period to obtain a second patient data; and

evaluating the experimental therapy by analyzing the first patient data and the second patient for both the control group and the intervention group.

26. The method of claim 25 wherein minimally invasively implanting the patient population comprises placing one or more device in between the skull and the scalp.

27. A method of evaluating an experimental anti-epileptic drug (AED) therapy for a patient population in a clinical trial, the method comprising:

enrolling a patient population in the clinical trial;

minimally invasively implanting one or more devices between the patient’s skull and scalp that are configured to substantially continuously sample an EEG signal from the patient for a baseline period;

wirelessly transmitting a signal encoded with the sampled EEG signals to a portable device that is external to the patient;

processing the EEG signal from the patients to obtain a seizure activity baseline for the patients in the patient population;

separating the patient population into a control group and an intervention group;

commencing a placebo AED therapy in the control group of the patient population;

commencing the experimental AED therapy in the intervention group of the patient population;

substantially continuously sampling the EEG signals from the control group and the intervention group with the implanted one or more devices for a selected time period after the patients have commenced the placebo therapy and experimental therapy, respectively;

processing the EEG signal from the patients from the selected time period to obtain a seizure activity outcome data; and

evaluating the experimental AED therapy by comparing the baseline seizure activity data with the seizure activity outcome data for both the control group and the intervention group.

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